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(71) Applicant (for all designated States except US):
SMITHKLINE BEECHAM CORPORATION
[US/US]; One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19101 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **RAFFERTY, Stephen, William** [US/US]; GlaxoSmithKline, c/o Corporate Intellectual Property Dept., Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709 (US). **TURNBULL, Philip, Stewart** [CA/US]; GlaxoSmithKline, c/o Corporate Intellectual Property Dept., Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709 (US). **STEWART, Eugene, Lee** [US/US]; GlaxoSmithKline, c/o Corporate Intellectual Property Dept., Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709 (US). **CALDWELL, Richard, Dana** [US/US]; GlaxoSmithKline, c/o Corporate Intellectual Property Dept., Five Moore

Drive, PO Box 13398, Research Triangle Park, NC 27709 (US).

(74) Agents: **DADSWELL, Charles, E.** et al.; GlaxoSmithKline, c/o Corporate Intellectual Property Dept., Five Moore Drive, Post Office Box 13398, Research Triangle Park, NC 27709 (US).

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(54) Title: NAPHTHALENE DERIVATIVES AS MODULATORS OF THE GLUCOCORTICOID RECEPTOR

(57) Abstract: The present invention relates to naphthalene derivatives of formula (I) that are modulators of the glucocorticoid receptor, and to processes for the preparation and use of the same.

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CHEMICAL COMPOUNDS

FIELD OF THE INVENTION

5 The present invention relates to naphthalene derivatives that are modulators of the glucocorticoid receptor, and to processes for the preparation and use of the same.

BACKGROUND OF THE INVENTION

 Nuclear receptors are a class of structurally related gene expression modulators that act as ligand-dependent transcription factors (R.M. Evans, (1988) *Science* **240**,
10 889). The steroid receptors, namely the androgen receptor (AR), the estrogen receptor (ER), the glucocorticoid receptor (GR), the mineralocorticoid receptor (MR), and the progesterone receptor (PR) represent a subclass of the nuclear receptor superfamily. Nuclear receptor ligands in this subclass exert their effects by binding to an intracellular steroid hormone receptor. After the receptor-ligand complex is translocated to the
15 nucleus of the cell, the complex binds to recognition sites on DNA, which allows for the modulation of certain genes.

 Certain ligands have demonstrated the ability to exhibit their activity in a tissue selective manner. In other words, tissue selectivity allows a nuclear receptor ligand to function as an agonist in some tissues, while having no effect or even an antagonist
20 effect in other tissues. The term "selective receptor modulator" (SRM) has been given to these molecules. A synthetic compound that binds to an intracellular receptor and mimics the effects of the native hormone is referred to as an agonist. A compound that inhibits the effect of the native hormone is called an antagonist. The term "modulators" refers to compounds that have a spectrum of activities ranging activation to inhibition of
25 a cellular function (M. Coghlan, (2003) *Curr. Topics Med. Chem.* **3**, 1617-1635).

 Glucocorticoids (GCs) exert several effects in tissues that express GR. They regulate the expression of several genes either positively or negatively and in a direct or indirect manner. GCs have been identified as a key player in glucose regulation. Hepatic glucose production is regulated by two main mechanisms: glycogenolysis and
30 gluconeogenesis. Glycogenolysis occurs within 2-3 hours after feeding in humans, while gluconeogenesis, a major source of glucose production in diabetic patients, becomes more important after prolonged fasting (Nordlie & Foster, (1999) *Annu. Rev. Nutr.* **19**, 379-406 and Pilkis & Granner (1992) *Annu. Rev. Physiol.* **54**, 885-909).

Hormones such as insulin, glucagon, and GCs have been shown to control the expression of genes that encode proteins important in gluconeogenesis regulation (Spiegelman et al., (2001) *Nature* **413**, 131-138).

There is much evidence that the GR is directly involved in glucose regulation. In one study, mice containing a homodimerizing-deficient GR (GR-dim mice) demonstrated an inability to regulate genes involved in gluconeogenesis (Reichardt et al., (1998) *Cell* **93**, 531-541). Also, RU-486, a non-selective steroidal GR antagonist, significantly lowered glucose in a type 2 diabetes animal model (Friedman et al., (1997) *J. Biol. Chem.* **272**, 31475-31481). The reduction in glucose was mainly due to a reduction in hepatic enzyme gene expression. However, the use of steroidal GR antagonists is limited by their side-effects.

Glucocorticoids are the end product of the HPA axis. Under normal conditions their secretion into the systemic circulation is tightly regulated by a negative feedback mechanism and marked increases in serum cortisol occur only in accord with a well-established circadian rhythm and in conditions of stress. It has been hypothesized that dysregulation of the HPA axis is a cause of depression (see, for example, Holsboer, F., (2000) *Neuropsychopharmacol* , **23**, 477-501). Hyperactivity of the HPA axis in patients with major depression is one of the most consistent findings in biological psychiatry (see, for example, Holsboer, F & Barden, N. (1996) *Endocr Rev*, **17**, 187-205). Patients with major depression have been shown to exhibit increased concentrations of cortisol in the plasma, urine and cerebrospinal fluid, exaggerated cortisol responses to exogenous ACTH and an enlargement of both the pituitary and the adrenal glands. In addition, a multitude of studies have demonstrated that the GC-mediated feedback inhibition of the HPA axis is impaired in depression; thus, unlike normal patients, approximately 50% of depressed patients fail to respond to synthetic GCs with a reduction in serum cortisol (Holsboer, F & Barden, N. (1996) *Endocr Rev*, **17**, 187-205; *Endocr Rev*, **17**, 187-205).

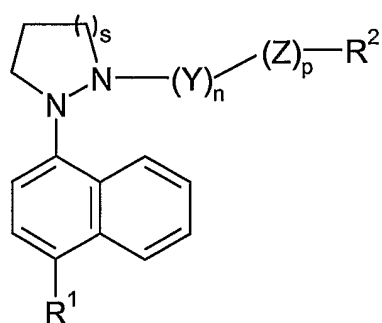
Evidence that dysregulation of the HPA axis is a cause of depression has emerged from studies in patients with Cushing's syndrome (a condition of excessive cortisol secretion) and subjects in whom the HPA axis has been stimulated pharmacologically, for example with interferon- α (IFN- α) (*J Psychopharmacol* **16**, 230-234) and that the severity of the symptoms correlates directly with the cytokine induced

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rise in serum cortisol (Am J Psychiatry, 160, 1342-1345). Further evidence of a role for the HPA axis in the pathogenesis of depression has emerged from the use of drugs to relieve depression which inhibit GC synthesis (such as ketoconazole, metyrapone and aminoglutethimide) or directly block the glucocorticoid receptor (such as RU38486 or Org-34517) (see, for example, Wolkowitz, O. et al., (1999) *Psychosom Med*, **61**, 698-711; Belanoff, J. et al., (2002) *Biol Psychiatry*, **52**, 386-392; *Int J Neuropsychopharmacol*, **5** (Suppl. 1): Abst P.3.E.044). These and other data support a primary role for HPA dysfunction as a crucial biological mechanism in the pathogenesis of depression.

10 SUMMARY OF THE INVENTION

Briefly, in one aspect, the present invention provides compounds of formula (I)



(I),

or a salt or solvate thereof, wherein

15 s is 1, 2, 3 or 4;

R¹ is cyano or nitro;

Y is -C(O)-;

Z is alkylene or -(R^a)_mO-;

R^a is alkylene;

20 m is 0 or 1;

n is 0 or 1;

p is 0 or 1;

R² is alkyl, cyano, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, aryl, substituted aryl, heteroaryl, substituted heteroaryl, haloalkyl, diphenylalkyl, alkylsilyl, amino, hydroxyl, -C(O)OCH₃, -CH(CN)CH₂Ph, -CH(OCH₂CH₃)Ph, or -NH(CH₂)₂Ph, wherein

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when R² is substituted cycloalkyl, substituted aryl, substituted heteroaryl, or substituted heterocycle, each substituent is independently selected from the group consisting of alkyl, alkenyl, aryl, alkylaryl, alkylthio, alkoxy, alkenoxy, aryloxy, aralkoxy, halo, haloalkyl, haloaryl, haloalkoxy, haloalkylthio, haloalkylaryl, alkylsulfonyl, cyano, 5 nitro, heterocycle, heteroaryl, cycloalkyl-alkylene, CH₃C(O)-, CH₃C(O)OCH₂-, and CH₃C(O)NH-.

Another aspect of the present invention provides a compound substantially as hereinbefore defined with reference to any one of the Examples.

Another aspect of the present invention provides a pharmaceutical composition 10 comprising a compound of the present invention.

Another aspect of the present invention provides a compound of the present invention for use as an active therapeutic substance.

Another aspect of the present invention provides a compound of the present invention for use in the treatment of conditions or disorders that respond to 15 glucocorticoid receptor modulation.

Another aspect of the present invention provides a compound of the present invention for use in the treatment of type 2 diabetes, type 1 diabetes, hyperglycemia, insulin resistance, metabolic syndrome X, diabetic dyslipidemia, bipolar disorder (manic depression), drug dependency, sleep disorders, schizophrenia, obsessive-compulsive 20 disorder, post-traumatic stress disorder, social anxiety disorder, and generalized anxiety disorder.

Another aspect of the present invention provides a method for the treatment of type 2 diabetes, type 1 diabetes, hyperglycemia, insulin resistance, metabolic syndrome X, diabetic dyslipidemia, bipolar disorder (manic depression), drug 25 dependency, sleep disorders, schizophrenia, obsessive-compulsive disorder, post-traumatic stress disorder, social anxiety disorder, and generalized anxiety disorder comprising the administration of a compound of the present invention.

Another aspect of the present invention provides a method for the treatment of 30 conditions or disorders that respond to glucocorticoid receptor modulation comprising the administration of a compound of the present invention.

Another aspect of the present invention provides the use of a compound of the present invention in the manufacture of a medicament for use in the treatment of type 2 diabetes, type 1 diabetes, hyperglycemia, insulin resistance, metabolic syndrome X, diabetic dyslipidemia, bipolar disorder (manic depression), drug dependency, sleep disorders, schizophrenia, obsessive-compulsive disorder, post-traumatic stress disorder, social anxiety disorder, and generalized anxiety disorder.

Another aspect of the present invention provides the use of a compound of the present invention in the manufacture of a medicament for use in the treatment of conditions or disorders that respond to glucocorticoid receptor modulation.

DETAILED DESCRIPTION OF THE INVENTION

Terms are used within their accepted meanings. The following definitions are meant to clarify, but not limit, the terms defined.

As used herein, "a compound of formula (I)" means a compound of formula (I) or a salt or solvate thereof.

As used herein the term "alkyl" refers to a straight or branched chain hydrocarbon, preferably having from one to twelve carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl, n-butyl, tert-butyl, isopentyl, and n-pentyl.

As used throughout this specification, the preferred number of atoms, such as carbon atoms, will be represented by, for example, the phrase "C_xC_y alkyl," which refers to an alkyl group, as herein defined, containing the specified number of carbon atoms. Similar terminology will apply for other preferred terms and ranges as well.

As used herein the term "alkenyl" refers to a straight or branched chain aliphatic hydrocarbon containing one or more carbon-to-carbon double bonds. Examples include, but are not limited to, vinyl and the like.

As used herein, the term "alkylene" refers to a straight or branched chain divalent hydrocarbon radical, preferably having from one to ten carbon atoms. Examples of "alkylene" as used herein include, but are not limited to, methylene (-CH₂-), ethylene (-CH₂-CH₂-), and branched versions thereof such as (-CH(CH₃)-) and the like.

As used herein, the term "cycloalkyl" refers to a non-aromatic cyclic hydrocarbon ring. Exemplary "cycloalkyl" groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like.

As used herein, the term "heterocycle" or "heterocyclyl" refers to a mono- or poly-cyclic ring system containing one or more heteroatoms and optionally containing one or more degrees of unsaturation. Preferred heteroatoms include N, O, and/or S, including N-oxides, sulfur oxides, and dioxides. Preferably the ring is three to ten-membered and is saturated. Such rings may be optionally fused to one or more of another "heterocyclic" ring(s), heteroaryl ring(s), aryl ring(s), or cycloalkyl ring(s).

Examples of "heterocyclic" groups include, but are not limited to, tetrahydrofuran, pyran, piperidine, pyrrolidine, pyrrolidinone, and morpholine.

The term "aryl" refers to an aromatic ring system, such as an benzene ring system, such as phenyl. The term encompasses fused systems where one or more benzene rings form, for example, anthracene, phenanthrene, or naphthalene ring systems. The term also includes an optional alkylene linker, such as C1-C6 alkylene, through which the aryl group may be attached. Examples of "aryl" groups include, but are not limited to phenyl, benzyl, 2-naphthyl, 1-naphthyl, biphenyl, as well as substituted derivatives thereof.

As used herein the term "aralkyl" refers to a group $-R_aR_b$, where R_a is an alkylene group and R_b is an aryl group as each is herein defined.

As used herein, the term "heteroaryl" refers to a monocyclic five to seven membered aromatic ring, or to a fused bicyclic aromatic ring system comprising two of such aromatic rings, which contain one or more nitrogen, sulfur, and/or oxygen atoms, where N-oxides, sulfur oxides, and dioxides are permissible heteroatom substitutions. Examples of "heteroaryl" groups used herein include, but should not be limited to, furan, thiophene, pyrrole, imidazole, pyrazole, triazole, tetrazole, thiazole, oxazole, isoxazole, oxadiazole, thiadiazole, isothiazole, pyridine, pyridazine, pyrazine, pyrimidine, quinoline, isoquinoline, benzofuran, benzothiophene, indole, indazole, and the like. Preferred heteroaryl groups include furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, isooxazolyl, pyridyl, piperonyl, and indolyl.

As used herein the term "alkylaryl" refers refers to a group $-R_aR_b$, where R_a is an arylene group and R_b is an alkyl group as each is herein defined.

As used herein the term "halo" or "halogen" refers to fluorine, chlorine, bromine, or iodine.

As used herein the term "haloalkyl" refers to an alkyl group, as defined herein that is substituted with at least one halogen. Examples of branched or straight chained "haloalkyl" groups useful in the present invention include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, and t-butyl substituted independently with one or more halogens, *e.g.*, fluoro, chloro, bromo, and iodo. The term "haloalkyl" should be interpreted to include such substituents such as $-\text{CF}_3$, $-\text{CH}_2\text{-CH}_2\text{-F}$, $-\text{CH}_2\text{-CF}_3$, and the like.

As used herein the term "haloaryl" refers to an aryl group, as defined herein that is substituted with at least one halogen. Examples of "haloaryl" groups useful in the present invention include, but are not limited to, phenyl and naphthyl, substituted independently with one or more halogens, *e.g.*, fluoro, chloro, bromo, and iodo.

As used herein the term "haloalkylaryl" refers to an aryl group, as defined herein, substituted with one or more haloalkyl groups, as defined herein.

As used herein the term "hydroxy" or "hydroxyl" refers to a group $-\text{OH}$.

As used herein the term "alkoxy" refers to a group $-\text{OR}_a$, where R_a is alkyl as herein defined.

As used herein the term "alkenoxy" refers to a group $-\text{OR}_a$, where R_a is alkenyl as herein defined.

As used herein the term "aryloxy" refers to a group $-\text{OR}_a$, where R_a is aryl as herein defined.

As used herein the term "aralkoxy" refers to a group $-\text{OR}_a$, where R_a is aralkyl as herein defined.

As used herein the term "haloalkoxy" refers to a group $-\text{OR}_a$, where R_a is haloalkyl as defined herein.

As used herein the term "alkylthio" refers to a group $-\text{SR}_a$, where R_a is alkyl as herein defined.

As used herein the term "haloalkylthio" refers to a group $-\text{SR}_a$, where R_a is haloalkyl as defined herein.

As used herein the term "alkylsulfonyl" refers to a group $-\text{SO}_2\text{R}_a$, where R_a is an alkyl group as herein defined.

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As used herein the term "alkylsilyl" refers to a group $-\text{Si}(\text{R}_a)_3$, where R_a is an alkyl group as herein defined.

As used herein the term "nitro" refers to a group $-\text{NO}_2$.

As used herein the term "cyano" refers to a group $-\text{CN}$.

5 As used herein the term "amino" refers to a group $-\text{NH}_2$, and also refers to a group $-\text{N}(\text{R}_a)(\text{R}_b)$, where one or both of R_a and R_b are other than H. For example, the term includes groups such as $-\text{N}(\text{CH}_3)(\text{CH}_3)$, $-\text{N}(\text{CH}_3)(\text{CH}_2\text{-CH}_3)$, and the like.

In one embodiment, the present invention provides compounds of formula (I) wherein s is 1, 2, or 3.

10 In another embodiment, s is 1, R^1 is cyano or nitro, Y is $-\text{C}(\text{O})-$, Z is alkylene, n is 0 or 1, p is 0 or 1, and R^2 is alkyl, cycloalkyl, heteroaryl, aryl, substituted aryl, haloalkyl, or amino, wherein when R^2 is substituted aryl, each substituent is independently selected from the group consisting of alkyl, alkoxy, halo, haloalkyl, haloalkoxy, cyano, and $\text{CH}_3\text{C}(\text{O})-$.

15 In another embodiment, s is 3, R^1 is cyano or nitro, Y is $-\text{C}(\text{O})-$, Z is alkylene, n is 0 or 1, p is 0 or 1, and R^2 is alkyl, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or haloalkyl, wherein when R^2 is substituted cycloalkyl, substituted aryl, substituted heteroaryl, or substituted heterocycle, each substituent is independently selected from
20 the group consisting of alkyl, alkenyl, aryl, alkylaryl, alkoxy, halo, haloalkyl, haloalkoxy, and cyano.

In another embodiment, s is 2, R^1 is cyano or nitro, Y is $-\text{C}(\text{O})-$, Z is alkylene or $-(\text{R}^a)_m\text{O}-$, R^a is alkylene, m is 0 or 1, n is 0 or 1, p is 0 or 1, and R^2 is alkyl, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, aryl, substituted aryl,
25 heteroaryl, substituted heteroaryl, haloalkyl, diphenylalkyl, amino, hydroxyl, or $-\text{C}(\text{O})\text{OCH}_3$, $-\text{CH}(\text{CN})\text{CH}_2\text{Ph}$, $-\text{CH}(\text{OCH}_2\text{CH}_3)\text{Ph}$, $-\text{NH}(\text{CH}_2)_2\text{Ph}$, wherein when R^2 is substituted cycloalkyl, substituted aryl, substituted heteroaryl, or substituted heterocycle, each substituent is independently selected from the group consisting of
30 alkyl, alkenyl, aryl, alkylaryl, alkylthio, alkoxy, alkenoxy, aryloxy, aralkoxy, halo, haloalkyl, haloaryl, haloalkoxy, haloalkylthio, haloalkylaryl, alkylsulfonyl, cyano, nitro, heterocyclyl, cycloalkyl-alkylene, $\text{CH}_3\text{C}(\text{O})-$, $\text{CH}_3\text{C}(\text{O})\text{OCH}_2-$, and $\text{CH}_3\text{C}(\text{O})\text{NH}-$.

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In another embodiment, s is 2, R¹ is cyano or nitro, Y is -C(O)-, Z is alkylene, n is 0 or 1, p is 1, and R² is heterocycle, substituted aryl, or substituted heteroaryl, wherein when R² is substituted aryl or substituted heteroaryl, each substituent is independently selected from the group consisting of alkyl, aryl, haloalkyl, haloalkoxy, cyano, and heteroaryl.

Preferably, R¹ is cyano.

Preferably, s is 2.

Preferably, n is 0.

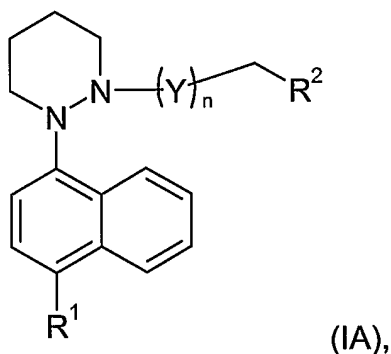
Preferably, Y is -C(O)- and n is 1.

Preferably, Z is alkylene and p is 1.

Preferably, Z is methylene and p is 1.

Preferably, R² is heterocycle, substituted aryl, or substituted heteroaryl, wherein when R² is substituted aryl or substituted heteroaryl, each substituent is independently selected from the group consisting of alkyl, aryl, haloalkyl, haloalkoxy, cyano, and heteroaryl.

In another embodiment, the present invention provides compounds of formula (IA)



or a salt or solvate thereof, wherein R¹ is cyano or nitro, Y is -C(O)-, n is 0 or 1, and R² is substituted aryl, heterocycle, or substituted heteroaryl, wherein when R² is substituted aryl or substituted heteroaryl, each substituent, is independently selected from the group consisting of alkyl, haloalkyl, haloalkoxy, heteroaryl, cyano and aryl.

While the preferred groups for each variable have generally been listed above separately for each variable, preferred compounds of this invention include those in which several of each variable in Formula (I) is selected from the preferred, more preferred, or most preferred groups for each variable. Therefore, this invention is

intended to include all combinations of preferred, more preferred, and most preferred groups.

The compounds of formula (I) may crystallize in more than one form, a characteristic known as polymorphism, and such polymorphic forms ("polymorphs") are within the scope of formulas (I). Polymorphism generally can occur as a response to changes in temperature, pressure, or both. Polymorphism can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics known in the art such as x-ray diffraction patterns, solubility, and melting point.

Certain of the compounds described herein contain one or more chiral centers, or may otherwise be capable of existing as multiple stereoisomers. The scope of the present invention includes mixtures of stereoisomers as well as purified enantiomers or enantiomerically/diastereomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds represented by formulas (I), as well as any wholly or partially equilibrated mixtures thereof. The present invention also includes the individual isomers of the compounds represented by the formulas above as mixtures with isomers thereof in which one or more chiral centers are inverted.

Typically, but not absolutely, the salts of the present invention are pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Salts of the compounds of the present invention may comprise acid addition salts. Representative salts include acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, monopotassium maleate, mucate, napsylate, nitrate, N-methylglucamine, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, potassium, salicylate, sodium, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, tosylate, triethiodide,

trimethylammonium, and valerate salts. Other salts, which are not pharmaceutically acceptable, may be useful in the preparation of compounds of this invention and these should be considered to form a further aspect of the invention.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of Formula I, Formula II, or a salt or physiologically functional derivative thereof) and a solvent. Such solvents, for the purpose of the invention, should not interfere with the biological activity of the solute. Non-limiting examples of suitable solvents include, but are not limited to water, methanol, ethanol, and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Non-limiting examples of suitable pharmaceutically acceptable solvents include water, ethanol, and acetic acid. Most preferably the solvent used is water.

As used herein, the term "physiologically functional derivative" refers to any pharmaceutically acceptable derivative of a compound of the present invention that, upon administration to a mammal, is capable of providing (directly or indirectly) a compound of the present invention or an active metabolite thereof. Such derivatives, for example, esters and amides, will be clear to those skilled in the art, without undue experimentation. Reference may be made to the teaching of *Burger's Medicinal Chemistry And Drug Discovery*, 5th Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the extent that it teaches physiologically functional derivatives.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought, for instance, by a researcher or clinician. The biological or medical response may be considered a prophylactic response or a treatment response. The term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function. For use in therapy, therapeutically effective amounts of a

compound of formula (I) may be administered as the raw chemical. Additionally, the active ingredient may be presented as a pharmaceutical composition.

Accordingly, the invention further provides pharmaceutical compositions that include compounds of the formula (I) and one or more pharmaceutically acceptable carriers, diluents, or excipients. The compounds of formula (I) are as herein described. The carrier(s), diluent(s) or excipient(s) must be acceptable, in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient of the pharmaceutical composition.

In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of the formula (I) with one or more pharmaceutically acceptable carriers, diluents or excipients.

A therapeutically effective amount of a compound of the present invention will depend upon a number of factors. For example, the species, age, and weight of the recipient, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration are all factors to be considered. The therapeutically effective amount ultimately should be at the discretion of the attendant physician or veterinarian. More usually, the effective amount should be in the range of 0.1 to 10 mg/kg body weight per day. Thus, for a 70 kg adult mammal the actual amount per day would usually be from 7 to 700 mg. This amount may be given in a single dose per day or in a number (such as two, three, four, five, or more) of sub-doses per day such that the total daily dose is the same. An effective amount of a salt, solvate, or physiologically functional derivative thereof, may be determined as a proportion of the effective amount of the compound of formula (I) *per se*. Similar dosages should be appropriate for treatment or prophylaxis of the other conditions referred to herein.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain, as a non-limiting example, 0.5 mg to 1 g of a compound of the formula (I), depending on the condition being treated, the route of administration, and the age, weight, and condition of the patient. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active

ingredient. Such pharmaceutical formulations may be prepared by any of the methods well known in the pharmacy art.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by an oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal, or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions, each with aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions. For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Generally, powders are prepared by comminuting the compound to a suitable fine size and mixing with an appropriate pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavorings, preservatives, dispersing agents, and coloring agents can also be present.

Capsules may be made by preparing a powder, liquid, or suspension mixture and encapsulating with gelatin or some other appropriate shell material. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate, or solid polyethylene glycol can be added to the mixture before the encapsulation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Examples of suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants useful in these dosage forms include, for example, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and

the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

Tablets may be formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant, and pressing into tablets.

5 A powder mixture may be prepared by mixing the compound, suitably comminuted, with a diluent or base as described above. Optional ingredients include binders such as carboxymethylcellulose, alginates, gelatins, or polyvinyl pyrrolidone, solution retardants such as paraffin, resorption accelerators such as a quaternary salt, and/or absorption agents such as bentonite, kaolin, or dicalcium phosphate. The powder mixture can be
10 wet-granulated with a binder such as syrup, starch paste, acacia mucilage or solutions of cellulosic or polymeric materials, and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a
15 stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material, and a polish coating of wax can be
20 provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solutions, syrups, and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared, for example, by dissolving the compound in a suitably flavored
25 aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated generally by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives; flavor additives such as peppermint oil, or natural sweeteners, saccharin, or other artificial sweeteners; and the like can also
30 be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the

release as for example by coating or embedding particulate material in polymers, wax or the like.

The compounds of formula (I) can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and
5 multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

The compounds of formula (I) may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled.

The compounds may also be coupled with soluble polymers as targetable drug
10 carriers. Such polymers can include polyvinylpyrrolidone (PVP), pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethyl-aspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug; for example, polylactic acid, polyepsilon caprolactone,
15 polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may
20 be delivered from the patch by iontophoresis as generally described in *Pharmaceutical Research*, 3(6), 318 (1986), incorporated herein by reference as related to such delivery systems.

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes,
25 gels, sprays, aerosols, or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the formulations may be applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a
30 cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth
5 include lozenges, pastilles, and mouthwashes.

Pharmaceutical formulations adapted for nasal administration, where the carrier is a solid, include a coarse powder having a particle size for example in the range 20 to 500 microns. The powder is administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nasal passage from a container of the powder held close
10 up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered
15 dose pressurized aerosols, nebulizers, or insufflators.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulations.

20 Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented
25 in unit-dose or multi-dose containers, for example sealed ampules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

30 In addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in

question. For example, formulations suitable for oral administration may include flavoring or coloring agents.

The present invention provides methods for the treatment of several conditions or diseases, all of which comprise the step of administering a compound of formula (I).

5 As used herein, the term "treatment" refers to alleviating the specified condition, eliminating or reducing the symptoms of the condition, slowing or eliminating the progression of the condition and preventing or delaying the initial occurrence of the condition in a subject, or reoccurrence of the condition in a previously afflicted subject.

A further aspect of the invention provides a method of treatment of a mammal
10 requiring the treatment of a variety of disorders including, but not limited to type 2 diabetes, type 1 diabetes, hyperglycemia, insulin resistance, metabolic syndrome X, diabetic dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertension, obesity, cardiovascular disease/atherosclerosis, bipolar disorder (manic depression), drug dependency, sleep disorders, schizophrenia, obsessive-compulsive disorder, post-
15 traumatic stress disorder, social anxiety disorder, generalized anxiety disorder, hypogonadism, sexual dysfunction, Cushing's Syndrome, inflammation, liver fibrosis, tissue rejection, auto-immunity, various malignancies, such as leukemias and lymphomas, rheumatic fever, polyarteritis nodosa, granulomatous polyarteritis, immune proliferation/apoptosis, chronic kidney disease, stroke and spinal cord injury,
20 hypercalcemia, acute and chronic adrenal insufficiency, cerebral edema, Little's syndrome, inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, rhinitis, asthma, tendonitis, and Crohn's disease, which use includes administering to a subject a compound of formula (I). The mammal requiring treatment with a compound of the present invention is typically a human being.

25 The compounds of the present invention and their salts and solvates thereof, may be employed alone or in combination with other therapeutic agents for the treatment of the above-mentioned conditions. For example, in type 2 diabetes, combination may be had with other glucose lowering therapeutic agents. As one example, type 2 diabetes combination therapies according to the present invention
30 would thus comprise the administration of at least one compound of formula (I) and the use of at least one other glucose lowering therapy. As a further example, combination therapies according to the present invention include the administration of at least one

compound of formula (I) and at least one other glucose lowering treatment agent, for example, a sulfonourea. The compound(s) of formula (I) and the other pharmaceutically active agent(s) may be administered together or separately and, when administered separately, administration may occur simultaneously or sequentially, in any order. The amounts of the compound(s) of formula (I) and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. The administration in combination of a compound of formula (I) with other treatment agents may be in combination by administration concomitantly in: (1) a unitary pharmaceutical composition including both compounds; or (2) separate pharmaceutical compositions each including one of the compounds. Alternatively, the combination may be administered separately in a sequential manner wherein one treatment agent is administered first and the other second or vice versa. Such sequential administration may be close in time or remote in time.

Another embodiment of the present invention includes compounds that are selective for GR. As used herein, the term "selective" means a compound having an IC₅₀ in one receptor assay that is at least 10 fold lower than the IC₅₀ in the other receptor assay, as described below. For example, a GR selective compound is a compound that would have an IC₅₀ in the GR fluorescence polarization assay that is at least 10 fold less than the IC₅₀ of that same compound in the AR fluorescence polarization assay.

The compounds of the present invention may be used in the treatment of a variety of disorders and conditions and, as such, the compounds of the present invention may be used in combination with a variety of other suitable therapeutic agents useful in the treatment of those disorders or conditions. Non-limiting examples include combinations of the present invention with anti-diabetic agents, anti-osteoporosis agents, anti-obesity agents, anti-inflammatory agents, anti-anxiety agents, anti-depressants, anti-hypertensive agents, anti-platelet agents, anti-thrombotic and thrombolytic agents, cardiac glycosides, cholesterol or lipid lowering agents, mineralocorticoid receptor antagonists, phosphodiesterase inhibitors, kinase inhibitors, thyroid mimetics, anabolic agents, viral therapies, cognitive disorder therapies, sleeping disorder therapies, sexual dysfunction therapies, contraceptives, cytotoxic agents,

radiation therapy, anti-proliferative agents, and anti-tumor agents. Additionally, the compounds of the present invention may be combined with nutritional supplements such as amino acids, triglycerides, vitamins, minerals, creatine, pilolic acid, carnitine, or coenzyme Q10.

5 The compounds of this invention may be made by a variety of methods. Illustrative general synthetic methods are set out below and then specific compounds of the invention are prepared in the working Examples.

 In all of the examples described below, protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of
10 synthetic chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Green and P. G. M. Wuts (1991) *Protecting Groups in Organic Synthesis*, John Wiley & Sons, incorporated by reference with regard to protecting groups). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The
15 selection of processes as well as the reaction conditions and order of their execution shall be consistent with the preparation of compounds of formula (I).

 Those skilled in the art will recognize if a stereocenter exists in compounds of formula (I). Accordingly, the present invention includes all possible stereoisomers and includes not only racemic compounds but the individual enantiomers as well. When a
20 compound is desired as a single enantiomer, such may be obtained by stereospecific synthesis, by resolution of the final product or any convenient intermediate, or by chiral chromatographic methods as are known in the art. Resolution of the final product, an intermediate, or a starting material may be effected by any suitable method known in the art. See, for example, *Stereochemistry of Organic Compounds* by E. L. Eliel, S. H.
25 Wilens, and L. N. Mander (Wiley-Interscience, 1994), incorporated by reference with regard to stereochemistry.

 Suitable compounds of the present invention include:

 4-[2-(phenylmethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

 4-[2-{[4-(methyloxy)phenyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-
30 naphthalenecarbonitrile;

 4-[2-{[3-(ethyloxy)phenyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-
naphthalenecarbonitrile;

4-[2-[[4-(ethyloxy)phenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[4-(butyloxy)phenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

5 4-[2-[[4-(4-ethylphenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[4-(1-methylethyl)phenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

10 4-[2-[[2-bromophenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[3-bromophenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[4-bromophenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

15 4-[2-[[2-chlorophenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[2-methylphenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

20 4-[2-[[3-chlorophenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[4-chlorophenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[2-fluorophenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

25 4-[2-[[3-fluorophenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[4-fluorophenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

30 4-[2-[[2-cyanophenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[3-cyanophenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(4-cyanophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{[4-(methylthio)phenyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

5 4-[2-[(3,4-dichlorophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(3-methylphenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

10 4-[2-[(4-acetylphenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{[4-(methylsulfonyl)phenyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{[4-(phenyloxy)phenyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

15 4-[2-[(4-butylphenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{[2-[(1,1-dimethylethyl)thio]phenyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

20 4-[2-{[3-[(trifluoromethyl)thio]phenyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{[2,4-bis(trifluoromethyl)phenyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{[3,5-bis(trifluoromethyl)phenyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

25 4-[2-[(4-methylphenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(1-naphthalenylmethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

30 4-[2-(2-naphthalenylmethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(3-thienylmethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[2,4-bis(methyloxy)phenyl]methyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[2-(trifluoromethyl)phenyl]methyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

5 4-[2-[[4-(trifluoromethyl)phenyl]methyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[2-(methyloxy)phenyl]methyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

10 4-[2-[[3-(methyloxy)phenyl]methyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[3-(phenyloxy)phenyl]methyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(cyclohexylmethyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

15 4-[2-[[2-(2-propen-1-yloxy)phenyl]methyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(2,1,3-benzoxadiazol-4-ylmethyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[1-(1,1-dimethylethyl)-5-methyl-1*H*-pyrazol-3-yl]methyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

20 4-[2-[[5-(2-pyridinyl)-2-thienyl]methyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[1-phenyl-1*H*-pyrazol-5-yl]methyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

25 4-[2-[[2-phenyl-1*H*-imidazol-4-yl]methyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[3-phenyl-1*H*-pyrazol-4-yl]methyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

N-(5-[[2-(4-cyano-1-naphthalenyl)tetrahydro-1(2*H*)-pyridazinyl]methyl]-1,3-thiazol-2-yl)acetamide;

30 4-[2-(2-pyridinylmethyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

(5-[[2-(4-cyano-1-naphthalenyl)tetrahydro-1(2*H*)-pyridazinyl]methyl]-2-furanyl)methyl acetate;

4-[2-[(1-phenyl-1*H*-imidazol-2-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[6-(methyloxy)-2-pyridinyl]methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

5 4-[2-(1*H*-pyrazol-3-ylmethyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(2-ethyl-4-methyl-1*H*-imidazol-5-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

10 5-[[2-(4-cyano-1-naphthalenyl)tetrahydro-1(2*H*)-pyridazinyl]methyl]-3-pyridinecarbonitrile;

4-[2-[(1-phenyl-1*H*-pyrazol-4-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(3-methyl-2-thienyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

15 4-[2-[(5-methyl-2-thienyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(1*H*-imidazol-4-ylmethyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

20 4-[2-[(3,5-dichlorophenyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(5-chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(3,5-dibromophenyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

25 4-[2-({5-[3-(trifluoromethyl)phenyl]-2-furanyl)methyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[1-(3,5-dichlorophenyl)-1*H*-pyrrol-2-yl]methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

30 4-[2-[[3-fluoro-5-(trifluoromethyl)phenyl]methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(3,5-difluorophenyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[3,5-bis(methyloxy)phenyl]methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(5-ethyl-2-furanyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

5 4-[2-[(5-bromo-2-furanyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(4,5-dimethyl-2-furanyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(3-pyridinylmethyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile

10 4-[2-[(6-methyl-2-pyridinyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(4-bromo-1*H*-pyrazol-3-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

15 4-[2-[(5-bromo-2-thienyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[5-chloro-1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(1-methyl-1*H*-imidazol-2-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

20 4-[2-[(4-methyl-1*H*-imidazol-5-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[4-chloro-2-(cyclopropylmethyl)-1*H*-imidazol-5-yl]methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

25 4-[2-[(2-butyl-1*H*-imidazol-4-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(3-bromo-4-pyridinyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-({6-[(1,1-dimethylethyl)oxy]-2-pyridinyl)methyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

30 4-[2-[(2-ethyl-1*H*-imidazol-4-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(4-bromo-2-thienyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(1*H*-pyrazol-4-ylmethyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

5 4-[2-[(5-methyl-2-furanyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(5-bromo-3-thienyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

10 4-[2-[(1,3-dimethyl-1*H*-pyrazol-5-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(6-bromo-3-pyridinyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(1*H*-1,2,3-triazol-4-ylmethyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

15 4-[2-(1*H*-imidazol-2-ylmethyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-(2-{[1-(1,1-dimethylethyl)-5-methyl-1*H*-pyrazol-3-yl]methyl}hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

20 4-[2-{[2-[(trifluoromethyl)oxy]phenyl]methyl}hexahydro-1*H*-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile;

4-[2-(1*H*-1,2,3-triazol-4-ylmethyl)hexahydro-1*H*-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile;

4-[2-(phenylmethyl)hexahydro-1*H*-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile;

25 4-[2-[(4-phenyl-1*H*-imidazol-5-yl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile;

4-(2-hexylhexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

4-{2-[(3-ethenylphenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

30 4-{2-[(2-fluorophenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-{2-[(1-phenyl-1*H*-pyrazol-4-yl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

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4-[2-(2-pyridinylmethyl)hexahydro-1*H*-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile;

4-{2-[(3,5-dimethylphenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

5 4-{2-[(3-methyl-5-phenyl-4-isoxazolyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-{2-[(2-methylphenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

10 4-(2-{2-[(trifluoromethyl)phenyl]methyl}hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

4-[2-(3-pyridinylmethyl)hexahydro-1*H*-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile;

4-{2-[(3-phenyl-1*H*-pyrazol-5-yl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

15 5-{[2-(4-cyano-1-naphthalenyl)hexahydro-1*H*-1,2-diazepin-1-yl]methyl}-3-pyridinecarbonitrile;

4-{2-[(2,2,3,3-tetramethylcyclopropyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

20 4-{2-[(1,3-dimethyl-1*H*-pyrazol-5-yl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-{2-[(1-phenyl-1*H*-pyrazol-5-yl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-{2-[(4-bromo-1*H*-pyrazol-3-yl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

25 4-{2-[(3-methylphenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-{2-[(2-cyanophenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

30 4-(2-{[3-(4-methylphenyl)-1*H*-pyrazol-4-yl]methyl}hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

4-{2-[(6-methyl-2-pyridinyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

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4-{2-[(4-cyanophenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-{2-(1*H*-pyrazol-3-ylmethyl)hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

5 4-{2-(4-pyridinylmethyl)hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-{2-(2-cyclopentylethyl)hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

10 4-{2-[(3-cyanophenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-(2-{[4-(trifluoromethyl)phenyl]methyl}hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

4-(2-{[2-fluoro-3-(trifluoromethyl)phenyl]methyl}hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

15 4-(2-{[3-(ethyloxy)phenyl]methyl}hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

4-{2-[(3-fluorophenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

20 4-{2-[(3-methyl-2-thienyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-(2-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

4-[2-({3-[(trifluoromethyl)oxy]phenyl}methyl)hexahydro-1*H*-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile;

25 4-[2-({3-[(trifluoromethyl)oxy]phenyl}methyl)hexahydro-1*H*-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile;

4-{2-[(5-methyl-2-thienyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

30 4-[2-(2-naphthalenylmethyl)hexahydro-1*H*-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile;

4-{2-[(3-phenyl-1*H*-pyrazol-4-yl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-(2-{{3-(trifluoromethyl)phenyl}methyl}hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

4-(2-{{6-(methoxy)-2-pyridinyl}methyl}hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

5 4-{2-[(3,5-difluorophenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-{2-[(4,5-dimethyl-2-furanyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

10 4-(2-{{3,5-bis(trifluoromethyl)phenyl}methyl}hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

4-[2-(1-naphthalenylmethyl)hexahydro-1*H*-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile;

4-(2-{{4-(methoxy)phenyl}methyl}hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

15 4-(2-{{3-(methoxy)phenyl}methyl}hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

4-(2-{{2-(methoxy)phenyl}methyl}hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

20 4-{{2-(4-nitro-1-naphthalenyl)tetrahydro-1(2*H*)-pyridazinyl}methyl}benzonitrile;
1-{{4-(1-methylethyl)phenyl}methyl}-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-(4-nitro-1-naphthalenyl)-2-(phenylmethyl)hexahydropyridazine;

1-(cyclohexylmethyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

4-[2-(3-phenylbutyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

25 4-[2-(3-phenylpropyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

1-(4-nitro-1-naphthalenyl)-2-(3-phenylbutyl)hexahydropyridazine;

1-(4-nitro-1-naphthalenyl)-2-(3-phenylpropyl)hexahydropyridazine;

1-methyl-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

Methyl 6-[2-(4-nitro-1-naphthalenyl)tetrahydro-1(2*H*)-pyridazinyl]hexanoate;

30 4-{2-[(3-bromophenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

4-[2-(3-thienylmethyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;

4-(2-[[2,4-bis(trifluoromethyl)phenyl]methyl]-1-pyrazolidinyl)-1-naphthalenecarbonitrile;

4-{2-[(3-fluorophenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

4-{2-[(2-bromophenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

5 4-{2-[(4-acetylphenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

4-(2-[[2-(trifluoromethyl)phenyl]methyl]-1-pyrazolidinyl)-1-

naphthalenecarbonitrile;

4-(2-[[4-(1-methylethyl)phenyl]methyl]-1-pyrazolidinyl)-1-naphthalenecarbonitrile;

4-{2-[(4-fluorophenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

10 4-(2-[[4-(trifluoromethyl)phenyl]methyl]-1-pyrazolidinyl)-1-

naphthalenecarbonitrile;

4-[2-({3-[(trifluoromethyl)oxy]phenyl)methyl}-1-pyrazolidinyl]-1-

naphthalenecarbonitrile;

4-{2-[(2-fluorophenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

15 4-(2-{{3-(methyloxy)phenyl}methyl}-1-pyrazolidinyl)-1-naphthalenecarbonitrile;

4-(2-{{3,5-bis(trifluoromethyl)phenyl}methyl}-1-pyrazolidinyl)-1-

naphthalenecarbonitrile;

4-(2-{{3-fluoro-5-(trifluoromethyl)phenyl}methyl}-1-pyrazolidinyl)-1-

naphthalenecarbonitrile;

20 4-(2-{{3-(trifluoromethyl)phenyl}methyl}-1-pyrazolidinyl)-1-

naphthalenecarbonitrile;

4-{2-[(4-methylphenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

4-[2-(1-naphthalenylmethyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;

4-[2-(phenylmethyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;

25 4-{2-[(3,4-dichlorophenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

4-(2-{{4-(methyloxy)phenyl}methyl}-1-pyrazolidinyl)-1-naphthalenecarbonitrile;

4-(2-{{3-(ethyloxy)phenyl}methyl}-1-pyrazolidinyl)-1-naphthalenecarbonitrile;

4-{2-[(4-cyanophenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

4-{2-[(3-cyanophenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

30 4-{2-[(2-methylphenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

4-[2-[(4-phenyl-1*H*-imidazol-5-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-

naphthalenecarbonitrile;

4-[2-[[3-(1-methylethyl)-1*H*-pyrazol-4-yl]methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[3-(1-methylethyl)-1*H*-pyrazol-4-yl]methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

5 4-[2-[(3-ethyl-1*H*-pyrazol-4-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(3-propyl-1*H*-pyrazol-4-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

10 4-[2-[[3-(2-pyridinyl)-1*H*-pyrazol-4-yl]methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[3-(3-methylphenyl)-1*H*-pyrazol-4-yl]methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

1-(2-[[[(1,1-dimethylethyl)(dimethyl)silyl]oxy]ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

15 4-[2-(2-[[[(1,1-dimethylethyl)(dimethyl)silyl]oxy]ethyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-(trifluoromethyl)phenyl]ethyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

20 4-[2-[2-(3,4-dichlorophenyl)ethyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-(3-fluorophenyl)ethyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-(2-methylphenyl)ethyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

25 4-[2-[2-[3-(methyloxy)phenyl]ethyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-(4-fluorophenyl)ethyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

30 4-[2-[2-(4-methylphenyl)ethyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-(2-bromophenyl)ethyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-(3-methylphenyl)ethyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-(2,4-dichlorophenyl)ethyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

5 4-[2-(2-phenylethyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-(1-naphthalenyl)ethyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{2-[3-(trifluoromethyl)phenyl]ethyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

10 4-[2-[2-(3-bromophenyl)ethyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-(2,6-dichlorophenyl)ethyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-(2-chloro-4-fluorophenyl)ethyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

15 4-[2-[2-(2-chlorophenyl)ethyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-(2,4,6-trimethylphenyl)ethyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

20 1-[2-(2,6-dichlorophenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-[2-(2-chloro-4-fluorophenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-[2-(2-chlorophenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-(4-nitro-1-naphthalenyl)-2-[2-(2,4,6-trimethylphenyl)ethyl]hexahydropyridazine;

25 1-[2-(2-methylphenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-[2-[3-(methyloxy)phenyl]ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-(4-nitro-1-naphthalenyl)-2-{2-[2-(trifluoromethyl)phenyl]ethyl}hexahydropyridazine;

1-[2-(2-bromophenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

30 1-(4-nitro-1-naphthalenyl)-2-[2-(3-nitrophenyl)ethyl]hexahydropyridazine;

1-[2-(3-methylphenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-[2-(2,4-dichlorophenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

- 1-[2-(1-naphthalenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
1-(4-nitro-1-naphthalenyl)-2-{2-[3-(trifluoromethyl)phenyl]ethyl}hexahydropyridazine;
1-[2-(3-bromophenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
5 1-[2-(4-fluorophenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
4-{2-[2-(4-nitro-1-naphthalenyl)tetrahydro-1(2H)-pyridazinyl]ethyl}benzonitrile;
1-[2-(4-chlorophenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
1-{2-[4-(ethyloxy)phenyl]ethyl}-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
1-(4-nitro-1-naphthalenyl)-2-(2-phenylethyl)hexahydropyridazine;
10 4-[2-(cyclohexylcarbonyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
4-(2-pentanoyltetrahydro-1(2H)-pyridazinyl)-1-naphthalenecarbonitrile;
4-[2-({3-[(phenylmethyl)oxy]phenyl}acetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
4-[2-(cyclopentylacetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
15 4-[2-(phenylacetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
4-[2-(2-phenylbutanoyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
4-[2-{{(1S,2S)-2-phenylcyclopropyl}carbonyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
4-[2-(3-phenylpropanoyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
20 4-[2-(3,3-dimethylbutanoyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
4-[2-{{4-(methyloxy)phenyl}carbonyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
4-[2-({3-[(trifluoromethyl)oxy]phenyl}carbonyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
25 4-[2-{{3-(methyloxy)phenyl}carbonyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
4-[2-{{2-(methyloxy)phenyl}carbonyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
30 4-[2-{{2-(trifluoromethyl)phenyl}carbonyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{{3-(trifluoromethyl)phenyl}carbonyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{{4-{{(trifluoromethyl)oxy}phenyl}carbonyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

5 4-[2-{{3-cyanophenyl}carbonyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{{4-(trifluoromethyl)phenyl}carbonyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

10 4-[2-{{2-{{(trifluoromethyl)oxy}phenyl}carbonyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

1-(4-nitro-1-naphthalenyl)-2-pentanoylhexahydropyridazine;

1-(4-nitro-1-naphthalenyl)-2-{{3-(trifluoromethyl)phenyl}carbonyl}hexahydropyridazine;

15 1-(4-nitro-1-naphthalenyl)-2-{{4-(trifluoromethyl)phenyl}carbonyl}hexahydropyridazine;

4-{{2-(4-nitro-1-naphthalenyl)tetrahydro-1(2*H*)-pyridazinyl}carbonyl}benzonitrile;

1-{{3-(methyloxy)phenyl}carbonyl}-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

20 1-{{4-(methyloxy)phenyl}carbonyl}-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-(1-naphthalenylcarbonyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-(2-naphthalenylcarbonyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-(4-nitro-1-naphthalenyl)-2-(2-thienylcarbonyl)hexahydropyridazine;

1-(2-methylpropanoyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

25 1-{{2-bromophenyl}carbonyl}-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-{{3-bromophenyl}carbonyl}-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-{{4-bromophenyl}carbonyl}-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-{{2,4-dichlorophenyl}carbonyl}-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-{{4-(1,1-dimethylethyl)phenyl}carbonyl}-2-(4-nitro-1-

30 naphthalenyl)hexahydropyridazine;

1-(4-nitro-1-naphthalenyl)-2-{{(phenyloxy)acetyl}hexahydropyridazine;

1-(4-nitro-1-naphthalenyl)-2-(2-phenylbutanoyl)hexahydropyridazine;

- 1-(4-nitro-1-naphthalenyl)-2-(phenylacetyl)hexahydropyridazine;
 1-(cyclopropylcarbonyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
 1-(3-methylbutanoyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
 1-(cyclohexylcarbonyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
 5 1-[(3-methylphenyl)carbonyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
 1-[(4-methylphenyl)carbonyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
 1-(4-nitro-1-naphthalenyl)-2-[[2-(trifluoromethyl)phenyl]carbonyl]hexahydropyridazine;
 1-[[3-(methyloxy)phenyl]acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
 10 1-[[4-(butyloxy)phenyl]carbonyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
 1-(cyclobutylcarbonyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
 1-(cyclopentylcarbonyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
 1-(cyclopentylacetyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
 1-(2-methylpentanoyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
 15 1-(3-cyclopentylpropanoyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
 1-[(2-bromophenyl)acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
 1-(3,3-dimethylbutanoyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
 1-(4-nitro-1-naphthalenyl)-2-[[[(1S,2S)-2-phenylcyclopropyl]carbonyl]hexahydropyridazine;
 20 1-(4-nitro-1-naphthalenyl)-2-(3-phenylpropanoyl)hexahydropyridazine;
 1-[(4-chlorophenyl)acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
 1-(diphenylacetyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
 1-[[4-(methyloxy)phenyl]acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
 1-(4-nitro-1-naphthalenyl)-2-({3-
 25 [(trifluoromethyl)oxy]phenyl}carbonyl)hexahydropyridazine;
 4-(2-acetyl-1-pyrazolidinyl)-1-naphthalenecarbonitrile;
 4-[2-(2-methylpropanoyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;
 4-[2-(3-phenylpropanoyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;
 4-(2-butanoyl-1-pyrazolidinyl)-1-naphthalenecarbonitrile;
 30 4-[2-(cyclopropylcarbonyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;
 4-[2-(3-methylbutanoyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;
 4-[2-(phenylcarbonyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;

4-(2-([3-(trifluoromethyl)phenyl]carbonyl)-1-pyrazolidinyl)-1-naphthalenecarbonitrile;

4-[2-[(2-fluorophenyl)carbonyl]-1-pyrazolidinyl]-1-naphthalenecarbonitrile;

4-[2-[(3-methylphenyl)carbonyl]-1-pyrazolidinyl]-1-naphthalenecarbonitrile;

5 4-[2-(2-furanylcarbonyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;

4-[2-[(3-fluorophenyl)carbonyl]-1-pyrazolidinyl]-1-naphthalenecarbonitrile;

4-[2-[(2-methylphenyl)carbonyl]-1-pyrazolidinyl]-1-naphthalenecarbonitrile;

4-[2-(cyclopentylcarbonyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;

4-[2-(2-phenylbutanoyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;

10 4-[2-([2-[(trifluoromethyl)oxy]phenyl]acetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-([2-(methyloxy)phenyl]acetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

15 4-[2-([4-(ethyloxy)phenyl]acetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-([2-(ethyloxy)phenyl]acetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-([3-(methyloxy)phenyl]acetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

20 4-[2-([3-(ethyloxy)phenyl]acetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-([4-[(trifluoromethyl)oxy]phenyl]acetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

25 4-[2-([2-fluoro-6-(trifluoromethyl)phenyl]acetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(2-fluorophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(2,3-difluorophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

30 4-[2-([2-(phenyloxy)phenyl]acetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(2-iodophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(pentafluorophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

5 4-[2-(2-naphthalenylacetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(2-bromophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

10 4-[2-[[3-(trifluoromethyl)phenyl]acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(2,4-difluorophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(2-[(phenylmethyl)oxy]phenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

15 4-[2-[[2-(trifluoromethyl)phenyl]acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(2,6-difluorophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

20 4-[2-[(2-chloro-4-fluorophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(4-fluorophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(3-nitrophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

25 4-[2-[(3,4-dichlorophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(2-chloro-6-fluorophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

30 4-[2-[(2-methylphenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(3-methylphenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-({3-[(trifluoromethyl)oxy]phenyl}acetyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-({3-[(trifluoromethyl)oxy]phenyl}acetyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;

5 4-[2-({3-[(trifluoromethyl)oxy]phenyl}acetyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;

4-{2-[(2-fluorophenyl)acetyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

4-(2-{[3-(trifluoromethyl)phenyl]acetyl}-1-pyrazolidinyl)-1-naphthalenecarbonitrile;

4-{2-[(2-bromophenyl)acetyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

10 4-{2-[(3-methylphenyl)acetyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

4-{2-[(2-methylphenyl)acetyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

4-{2-[(3,4-dichlorophenyl)acetyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

4-[2-({2-[(trifluoromethyl)oxy]phenyl}acetyl)-1-pyrazolidinyl]-1-

naphthalenecarbonitrile;

15 4-[2-(3-isoxazolylacetyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(1-methyl-1*H*-indol-3-yl)acetyl]tetrahydro-1(2*H*)-pyridazinyl]-1-

naphthalenecarbonitrile;

4-[2-[(ethyloxy)(phenyl)acetyl]tetrahydro-1(2*H*)-pyridazinyl]-1-

naphthalenecarbonitrile;

20 4-[2-(2-thienylacetyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(3-thienylacetyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(2-furanylacetyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[3-(4-fluorophenyl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-

naphthalenecarbonitrile;

25 4-[2-[3-(3-bromophenyl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-

naphthalenecarbonitrile;

4-[2-[3-(3,4-dichlorophenyl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-

naphthalenecarbonitrile;

4-[2-[3-(1,3-benzodioxol-5-yl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-

30 naphthalenecarbonitrile;

4-[2-({3-[3,5-bis(trifluoromethyl)phenyl]propanoyl}tetrahydro-1(2*H*)-pyridazinyl)-1-

naphthalenecarbonitrile;

4-[2-[(3*R*)-3-phenylbutanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{3-[4-(trifluoromethyl)phenyl]propanoyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

5 4-[2-(3-{4-[(trifluoromethyl)oxy]phenyl}propanoyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[3-(3,4-difluorophenyl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

10 4-[2-{3-[2-(methyloxy)phenyl]propanoyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[3-(2-bromophenyl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[3-(3-chlorophenyl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

15 4-[2-(3,3-diphenylpropanoyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile

4-[2-{3-[3-(methyloxy)phenyl]propanoyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

20 4-[2-[3-(2-chlorophenyl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[3-(4-methylphenyl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{3-[3-(trifluoromethyl)phenyl]propanoyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

25 4-[2-{3-[4-(methyloxy)phenyl]propanoyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(3-phenylbutanoyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;
4-[2-[3-(2-fluorophenyl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

30 4-[2-{[4-fluoro-2-(trifluoromethyl)phenyl]acetyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[3-(2-methylphenyl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[3-(3-fluorophenyl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

5 4-[2-[3-(4-bromophenyl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-(phenyloxy)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

10 4-[2-(2-cyano-3-phenylpropanoyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[3-methyl-3-(1*H*-pyrrol-1-yl)butanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[3-(2-furanyl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

15 4-[2-[3-(4-methyl-1,3-thiazol-5-yl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-(phenyloxy)butanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

1-[4-methylphenyl]acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

20 1-(4-nitro-1-naphthalenyl)-2-[[4-(trifluoromethyl)phenyl]acetyl]hexahydropyridazine;

1-(4-nitro-1-naphthalenyl)-2-([2-(trifluoromethyl)oxy]phenyl)acetyl]hexahydropyridazine;

25 1-(4-nitro-1-naphthalenyl)-2-[[3-(trifluoromethyl)phenyl]acetyl]hexahydropyridazine;

1-[(3-bromophenyl)acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-(4-nitro-1-naphthalenyl)-2-([2-(phenylmethyl)oxy]phenyl)acetyl]hexahydropyridazine;

30 1-[[2-(ethyloxy)phenyl]acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-(4-nitro-1-naphthalenyl)-2-[[2-(trifluoromethyl)phenyl]acetyl]hexahydropyridazine;

1-[(3-methylphenyl)acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

- 1-[[3-(ethyloxy)phenyl]acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
1-(2-naphthalenylacetyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
1-[[2-(methyloxy)phenyl]acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
1-[[4-(ethyloxy)phenyl]acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
5 1-[(4-bromophenyl)acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
1-[(2-methylphenyl)acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
1-(4-nitro-1-naphthalenyl)-2-[[3-(phenyloxy)phenyl]acetyl]hexahydropyridazine;
1-[[3,4-bis(methyloxy)phenyl]acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
10 4-[2-(2-hydroxyethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
2-[2-(4-nitro-1-naphthalenyl)tetrahydro-1(2H)-pyridazinyl]ethanol;
4-[2-[2-(phenyloxy)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
4-[2-{2-[(3-chlorophenyl)oxy]ethyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
15 1-(4-nitro-1-naphthalenyl)-2-[2-(phenyloxy)ethyl]hexahydropyridazine;
1-{2-[(2-methylphenyl)oxy]ethyl}-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
1-{2-[(3-chlorophenyl)oxy]ethyl}-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
1-{2-[(4-methylphenyl)oxy]ethyl}-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
2-(4-cyano-1-naphthalenyl)tetrahydro-1(2H)-pyridazinecarbonitrile;
20 2-(4-nitro-1-naphthalenyl)tetrahydro-1(2H)-pyridazinecarbonitrile;
4-[2-(2,2,2-trifluoroethyl)hexahydro-1H-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile;
4-[2-({3-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
25 4-[2-({3-[2-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
4-[2-({3-(4-chlorophenyl)-1H-pyrazol-4-yl}methyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
4-[2-({3-(4-fluorophenyl)-1H-pyrazol-4-yl}methyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
30 4-[2-({3-[3-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

or a salt or solvate thereof.

ABBREVIATIONS

As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, *The Journal of the American Chemical Society* or *the Journal of Biological Chemistry*. Specifically, the following abbreviations may be used in the examples and throughout the specification:

g (grams);	mg (milligrams);
L (liters);	ml (milliliters);
10 μ L (microliters);	psi (pounds per square inch);
M (molar);	mM (millimolar);
Hz (Hertz);	MHz (megahertz);
mol (mol(s));	mmol (millimol(s));
rt (room temperature);	eq (equivalent);
15 min (minutes);	h (hours);
mp (melting point);	TLC (thin layer chromatography);
T_r (retention time);	RP (reverse phase);
TEA (triethylamine);	TFA (trifluoroacetic acid);
THF (tetrahydrofuran);	$CDCl_3$ (deuterated chloroform);
20 CD_3OD (deuterated methanol);	SiO_2 (silica);
H_2O_2 (hydrogen peroxide);	H_2SO_4 (sulfuric acid);
DMSO (dimethylsulfoxide);	EtOAc (ethyl acetate);
HCl (hydrochloric acid);	CH_2Cl_2 (methylene chloride);
$LiAlH_4$ (lithium aluminum hydride);	$CHCl_3$ (chloroform);
25 DMF (<i>N,N</i> -dimethylformamide);	HOAc (acetic acid);
BOC (<i>tert</i> -butoxycarbonyl);	LiOH (lithium hydroxide);
Ac (acetyl);	atm (atmosphere);

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- TBS (*t*-butyldimethylsilyl);
 Et (ethyl);
 MeOH (methanol);
 PtO₂ (platinum dioxide).
 5 w/w (weight/weight);
 ppm (parts-per-million);
 t (triplet);
 J (coupling constant);
 ESI (electrospray injection);
 10 ES⁺ (electrospray ionization in positive mode); m/z (mass-charge ratio);
 MS (mass spectrometry);
 HPLC (high pressure liquid chromatography);
 mBar (millibar);
 HATU (O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate);
 15 PS (polystyrene);
 DMEM= Dulbecco's modified Eagle's medium; FBS= fetal calf serum;
 Pen/Strep= penicillin and streptomycin; PBS= phosphate-buffered saline;
 DTT= Dithiothreitol; ip=intraperitoneal.

Unless otherwise indicated, all temperatures are expressed in °C (degrees
 20 Centigrade). All reactions conducted under an inert atmosphere at room temperature
 unless otherwise noted.

¹H NMR spectra were recorded on a Varian VXR-300, a Varian Unity-300, a Varian
 Unity-400 instrument, or a General Electric QE-300. Chemical shifts are expressed in
 parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting
 25 patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t
 (triplet), q (quartet), m (multiplet), or br (broad).

Compounds were analyzed on a Micromass ZMD LC/MS using either Conditions I or Conditions II (below). Retention times were recorded for each compound.

Conditions I: The column was a C18 Phenomenex Luna, 20 x 4.0 mm, 3-micron column 90% H₂O, 10% MeOH to 100% MeOH in 3 minutes, holding at 100% MeOH for final 1 minute. Water contained 0.1% v/v formic acid, MeOH contains 0.075% v/v formic acid. The flow rate was 2 ml/min with 3uL of solution injected. Mass spectra were recorded on a Micromass ZMD utilizing electrospray ionization or atmospheric pressure chemical ionization (APCI) switching between positive and negative modes with DAD (Waters 996 DAD) scanning from 210 to 400nm.

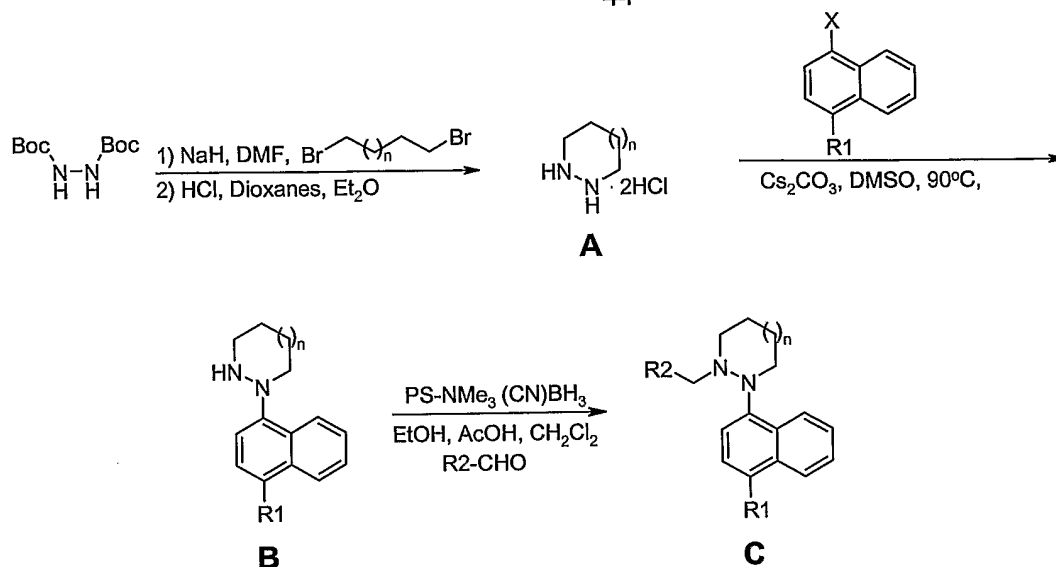
Conditions II: The column was a C18 Phenomenex Luna, 20 x 4.0 mm, 3-micron column 98% H₂O, 2% MeOH to 100% MeOH in 3 minutes, holding at 100% MeOH for final 1 minute. Water contained 0.1% v/v formic acid, MeOH contains 0.075% v/v formic acid. The flow rate was 2 ml/min with 3uL of solution injected. Mass spectra were recorded on a Micromass ZMD utilizing electrospray ionization or atmospheric pressure chemical ionization (APCI) switching between positive and negative modes with DAD (Waters 996 DAD) scanning from 210 to 400nm.

Compounds were purified on an Agilent 1100 HPLC using a Phenomenex Luna C-18(2), 150 x 21.2 mm, 5 micron column; a linear gradient of 10-90% ACN/H₂O/0.1% TFA or 30% ACN/H₂O/0.1% TFA was run over 10 minutes, followed by 2 minutes at 100% ACN. The flow rate was 20mL/min with DAD at 254nm or 214nm.

The syntheses of compounds of formula (I) proceeded via the formation of the mono-substituted cyclic hydrazine **B** which is derived from the nucleophilic addition of the cyclic hydrazine dihydrochloride salt to various electron deficient naphthalenes (Scheme 1, n=0-2). Intermediate **B** can then be used in reductive amination reactions to produce compounds **C** (Scheme 1, PS=polystyrene) or amide coupling transformations utilizing the three methods illustrated in Scheme 2 to furnish compounds **D**.

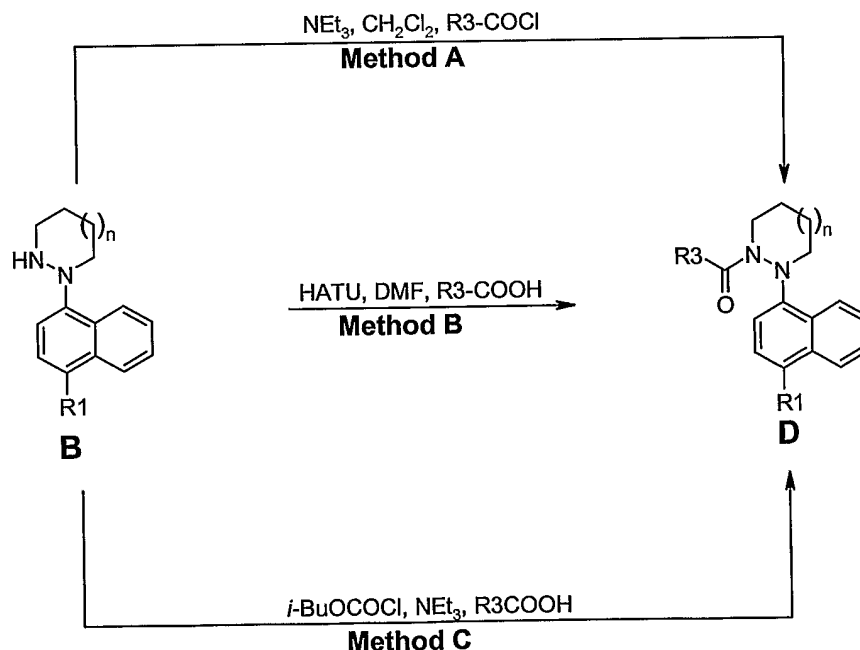
Scheme 1

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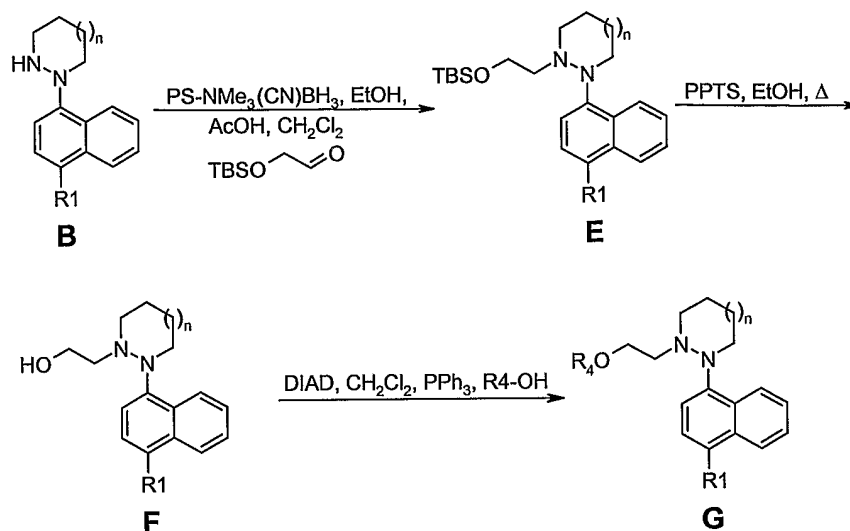
The first illustrated method in Scheme 2, Method A, involves coupling of intermediate **B** with various carboxylic acid chlorides. Method B proceeds via a HATU mediated amide coupling, while Method C utilizes a mixed-anhydride approach to furnish compounds **D**.

5 Scheme 2

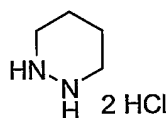


Intermediate **B** has also been used to install aryloxyethyl- sidechains as shown in Scheme 3. This method utilizes similar reductive amination methodology as illustrated in Scheme 1 to arrive at intermediate **E**. After subsequent TBDMS deprotection with refluxing ethanol, standard Mitsunobu conditions were employed to yield compounds **G**.

Scheme 3



EXAMPLES

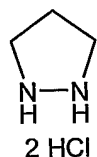
5 **A Hexahydropyridazine dihydrochloride (A1)**

To a 1-L 3-neck round bottom flask equipped with a magnetic stirbar, an addition funnel, and nitrogen flow, was added 7.6g NaH (60% w/w dispersion in mineral oil, 0.19 moles, 2.2eq). The NaH was washed three times with hexanes after which were added 350ml of dry DMF. The reaction mixture was cooled to 0 °C via an ice bath, then 20g *t*-butyl carbazate (0.086 moles, 1eq) in 50ml dry DMF was added dropwise via the addition funnel. After the addition was complete, the reaction was allowed to warm to room temperature and stirred for 30 minutes. Then 10.27 ml of 1,4-dibromobutane (0.086 moles, 1eq) was added all at once at room temperature and stirred overnight. The reaction mixture was quenched with water until gas evolution ceased, then partitioned between diethyl ether and water. The phases were separated and the organic fraction was washed twice with water. The ether layer was concentrated *in vacuo*. The residue was dissolved in 300ml of 4N HCl in dioxanes to which was added 300ml of diethyl ether. This mixture was stirred at room temperature for 1 hour, at which time a white solid precipitated. The solids were isolated (13.7g, 100% yield) by filtration and dried under vacuum.

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¹H NMR (400 MHz, DMSO-D₆) δ ppm 1.6 (m, 4 H) 3.0 (m, 4 H)

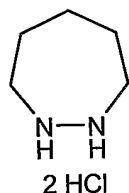
The following compounds were synthesized according to the same general procedure as used for intermediate A1:



5 **Pyrrolidine dihydrochloride (A2)**

From 1,3-dibromopropane the title compound was obtained.

¹H NMR (300 MHz, DMSO-D₆) δ ppm 2.0 (m, 2 H) 3.0 (m, 4 H)

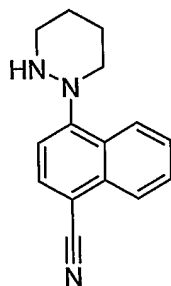


Hexahydro-1H-1,2-diazepine dihydrochloride (A3)

10 From 1,5-dibromopentane the title compound was obtained.

¹H NMR (400 MHz, DMSO-D₆) δ ppm 1.6 (m, 6 H) 3.0 (m, 2 H) 3.7 (m, 2 H)

Cyclic Hydrazine Additions



B. 4-(tetrahydro-1(2H)-pyridazinyl)-1-naphthalenecarbonitrile (B1)

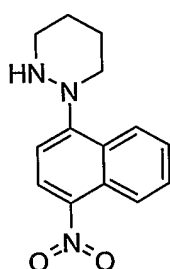
15 To a 500ml round bottom flask equipped with a magnetic stirbar, an addition funnel, and nitrogen flow was added 7.0g hexahydropyridazine dihydrochloride (43.18 mmol, 1.5eq) in 100ml dry DMSO, then 33g cesium carbonate (0.102 mol, 3.5eq) was added all at once. The reaction mixture was heated to 80 °C via an oil bath, at which point, 5g 4-fluoro-1-naphthalenecarbonitrile (29.21 mmol, 1eq) in 20ml DMSO was
20 added dropwise. The reaction was stirred at 80 °C overnight. After cooling to ambient

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temperature, 100ml distilled water was added, which resulted in the precipitation of a 5.6g (80% yield) of the title compound as a yellow solid.

¹H NMR (400 MHz, DMSO-D₆) δ ppm 1.6 (m, 2 H) 1.9 (m, 2 H) 3.1 (m, 2 H) 3.4 (m, 2 H) 4.5 (m, 1 H) 7.2 (d, $J=8.6$ Hz, 1 H) 7.6 (m, 1 H) 7.7 (m, 1 H) 8.3 (m, 2 H) 8.5 (d, $J=8.1$ Hz, 1 H)

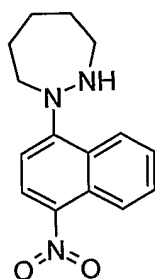
The following compounds were synthesized according to the same general procedure as used for intermediate **B1**:



1-(4-nitro-1-naphthalenyl)hexahydropyridazine (**B2**)

From 1-chloro-4-nitronaphthalene and **A1** the title compound was isolated as an orange solid.

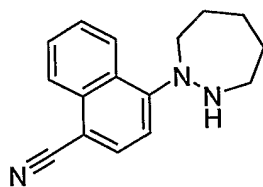
¹H NMR (400 MHz, DMSO-D₆) δ ppm 1.6 (m, 2 H) 1.9 (m, 2 H) 3.1 (m, 2 H) 3.4 (m, 2 H) 4.5 (m, 1 H) 7.2 (d, $J=8.6$ Hz, 1 H) 7.6 (m, 1 H) 7.7 (m, 1 H) 8.3 (m, 2 H) 8.5 (d, $J=8.1$ Hz, 1 H)



4-(hexahydro-1H-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile (**B3**)

From 1-chloro-4-nitronaphthalene and **A3** the title compound was obtained.

MS (m/z) ESI ES⁺ = 272

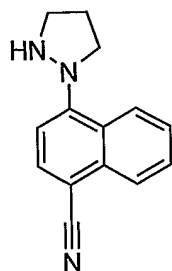


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4-(hexahydro-1H-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile (B4)

From 4-fluoro-1-naphthalenecarbonitrile and **A3** the title compound was obtained.

MS (m/z) ESI ES⁺ = 252



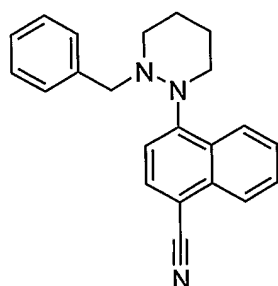
5 **4-(1-pyrazolidinyl)-1-naphthalenecarbonitrile (B5)**

From 4-fluoro-1-naphthalenecarbonitrile and **A2** the title compound was obtained.

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 2.1 (m, 2 H) 3.2 (m, J=7.1, 7.1 Hz, 2 H) 3.6 (m, 2 H) 7.5 (m, 2 H) 7.6 (m, 1 H) 7.8 (d, J=8.1 Hz, 1 H) 8.2 (m, 1 H) 8.2 (m, 1 H)

Cyclic Hydrazine Reductive Aminations Excluding Phenylacetaldehydes

10 **Example 1**



C. 4-[2-(phenylmethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C1)

To a 40ml scintillation vial was added 75mg **B1** (0.316 mmoles, 1eq), 1ml ethanol, 15 0.5ml acetic acid, 1ml dichloromethane, and 0.042ml benzaldehyde (0.411mmoles, 1.3eq). Then 400mg (polystyrylmethyl)trimethylammoniumcyanoborohydride resin (Novabiochem, 4.3mmol/g, 5eq) was added and the reaction was shaken on an orbital shaker overnight. The reaction was filtered and concentrated *in vacuo*. The residue was purified via preparative HPLC (Phenomenex column Luna C18, 75mm x 30mm, 5 20 micron), 50% acetonitrile/water (0.01% TFA) to 100% acetonitrile, to yield 15mg of the title compound as a yellow solid.

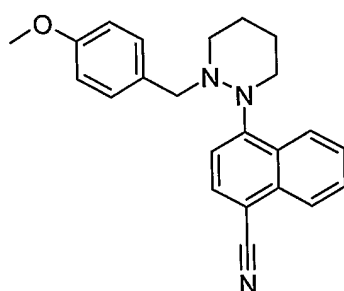
49

¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.8 (m, 4 H) 3.0 (m, 2 H) 3.5 (m, 2 H) 3.9 (m, 2 H) 4.1 (m, 2 H) 6.9 (m, 2 H) 7.0 (d, $J=7.8$ Hz, 1 H) 7.1 (m, 3 H) 7.6 (t, $J=7.3$ Hz, 1 H) 7.7 (t, $J=7.1$ Hz, 1 H) 7.9 (d, $J=8.3$ Hz, 1 H) 8.0 (d, $J=8.3$ Hz, 1 H) 8.4 (d, $J=8.8$ Hz, 1 H)

The following compounds were synthesized according to a similar general

5 procedure as used for **C1**:

Example 2

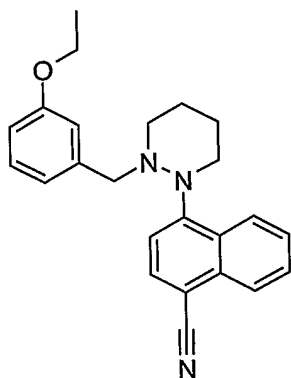


10 **4-[2-[[4-(methoxy)phenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C2)**

From **B1** and 4-(methoxy)benzaldehyde the title compound was isolated as an orange oil.

¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.7 (m, 4 H) 3.0 (m, 2 H) 3.6 (s, 3 H) 3.8 (m, 2 H) 6.6 (d, $J=8.3$ Hz, 2 H) 6.8 (d, $J=8.3$ Hz, 2 H) 7.0 (d, $J=8.3$ Hz, 1 H) 7.6 (t, $J=7.6$ Hz, 1 H) 7.7 (t, $J=7.6$ Hz, 1 H) 7.9 (d, $J=8.3$ Hz, 1 H) 8.0 (d, $J=8.3$ Hz, 1 H) 8.4 (d, $J=8.8$ Hz, 1 H)

Example 3



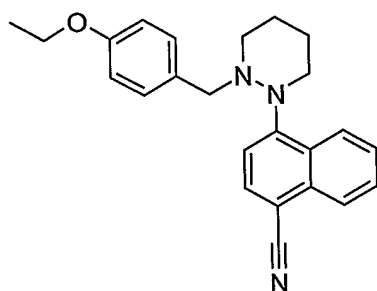
20 **4-[2-[[3-(ethoxy)phenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C3)**

50

From **B1** and 3-(ethyloxy)benzaldehyde the title compound was isolated as a yellow solid.

¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.1 (t, $J=7.1$ Hz, 3 H) 1.8 (m, 4 H) 3.1 (m, 2 H) 3.5 (q, $J=7.1$ Hz, 2 H) 3.8 (m, 2 H) 6.3 (s, 1 H) 6.5 (d, $J=7.3$ Hz, 1 H) 6.6 (m, $J=8.3$ Hz, 1 H) 7.0 (m, 2 H) 7.6 (t, $J=7.6$ Hz, 1 H) 7.7 (t, $J=7.1$ Hz, 1 H) 7.9 (d, $J=8.3$ Hz, 1 H) 8.0 (d, $J=8.3$ Hz, 1 H) 8.4 (d, $J=8.3$ Hz, 1 H)

Example 4

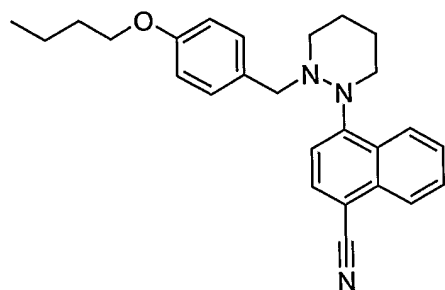


4-[2-[[4-(ethyloxy)phenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C4)

From **B1** and 4-(ethyloxy)benzaldehyde the title compound was isolated as an orange oil.

¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.2 (t, $J=7.1$ Hz, 3 H) 1.7 (m, 4 H) 3.0 (m, 3 H) 3.5 (m, 2 H) 3.8 (m, 2 H) 3.9 (q, $J=6.8$ Hz, 2 H) 6.6 (d, $J=8.8$ Hz, 2 H) 6.8 (d, $J=8.3$ Hz, 2 H) 7.0 (d, $J=8.3$ Hz, 1 H) 7.6 (t, $J=7.8$ Hz, 1 H) 7.7 (t, $J=7.6$ Hz, 1 H) 7.9 (d, $J=8.3$ Hz, 1 H) 8.0 (d, $J=8.3$ Hz, 1 H) 8.4 (d, $J=8.3$ Hz, 1 H)

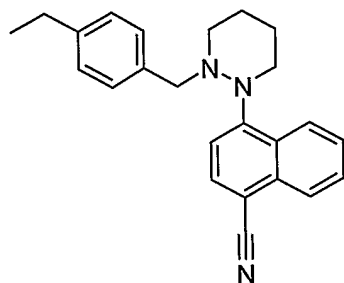
Example 5



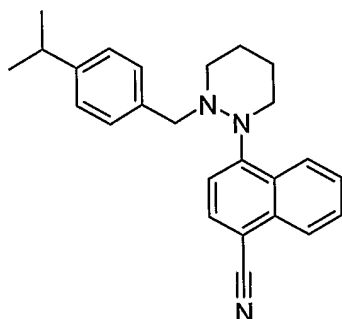
4-[2-[[4-(butyloxy)phenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C5)

From **B1** and 4-(butyloxy)benzaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 400

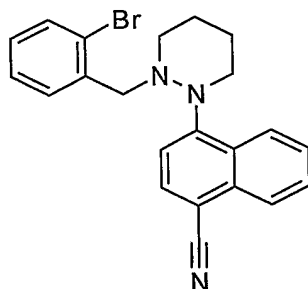
Example 6**4-[2-[(4-ethylphenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C6)**

- 5 From **B1** and 4-ethylbenzaldehyde the title compound was isolated as a yellow solid.
- ¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.0 (t, $J=7.6$ Hz, 3 H) 1.8 (m, 4 H) 2.4 (q, $J=7.3$ Hz, 2 H) 3.0 (m, 2 H) 3.4 (m, 2 H) 3.8 (m, 2 H) 6.8 (d, $J=7.8$ Hz, 2 H) 6.9 (d, $J=7.8$ Hz, 2 H) 7.0 (d, $J=8.3$ Hz, 1 H) 7.6 (t, $J=7.3$ Hz, 1 H) 7.7 (t, $J=7.6$ Hz, 1 H) 7.9 (d, $J=8.3$ Hz, 1 H) 8.0 (d, $J=8.3$ Hz, 1 H) 8.4 (d, $J=8.8$ Hz, 1 H)

10 **Example 7****4-[2-[[4-(1-methylethyl)phenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C7)**

- 15 From **B1** and 4-(1-methylethyl)benzaldehyde the title compound was isolated as a yellow solid.
- ¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.0 (d, $J=6.8$ Hz, 6 H) 1.8 (m, 4 H) 2.7 (m, 1 H) 3.0 (m, 2 H) 3.4 (m, 2 H) 3.8 (m, 2 H) 6.8 (d, $J=7.8$ Hz, 2 H) 6.9 (d, $J=7.8$ Hz, 2 H) 7.0 (d, $J=8.3$ Hz, 1 H) 7.6 (t, $J=7.8$ Hz, 1 H) 7.7 (t, $J=7.3$ Hz, 1 H) 7.9 (d, $J=8.3$ Hz, 1 H) 8.0 (d, $J=8.3$ Hz, 1 H) 8.4 (d, $J=8.3$ Hz, 1 H)

20 **Example 8**

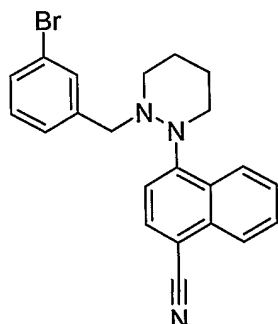


4-[2-[(2-bromophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C8)

From **B1** and 2-bromobenzaldehyde the title compound was isolated as a yellow solid.

- 5 ¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.8 (m, 4 H) 3.4 (m, 2 H) 3.5 (m, 2 H) 4.0 (m, 2 H) 6.9 (dd, *J*=6.8, 2.4 Hz, 1 H) 7.0 (m, 2 H) 7.1 (d, *J*=8.3 Hz, 1 H) 7.3 (m, 1 H) 7.5 (t, *J*=7.1 Hz, 1 H) 7.7 (t, *J*=7.1 Hz, 1 H) 7.9 (m, 2 H) 8.3 (d, *J*=8.3 Hz, 1 H)

Example 9

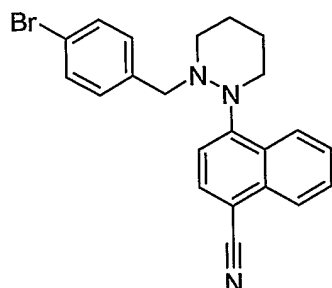


- 10 **4-[2-[(3-bromophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C9)**

From **B1** and 3-bromobenzaldehyde the title compound was isolated as a yellow solid.

- 1H NMR (500 MHz, DMSO-D₆) δ ppm 1.8 (m, 4 H) 3.4 (m, 2 H) 3.9 (m, 2 H) 6.9 (d, *J*=7.8 Hz, 1 H) 6.9 (s, 1 H) 7.0 (t, *J*=7.6 Hz, 2 H) 7.2 (d, *J*=7.8 Hz, 1 H) 7.6 (t, *J*=7.3 Hz, 1 H) 7.7 (t, *J*=7.1 Hz, 1 H) 7.9 (d, *J*=8.3 Hz, 1 H) 8.0 (d, *J*=8.3 Hz, 1 H) 8.4 (d, *J*=8.8 Hz, 1 H)

Example 10

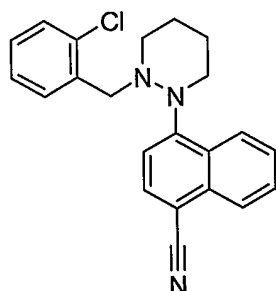


4-[2-[(4-bromophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C10)

From **B1** and 4-bromobenzaldehyde the title compound was isolated as a yellow oil.

- 5 ¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.7 (m, 4 H) 3.0 (m, 2 H) 3.4 (m, 2 H) 3.8 (m, 2 H) 6.8 (d, *J*=8.3 Hz, 2 H) 7.0 (d, *J*=7.8 Hz, 1 H) 7.2 (d, *J*=8.3 Hz, 2 H) 7.6 (t, *J*=7.8 Hz, 1 H) 7.7 (t, *J*=7.1 Hz, 1 H) 7.9 (d, *J*=8.3 Hz, 1 H) 8.0 (d, *J*=8.3 Hz, 1 H) 8.3 (d, *J*=8.3 Hz, 1 H)

Example 11



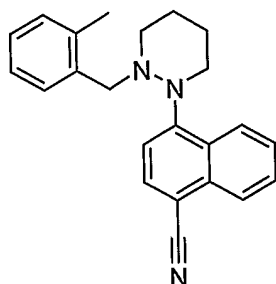
10

4-[2-[(2-chlorophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C11)

From **B1** and 2-chlorobenzaldehyde the title compound was isolated as a yellow solid.

- 15 ¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.8 (m, 4 H) 3.5 (m, 2 H) 4.0 (m, 2 H) 4.1 (m, 2 H) 6.9 (m, 2 H) 7.0 (m, *J*=9.0, 9.0 Hz, 2 H) 7.1 (d, *J*=7.8 Hz, 1 H) 7.5 (t, *J*=7.6 Hz, 1 H) 7.7 (t, *J*=7.6 Hz, 1 H) 7.9 (dd, *J*=7.8, 3.9 Hz, 2 H) 8.3 (d, *J*=8.8 Hz, 1 H)

Example 12

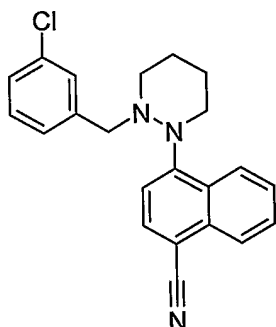


4-[2-[(2-methylphenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C12)

From **B1** and 2-methylbenzaldehyde the title compound was isolated as a yellow solid.

- 5 ¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.6 (s, 3 H) 1.8 (m, 4 H) 3.1 (m, 2 H) 3.5 (m, 2 H) 3.9 (m, 2 H) 6.8 (d, *J*=7.3 Hz, 1 H) 7.0 (m, 3 H) 7.0 (d, *J*=7.8 Hz, 1 H) 7.5 (t, *J*=7.6 Hz, 1 H) 7.7 (t, *J*=7.6 Hz, 1 H) 7.9 (t, *J*=8.3 Hz, 2 H) 8.3 (d, *J*=8.3 Hz, 1 H)

Example 13

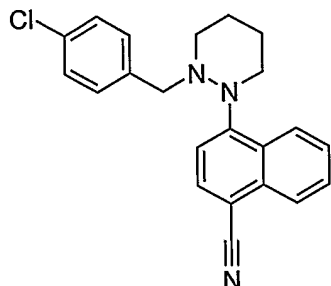


- 10 **4-[2-[(3-chlorophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C13)**

From **B1** and 3-chlorobenzaldehyde the title compound was isolated as a yellow solid.

- ¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.8 (m, 4 H) 3.1 (m, 2 H) 3.4 (m, 2 H) 3.9 (m, 2 H) 6.8 (s, 1 H) 6.9 (d, *J*=6.3 Hz, 1 H) 7.0 (d, *J*=8.3 Hz, 1 H) 7.1 (m, 2 H) 7.6 (t, *J*=7.8 Hz, 1 H) 7.7 (t, *J*=7.1 Hz, 1 H) 7.9 (d, *J*=7.8 Hz, 1 H) 8.0 (d, *J*=7.8 Hz, 1 H) 8.4 (d, *J*=8.8 Hz, 1 H)

Example 14

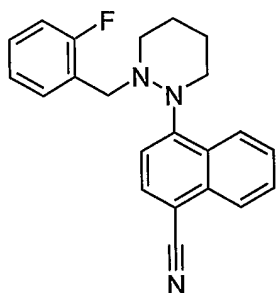


4-[2-[(4-chlorophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C14)

From **B1** and 4-chlorobenzaldehyde the title compound was isolated as a yellow oil.

- 5 ¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.8 (m, 4 H) 3.0 (m, 2 H) 3.5 (m, 2 H) 3.9 (m, 2 H) 6.9 (d, *J*=8.3 Hz, 2 H) 7.0 (d, *J*=8.3 Hz, 1 H) 7.1 (d, *J*=8.3 Hz, 2 H) 7.6 (t, *J*=7.6 Hz, 1 H) 7.7 (t, *J*=7.3 Hz, 1 H) 7.9 (d, *J*=7.8 Hz, 1 H) 8.0 (d, *J*=8.3 Hz, 1 H) 8.3 (d, *J*=8.3 Hz, 1 H)

Example 15



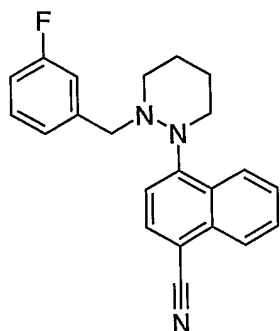
10

4-[2-[(2-fluorophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C15)

From **B1** and 2-fluorobenzaldehyde the title compound was isolated as a yellow solid.

- 15 ¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.8 (m, 4 H) 3.1 (m, 2 H) 3.5 (m, 2 H) 3.9 (m, 2 H) 6.8 (m, 2 H) 6.9 (m, 1 H) 7.0 (d, *J*=8.3 Hz, 1 H) 7.1 (m, 1 H) 7.5 (t, *J*=7.8 Hz, 1 H) 7.7 (t, *J*=7.6 Hz, 1 H) 7.9 (m, 2 H) 8.3 (d, *J*=8.8 Hz, 1 H)

Example 16

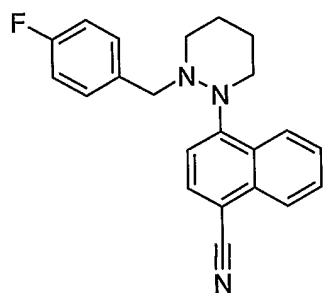


4-[2-[(3-fluorophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C16)

From **B1** and 3-fluorobenzaldehyde the title compound was isolated as a yellow solid.

5 MS (m/z) ESI ES⁺ = 346

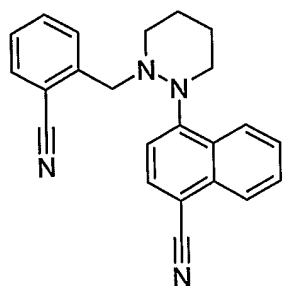
Example 17



4-[2-[(4-fluorophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C17)

10 From **B1** and 4-fluorobenzaldehyde the title compound was isolated as an orange oil.
 1H NMR (500 MHz, DMSO-D₆) δ ppm 1.7 (m, 4 H) 3.0 (m, 2 H) 3.5 (m, 2 H) 3.9 (m, 2 H) 6.9 (m, 4 H) 7.0 (d, J=7.8 Hz, 1 H) 7.6 (t, J=7.3 Hz, 1 H) 7.7 (t, J=7.6 Hz, 1 H) 7.9 (d, J=7.8 Hz, 1 H) 8.0 (d, J=8.3 Hz, 1 H) 8.4 (d, J=8.8 Hz, 1 H)

Example 18



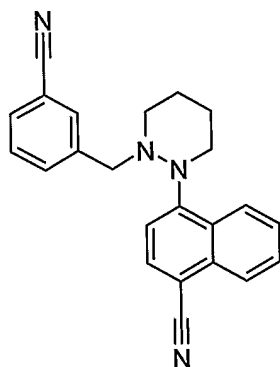
4-[2-[(2-cyanophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C18)

57

From **B1** and 2-cyanobenzaldehyde the title compound was isolated as a yellow solid.

¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.8 (m, 4 H) 3.2 (m, 2 H) 3.4 (m, 2 H) 3.5 (m, 2 H) 6.9 (d, $J=7.8$ Hz, 1 H) 7.0 (d, $J=7.8$ Hz, 1 H) 7.1 (t, $J=7.6$ Hz, 1 H) 7.2 (t, $J=7.8$ Hz, 1 H) 7.4 (d, $J=7.8$ Hz, 1 H) 7.5 (t, $J=7.6$ Hz, 1 H) 7.6 (t, $J=7.6$ Hz, 1 H) 7.8 (d, $J=8.3$ Hz, 2 H) 8.2 (d, $J=8.3$ Hz, 1 H)

Example 19

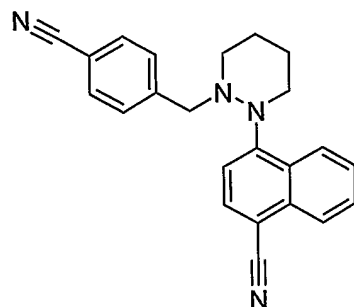


4-[2-[(3-cyanophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C19)

From **B1** and 3-cyanobenzaldehyde the title compound was isolated as a yellow oil.

¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.8 (m, 4 H) 3.1 (m, 2 H) 3.5 (m, 2 H) 3.9 (m, 2 H) 7.0 (d, $J=7.8$ Hz, 1 H) 7.2 (m, 3 H) 7.4 (d, $J=7.3$ Hz, 1 H) 7.6 (t, $J=7.3$ Hz, 1 H) 7.7 (t, $J=7.1$ Hz, 1 H) 7.9 (d, $J=7.8$ Hz, 1 H) 7.9 (d, $J=8.3$ Hz, 1 H) 8.3 (d, $J=8.3$ Hz, 1 H)

Example 20



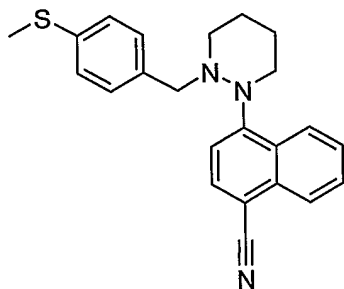
4-[2-[(4-cyanophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C20)

From **B1** and 4-cyanobenzaldehyde the title compound was isolated as a yellow solid.

¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.8 (m, 4 H) 3.1 (m, 2 H) 3.5 (m, 3 H) 4.0 (m, 2 H) 7.0 (d, $J=8.3$ Hz, 1 H) 7.1 (d, $J=8.3$ Hz, 2 H) 7.5 (d, $J=8.3$ Hz, 2 H) 7.6 (t, $J=7.3$ Hz, 1 H)

58

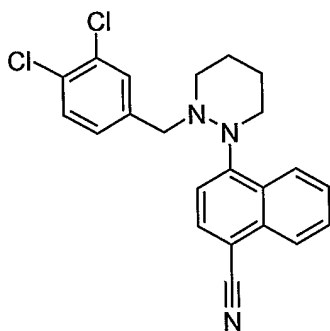
H) 7.7 (t, $J=7.1$ Hz, 1 H) 7.9 (d, $J=7.8$ Hz, 1 H) 8.0 (d, $J=8.3$ Hz, 1 H) 8.3 (d, $J=8.3$ Hz, 1 H)

Example 21

5 **4-[2-[[4-(methylthio)phenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C21)**

From **B1** and 4-(methylthio)benzaldehyde the title compound was isolated as a yellow oil.

1H NMR (500 MHz, DMSO-D6) δ ppm 1.7 (m, 4 H) 2.3 (s, 3 H) 3.0 (m, 2 H) 3.5 (m, 2 H) 3.8 (m, 2 H) 6.8 (d, $J=8.3$ Hz, 2 H) 6.9 (d, $J=8.3$ Hz, 2 H) 7.0 (d, $J=8.3$ Hz, 1 H) 7.6 (t, $J=7.3$ Hz, 1 H) 7.7 (t, $J=7.6$ Hz, 1 H) 7.9 (d, $J=8.3$ Hz, 1 H) 8.0 (d, $J=8.3$ Hz, 1 H) 8.4 (d, $J=8.3$ Hz, 1 H)

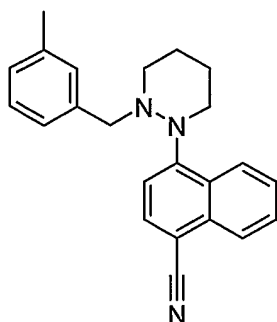
Example 22

15 **4-[2-[(3,4-dichlorophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C22)**

From **B1** and 3,4-dichlorobenzaldehyde the title compound was isolated as a yellow oil.

1H NMR (500 MHz, DMSO-D6) δ ppm 1.7 (m, 4 H) 3.1 (m, 2 H) 3.5 (m, 2 H) 3.9 (m, 2 H) 6.8 (dd, $J=8.3, 2.0$ Hz, 1 H) 7.0 (m, 2 H) 7.2 (d, $J=8.3$ Hz, 1 H) 7.6 (t, $J=7.3$ Hz, 1 H) 7.7 (t, $J=7.6$ Hz, 1 H) 7.9 (d, $J=7.8$ Hz, 1 H) 7.9 (d, $J=8.3$ Hz, 1 H) 8.3 (d, $J=8.8$ Hz, 1 H)

Example 23

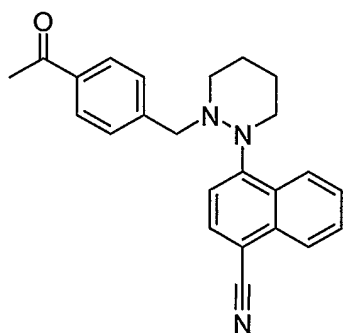


4-[2-[(3-methylphenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C23)

From **B1** and 3-methylbenzaldehyde the title compound was isolated as a yellow solid.

- 5 ¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.7 (m, 2 H) 1.9 (m, 2 H) 2.0 (s, 3 H) 3.0 (s, 2 H) 3.4 (m, 2 H) 3.8 (s, 2 H) 6.6 (s, 1 H) 6.7 (d, $J=7.3$ Hz, 1 H) 6.9 (d, $J=7.8$ Hz, 1 H) 6.9 (d, $J=7.6$ Hz, 1 H) 7.0 (d, $J=8.3$ Hz, 1 H) 7.6 (t, $J=7.3$ Hz, 1 H) 7.7 (t, $J=7.1$ Hz, 1 H) 7.9 (d, $J=8.3$ Hz, 1 H) 8.0 (d, $J=7.8$ Hz, 1 H) 8.4 (d, $J=8.8$ Hz, 1 H)

Example 24



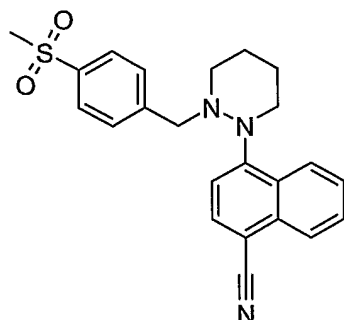
10

4-[2-[(4-acetylphenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C24)

From **B1** and 4-acetylbenzaldehyde the title compound was isolated as an orange oil.

- 15 ¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.7 (m, 4 H) 2.4 (s, 3 H) 3.1 (m, 2 H) 3.5 (m, 2 H) 3.9 (m, 2 H) 7.0 (m, 3 H) 7.6 (m, 3 H) 7.7 (t, $J=7.3$ Hz, 1 H) 7.9 (d, $J=7.8$ Hz, 1 H) 8.0 (d, $J=8.3$ Hz, 1 H) 8.4 (d, $J=8.3$ Hz, 1 H)

Example 25

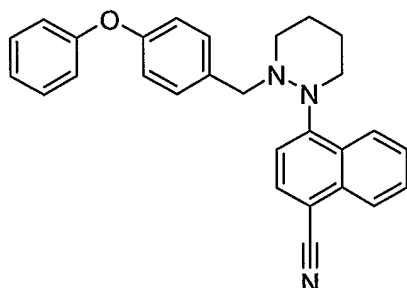


4-[2-{[4-(methylsulfonyl)phenyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C25)

From **B1** and 4-(methylsulfonyl)benzaldehyde the title compound was isolated as an orange oil.

¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.8 (m, 4 H) 3.0 (s, 3 H) 3.1 (m, 2 H) 3.5 (m, 2 H) 4.0 (m, 2 H) 7.0 (d, $J=7.8$ Hz, 1 H) 7.1 (d, $J=8.3$ Hz, 2 H) 7.5 (d, $J=8.3$ Hz, 2 H) 7.6 (t, $J=7.6$ Hz, 1 H) 7.7 (t, $J=7.6$ Hz, 1 H) 7.9 (d, $J=8.3$ Hz, 1 H) 7.9 (d, $J=8.3$ Hz, 1 H) 8.3 (d, $J=8.3$ Hz, 1 H)

Example 26



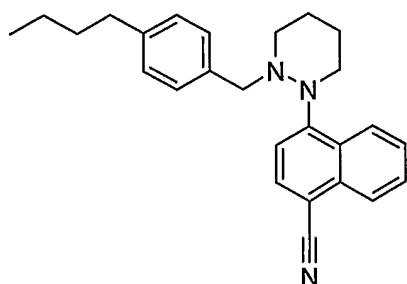
4-[2-{[4-(phenyloxy)phenyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C26)

From **B1** and 4-phenyloxybenzaldehyde the title compound was isolated as a yellow oil.

¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.8 (m, 4 H) 3.1 (m, 2 H) 3.5 (m, 2 H) 3.9 (m, 2 H) 6.6 (d, $J=8.3$ Hz, 2 H) 6.8 (d, $J=7.8$ Hz, 2 H) 6.9 (d, $J=8.3$ Hz, 2 H) 7.0 (d, $J=8.3$ Hz, 1 H) 7.1 (t, $J=7.3$ Hz, 1 H) 7.3 (t, $J=8.1$ Hz, 2 H) 7.6 (t, $J=7.3$ Hz, 1 H) 7.7 (t, $J=7.6$ Hz, 1 H) 7.9 (d, $J=8.3$ Hz, 1 H) 8.0 (d, $J=8.3$ Hz, 1 H) 8.4 (d, $J=8.3$ Hz, 1 H)

Example 27

61

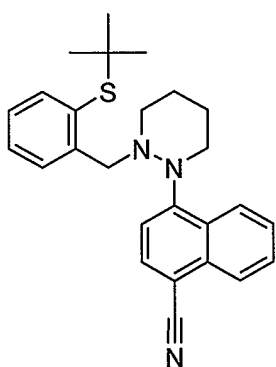


4-[2-[(4-butylphenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C27)

From **B1** and 4-butylbenzaldehyde the title compound was isolated as a yellow oil.

- 5 ¹H NMR (500 MHz, DMSO-D₆) δ ppm 0.8 (t, *J*=7.3 Hz, 3 H) 1.2 (m, 2 H) 1.4 (m, 2 H) 1.7 (m, 4 H) 2.4 (t, *J*=7.6 Hz, 2 H) 3.0 (m, 2 H) 3.4 (m, 2 H) 3.8 (m, 2 H) 6.7 (d, *J*=7.8 Hz, 2 H) 6.8 (d, *J*=7.8 Hz, 2 H) 7.0 (d, *J*=7.8 Hz, 1 H) 7.6 (t, *J*=7.6 Hz, 1 H) 7.7 (t, *J*=7.6 Hz, 1 H) 7.9 (d, *J*=7.8 Hz, 1 H) 8.0 (d, *J*=8.3 Hz, 1 H) 8.4 (d, *J*=8.8 Hz, 1 H)

Example 28



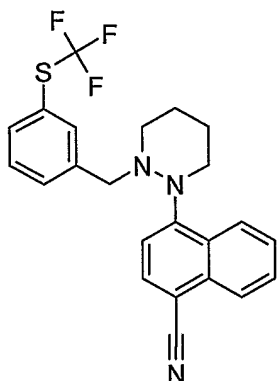
10

4-[2-[(2-[(1,1-dimethylethyl)thio]phenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C28)

From **B1** and 2-[(1,1-dimethylethyl)thio]benzaldehyde the title compound was isolated as a yellow solid.

- 15 ¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.0 (m, 9 H) 1.8 (m, 4 H) 3.0 (m, 2 H) 3.5 (m, 2 H) 4.1 (m, 2 H) 6.9 (d, *J*=5.9 Hz, 1 H) 7.0 (m, 3 H) 7.3 (d, *J*=7.3 Hz, 1 H) 7.5 (t, *J*=7.3 Hz, 1 H) 7.7 (t, *J*=7.1 Hz, 1 H) 8.3 (d, *J*=8.8 Hz, 1 H)

Example 29

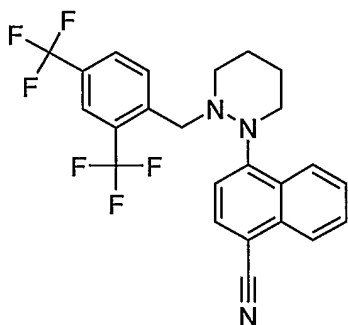


4-[2-({3-[(trifluoromethyl)thio]phenyl)methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C29)

From **B1** and 3-[(trifluoromethyl)thio]benzaldehyde the title compound was isolated as a yellow oil.

¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.7 (m, 4 H) 3.1 (m, 2 H) 3.5 (m, 2 H) 4.0 (m, 2 H) 7.0 (d, $J=7.8$ Hz, 1 H) 7.1 (m, 2 H) 7.2 (t, $J=7.6$ Hz, 1 H) 7.3 (d, $J=7.8$ Hz, 1 H) 7.5 (t, $J=7.6$ Hz, 1 H) 7.7 (t, $J=7.1$ Hz, 1 H) 7.9 (d, $J=7.8$ Hz, 1 H) 7.9 (d, $J=8.3$ Hz, 1 H) 8.3 (d, $J=8.3$ Hz, 1 H)

Example 30

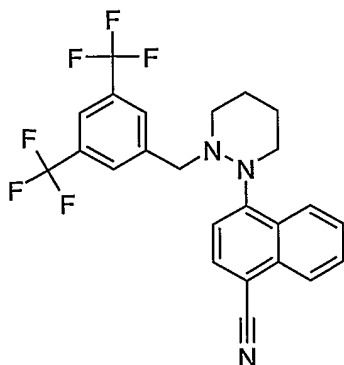


44-[2-{{2,4-bis(trifluoromethyl)phenyl}methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C30)

From **B1** and 2,4-bis(trifluoromethyl)benzaldehyde the title compound was isolated as a yellow solid.

¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.8 (m, 4 H) 3.2 (m, 2 H) 3.5 (m, 2 H) 4.2 (m, 2 H) 7.1 (d, $J=8.3$ Hz, 1 H) 7.3 (d, $J=8.3$ Hz, 1 H) 7.5 (d, $J=8.3$ Hz, 1 H) 7.6 (t, $J=8.3$ Hz, 1 H) 7.7 (m, 2 H) 7.9 (m, 2 H) 8.2 (d, $J=8.3$ Hz, 1 H)

Example 31

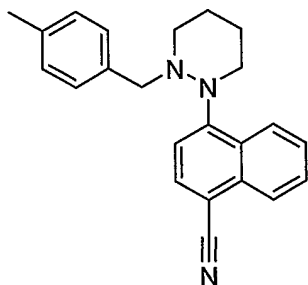


4-[2-[[3,5-bis(trifluoromethyl)phenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C31)

From **B1** and 3,5-bis(trifluoromethyl)benzaldehyde the title compound was isolated as a white solid.

¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.8 (m, 4 H) 3.3 (m, 2 H) 3.5 (m, 2 H) 4.1 (m, 2 H) 6.9 (d, $J=8.3$ Hz, 1 H) 7.4 (s, 2 H) 7.5 (m, 1 H) 7.6 (s, 1 H) 7.6 (t, $J=7.6$ Hz, 1 H) 7.8 (d, $J=7.8$ Hz, 1 H) 7.8 (d, $J=8.3$ Hz, 1 H) 8.3 (d, $J=8.3$ Hz, 1 H)

Example 32

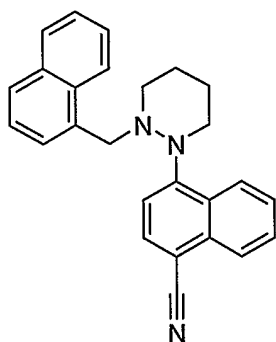


4-[2-[(4-methylphenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C32)

From **B1** and 4-methylbenzaldehyde the title compound was isolated as a yellow solid.

¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.7 (m, 4 H) 2.1 (s, 3 H) 3.0 (m, 2 H) 3.5 (m, 2 H) 3.8 (m, 2 H) 6.7 (d, $J=7.8$ Hz, 2 H) 6.9 (d, $J=7.8$ Hz, 2 H) 7.0 (d, $J=8.3$ Hz, 1 H) 7.6 (t, $J=7.6$ Hz, 1 H) 7.7 (t, $J=7.3$ Hz, 1 H) 7.9 (d, $J=7.8$ Hz, 1 H) 8.0 (d, $J=8.3$ Hz, 1 H) 8.4 (d, $J=8.3$ Hz, 1 H)

Example 33

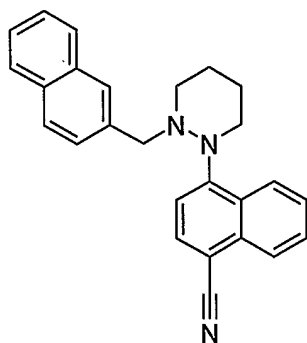


4-[2-(1-naphthalenylmethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C33)

From **B1** and 1-naphthalenecarbaldehyde the title compound was isolated as a yellow solid.

¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.8 (m, 4 H) 3.0 (m, 2 H) 3.6 (m, 2 H) 4.3 (m, 2 H) 6.7 (t, $J=7.6$ Hz, 1 H) 7.0 (d, $J=8.3$ Hz, 1 H) 7.1 (d, $J=8.3$ Hz, 1 H) 7.3 (m, 2 H) 7.4 (d, $J=6.8$ Hz, 1 H) 7.5 (t, $J=7.6$ Hz, 1 H) 7.7 (t, $J=9.3$ Hz, 3 H) 7.9 (d, $J=7.8$ Hz, 1 H) 8.0 (d, $J=8.3$ Hz, 1 H) 8.3 (d, $J=8.8$ Hz, 1 H)

Example 34



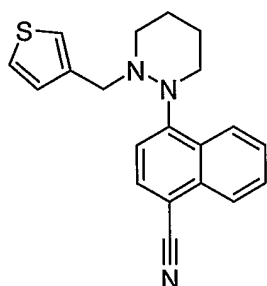
4-[2-(2-naphthalenylmethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C34)

From **B1** and 2-naphthalenecarbaldehyde the title compound was isolated as a yellow solid.

¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.8 (m, 4 H) 3.1 (m, 2 H) 3.5 (m, 2 H) 4.0 (m, 2 H) 6.8 (d, $J=8.8$ Hz, 1 H) 7.0 (d, $J=8.3$ Hz, 1 H) 7.4 (m, 2 H) 7.5 (s, 1 H) 7.5 (d, $J=8.8$ Hz, 1 H) 7.6 (m, 2 H) 7.7 (m, $J=7.3, 7.3$ Hz, 2 H) 7.9 (d, $J=7.8$ Hz, 1 H) 8.0 (d, $J=8.8$ Hz, 1 H) 8.5 (d, $J=8.8$ Hz, 1 H)

Example 35

65

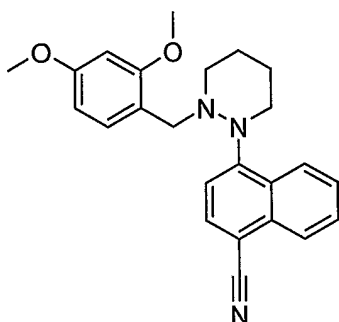


4-[2-(3-thienylmethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C35)

From **B1** and 3-thiophenecarbaldehyde the title compound was isolated as a yellow solid.

¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.7 (m, 4 H) 3.0 (m, 2 H) 3.4 (m, 2 H) 3.9 (m, 2 H) 6.4 (d, $J=3.9$ Hz, 1 H) 7.0 (d, $J=8.3$ Hz, 1 H) 7.1 (s, 1 H) 7.2 (dd, $J=4.9, 2.9$ Hz, 1 H) 7.6 (t, $J=7.3$ Hz, 1 H) 7.7 (t, $J=7.3$ Hz, 1 H) 7.9 (d, $J=8.3$ Hz, 1 H) 8.0 (d, $J=8.3$ Hz, 1 H) 8.4 (d, $J=8.3$ Hz, 1 H)

Example 36

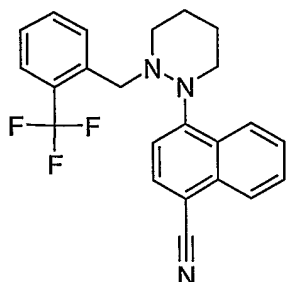


4-[2-[[2,4-bis(methyloxy)phenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C36)

From **B1** and 2,4-bis(methyloxy)benzaldehyde the title compound was isolated as a yellow solid.

¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.8 (m, 4 H) 3.0 (m, 2 H) 3.3 (s, 3 H) 3.4 (m, 2 H) 3.6 (s, 3 H) 3.8 (m, 2 H) 6.2 (dd, $J=8.3, 2.4$ Hz, 1 H) 6.2 (d, $J=2.4$ Hz, 1 H) 6.6 (d, $J=8.3$ Hz, 1 H) 6.9 (d, $J=7.8$ Hz, 1 H) 7.5 (t, $J=7.1$ Hz, 1 H) 7.7 (t, $J=7.3$ Hz, 1 H) 7.9 (d, $J=7.8$ Hz, 1 H) 7.9 (d, $J=8.3$ Hz, 1 H) 8.4 (d, $J=8.3$ Hz, 1 H)

Example 37

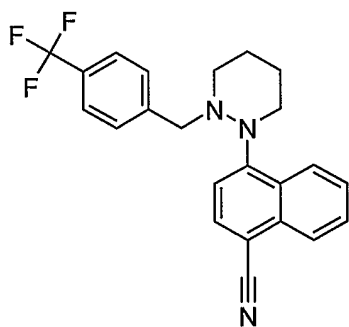


4-[2-{[2-(trifluoromethyl)phenyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C37)

From **B1** and 2-(trifluoromethyl)benzaldehyde the title compound was isolated as a yellow solid.

¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.7 (m, 4 H) 3.4 (m, 2 H) 3.5 (m, 2 H) 4.1 (m, 2 H) 7.1 (m, 2 H) 7.2 (m, 2 H) 7.5 (m, 1 H) 7.6 (t, *J*=7.3 Hz, 1 H) 7.7 (t, *J*=7.3 Hz, 1 H) 7.9 (m, 2 H) 8.3 (d, *J*=8.8 Hz, 1 H)

Example 38

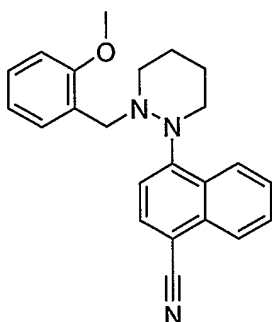


4-[2-{[4-(trifluoromethyl)phenyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C38)

From **B1** and 4-(trifluoromethyl)benzaldehyde the title compound was isolated as a yellow solid.

¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.8 (m, 4 H) 3.1 (m, 2 H) 3.5 (m, 2 H) 4.0 (m, 2 H) 7.0 (d, *J*=7.8 Hz, 1 H) 7.1 (d, *J*=8.3 Hz, 1 H) 7.3 (d, *J*=7.8 Hz, 1 H) 7.6 (t, *J*=7.8 Hz, 1 H) 7.7 (t, *J*=7.1 Hz, 1 H) 7.9 (d, *J*=8.3 Hz, 1 H) 8.3 (d, *J*=8.8 Hz, 1 H)

Example 39

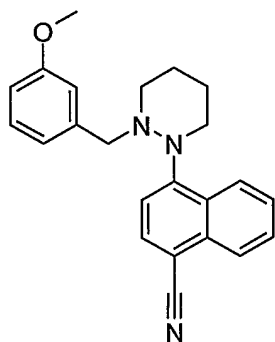


4-[2-[[2-(methyloxy)phenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C39)

From **B1** and 2-(methyloxy)benzaldehyde the title compound was isolated as a yellow solid.

¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.8 (m, 4 H) 3.1 (m, 2 H) 3.3 (s, 3 H) 3.5 (m, 2 H) 3.8 (m, 2 H) 6.6 (t, $J=7.3$ Hz, 1 H) 6.7 (d, $J=8.3$ Hz, 1 H) 6.8 (d, $J=7.3$ Hz, 1 H) 7.0 (d, $J=7.8$ Hz, 1 H) 7.0 (t, $J=7.8$ Hz, 1 H) 7.5 (t, $J=7.6$ Hz, 1 H) 7.7 (t, $J=7.6$ Hz, 1 H) 7.9 (d, $J=8.3$ Hz, 1 H) 7.9 (d, $J=8.3$ Hz, 1 H) 8.4 (d, $J=8.3$ Hz, 1 H)

Example 40

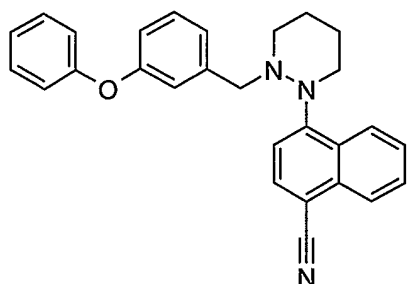


4-[2-[[3-(methyloxy)phenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C40)

From **B1** and 3-(methyloxy)benzaldehyde the title compound was isolated as a yellow solid.

¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.8 (m, 4 H) 3.1 (m, 2 H) 3.4 (s, 3 H) 3.8 (m, 2 H) 6.3 (s, 1 H) 6.5 (d, $J=7.3$ Hz, 1 H) 6.6 (dd, $J=8.3, 2.4$ Hz, 1 H) 7.0 (m, 2 H) 7.6 (t, $J=7.8$ Hz, 1 H) 7.7 (t, $J=7.6$ Hz, 1 H) 7.9 (d, $J=7.8$ Hz, 1 H) 8.0 (d, $J=8.3$ Hz, 1 H) 8.4 (d, $J=8.3$ Hz, 1 H)

Example 41

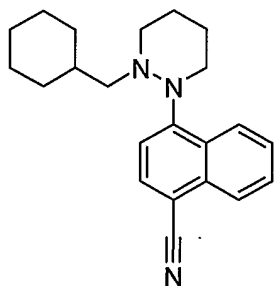


4-[2-[[3-(phenyloxy)phenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C41)

From **B1** and 3-(phenyloxy)benzaldehyde the title compound was isolated as a yellow solid.

¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.8 (m, 4 H) 3.1 (m, 2 H) 3.4 (m, 2 H) 3.9 (m, 2 H) 6.5 (s, 1 H) 6.7 (m, *J*=7.8 Hz, 1 H) 6.7 (m, *J*=8.3 Hz, 2 H) 7.0 (d, *J*=8.3 Hz, 1 H) 7.1 (m, 3 H) 7.3 (t, *J*=8.1 Hz, 2 H) 7.4 (m, 1 H) 7.6 (m, 1 H) 7.9 (m, 2 H) 8.3 (d, *J*=8.3 Hz, 1 H)

Example 42

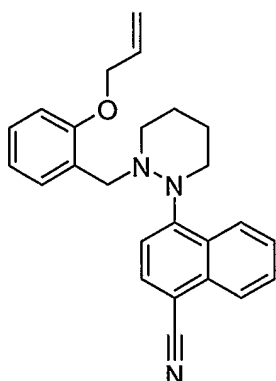


4-[2-(cyclohexylmethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C42)

From **B1** and cyclohexanecarbaldehyde the title compound was isolated as a yellow solid.

¹H NMR (500 MHz, DMSO-D₆) δ ppm 0.3 (m, 2 H) 0.9 (m, 4 H) 1.3 (m, 5 H) 1.7 (m, 4 H) 2.6 (m, 2 H) 3.2 (m, 2 H) 3.3 (m, 2 H) 7.0 (d, *J*=8.3 Hz, 1 H) 7.5 (t, *J*=7.1 Hz, 1 H) 7.7 (t, *J*=7.1 Hz, 1 H) 7.9 (m, 2 H) 8.3 (d, *J*=8.3 Hz, 1 H)

Example 43

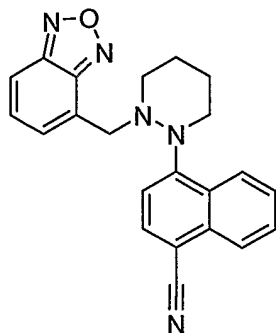


4-[2-[[2-(2-propen-1-yloxy)phenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C43)

From **B1** and 2-(2-propen-1-yloxy)benzaldehyde the title compound was isolated as a yellow solid.

¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.8 (m, 4 H) 3.1 (m, 2 H) 3.5 (m, 2 H) 3.9 (m, 2 H) 4.3 (m, *J*=4.9 Hz, 2 H) 5.2 (m, 1 H) 5.3 (m, 1 H) 5.8 (t, 1 H) 6.6 (t, *J*=7.3 Hz, 1 H) 6.7 (d, *J*=5.9 Hz, 1 H) 6.7 (d, *J*=8.3 Hz, 1 H) 7.0 (m, 2 H) 7.5 (t, *J*=7.1 Hz, 1 H) 7.7 (t, *J*=7.1 Hz, 1 H) 7.9 (m, 2 H) 8.4 (d, *J*=8.3 Hz, 1 H)

Example 44



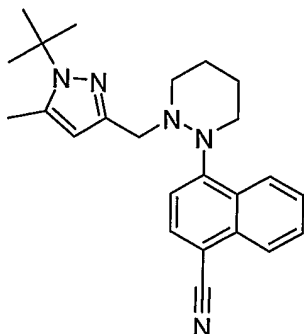
4-[2-(2,1,3-benzoxadiazol-4-ylmethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C44)

From **B1** and 2,1,3-benzoxadiazole-4-carbaldehyde the title compound was isolated as a yellow solid.

MS (*m/z*) ESI ES⁺ = 370

Example 45

70



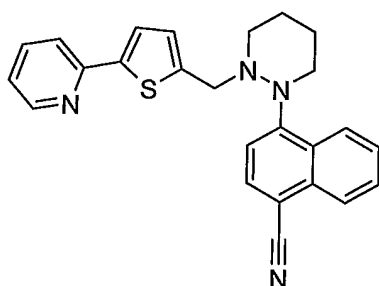
4-[2-[[1-(1,1-dimethylethyl)-5-methyl-1H-pyrazol-3-yl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C45)

From **B1** and 1-(1,1-dimethylethyl)-5-methyl-1H-pyrazole-3-carbaldehyde the title

5 compound was isolated as a brown oil.

MS (m/z) ESI ES⁺ = 388

Example 46



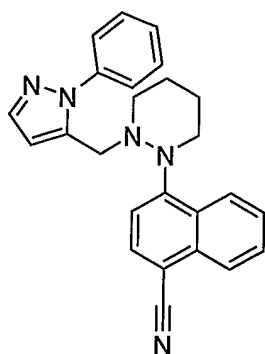
4-[2-[[5-(2-pyridinyl)-2-thienyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C46)

10

From **B1** and 5-(2-pyridinyl)-2-thiophenecarbaldehyde the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 411

Example 47



15

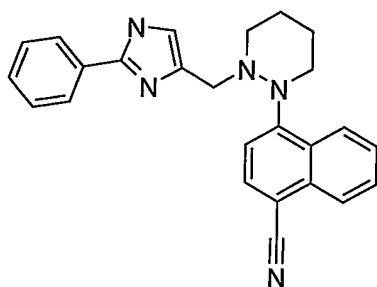
71

4-[2-[(1-phenyl-1*H*-pyrazol-5-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C47)

From **B1** and 1-phenyl-1*H*-pyrazole-5-carbaldehyde the title compound was isolated as a yellow solid.

5 MS (m/z) ESI ES⁺ = 394

Example 48

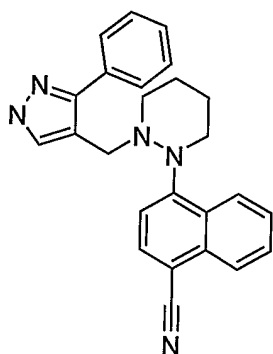


4-[2-[(2-phenyl-1*H*-imidazol-4-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C48)

10 From **B1** and 2-phenyl-1*H*-imidazol-4-carbaldehyde the title compound was isolated as a white solid.

MS (m/z) ESI ES⁺ = 394

Example 49



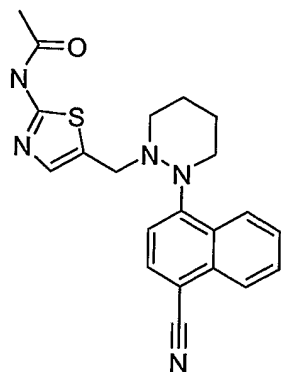
4-[2-[(3-phenyl-1*H*-pyrazol-4-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C49)

From **B1** and 3-phenyl-1*H*-pyrazol-4-carbaldehyde the title compound was isolated as a yellow solid.

20 MS (m/z) ESI ES⁺ = 394

Example 50

72

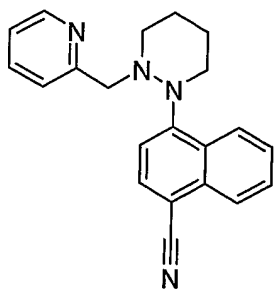


***N*-(5-([2-(4-cyano-1-naphthalenyl)tetrahydro-1(2*H*)-pyridazinyl]methyl)-1,3-thiazol-2-yl)acetamide (C50)**

From **B1** and *N*-(5-formyl-1,3-thiazol-2-yl)acetamide the title compound was isolated as a yellow solid.

MS (*m/z*) ESI ES⁺ = 392

Example 51

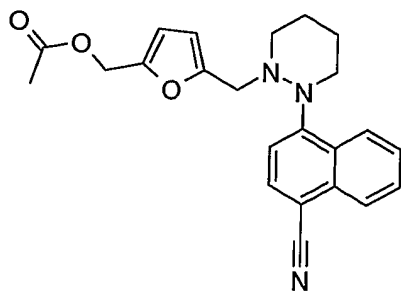


4-[2-(2-pyridinylmethyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C51)

From **B1** and 2-pyridinecarbaldehyde the title compound was isolated as a yellow oil.

MS (*m/z*) ESI ES⁺ = 329

Example 52



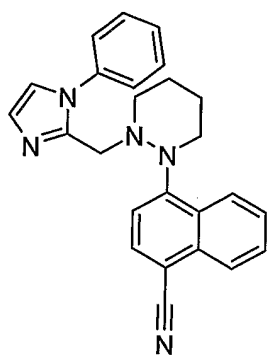
(5-([2-(4-cyano-1-naphthalenyl)tetrahydro-1(2*H*)-pyridazinyl]methyl)-2-furanyl)methyl acetate (C52)

73

From **B1** and (5-formyl-2-furanyl)methyl acetate the title compound was isolated as a brown oil.

MS (m/z) ESI ES⁺ = 390

Example 53



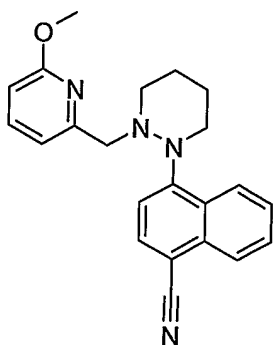
5

4-[2-[(1-phenyl-1H-imidazol-2-yl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C53)

From **B1** and 1-phenyl-1H-imidazol-2-carbaldehyde the title compound was isolated as a yellow oil.

10 MS (m/z) ESI ES⁺ = 394

Example 54

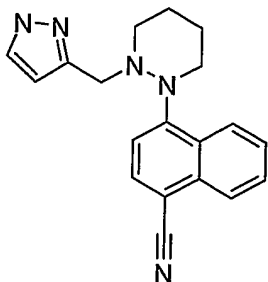


4-[2-[[6-(methoxy)-2-pyridinyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C54)

15 From **B1** and 6-(methoxy)-2-pyridinecarbaldehyde the title compound was isolated as a brown solid.

MS (m/z) ESI ES⁺ = 359

Example 55

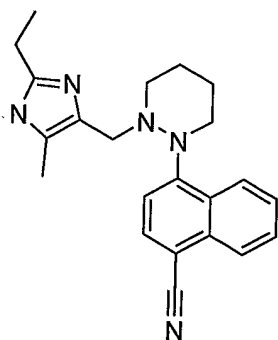


4-[2-(1*H*-pyrazol-3-ylmethyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C55)

From **B1** and 1*H*-pyrazol-3-carbaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 318

Example 56



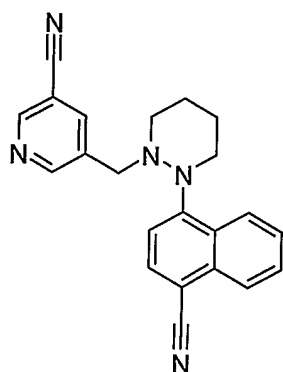
4-[2-[(2-ethyl-4-methyl-1*H*-imidazol-5-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C56)

From **B1** and 2-ethyl-4-methyl-1*H*-imidazol-5-carbaldehyde the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 360

Example 57

75

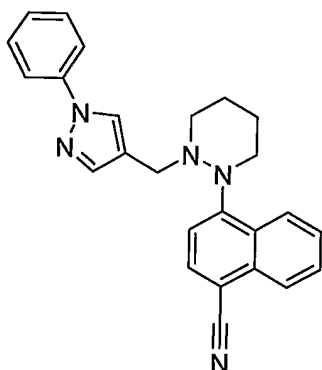


5-([2-(4-cyano-1-naphthalenyl)tetrahydro-1(2H)-pyridazinyl]methyl)-3-pyridinecarbonitrile (C57)

From **B1** and 5-formyl-3-pyridinecarbonitrile the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 354

Example 58



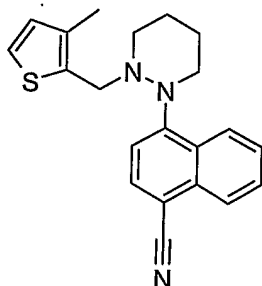
4-[2-[(1-phenyl-1H-pyrazol-4-yl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C58)

From **B1** and 1-phenyl-1H-pyrazol-4-carbaldehyde the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 394

Example 59

76

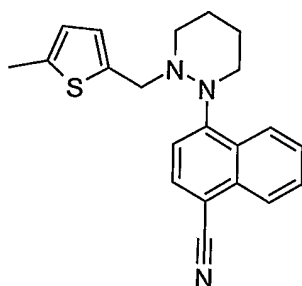


4-[2-[(3-methyl-2-thienyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C59)

From **B1** and 3-methyl-2-thiophenecarbaldehyde the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 348

Example 60

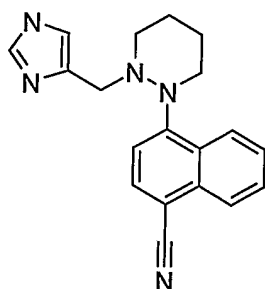


4-[2-[(5-methyl-2-thienyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C60)

From **B1** and 5-methyl-2-thiophenecarbaldehyde the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 348

Example 61



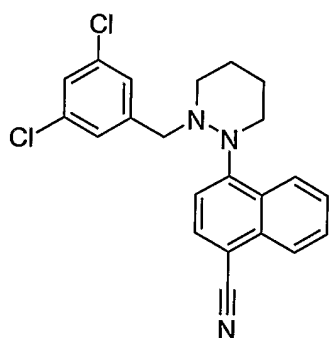
77

4-[2-(1*H*-imidazol-4-ylmethyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C61)

From **B1** and 1*H*-imidazol-4-carbaldehyde the title compound was isolated as a yellow oil.

5 MS (m/z) ESI ES⁺ = 318

Example 62

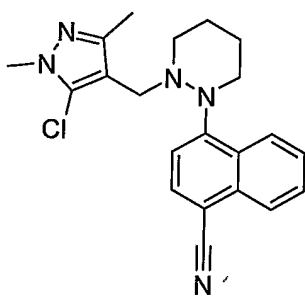


4-[2-[(3,5-dichlorophenyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C62)

10 From **B1** and 3,5-dichlorobenzaldehyde the title compound was isolated as a yellow solid.

MS (m/z) APCI AP⁺ = 396

Example 63



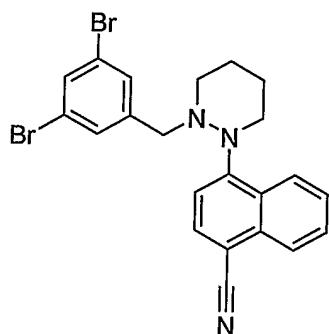
15 **4-[2-[(5-chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C63)**

From **B1** and 5-chloro-1,3-dimethyl-1*H*-pyrazol-4-carbaldehyde the title compound was isolated as a yellow solid.

MS (m/z) APCI AP⁺ = 380

20 **Example 64**

78

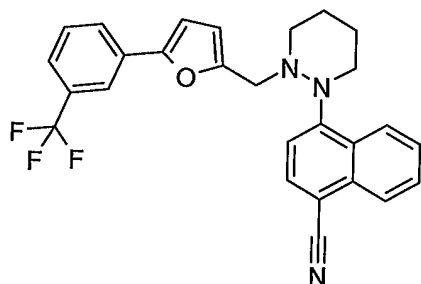


4-[2-[(3,5-dibromophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C64)

From **B1** and 3,5-dibromobenzaldehyde the title compound was isolated as a yellow solid.

MS (m/z) APCI AP⁺ = 486

Example 65

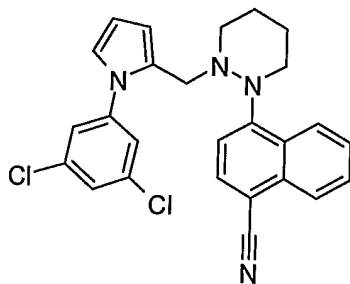


4-[2-[(5-[3-(trifluoromethyl)phenyl]-2-furanyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C65)

From **B1** and 5-[3-(trifluoromethyl)phenyl]-2-furancarbaldehyde the title compound was isolated as a red oil.

MS (m/z) APCI AP⁺ = 462

Example 66



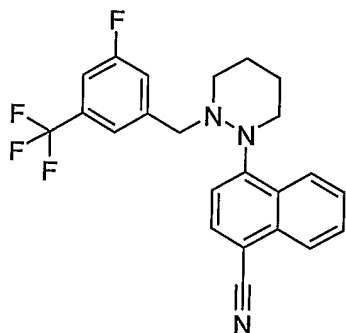
4-[2-[[1-(3,5-dichlorophenyl)-1H-pyrrol-2-yl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C66)

79

From **B1** and 3,5-dichlorophenyl)-1*H*-pyrrol-2-carbaldehyde the title compound was isolated as a purple solid.

MS (m/z) APCI AP⁺ = 461

Example 67



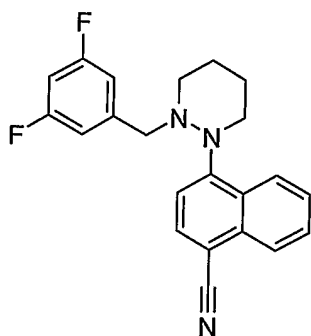
5

4-[2-([3-fluoro-5-(trifluoromethyl)phenyl]methyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C67)

From **B1** and 3-fluoro-5-(trifluoromethyl)benzaldehyde the title compound was isolated as a yellow oil.

10 MS (m/z) APCI AP⁺ = 414

Example 68



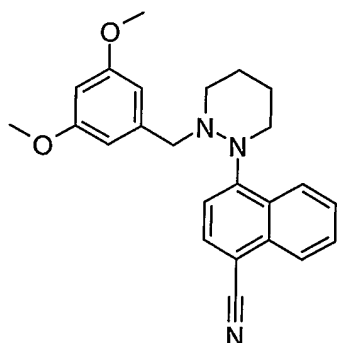
4-[2-[(3,5-difluorophenyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C68)

15 From **B1** and 3,5-difluorobenzaldehyde the title compound was isolated as a brown solid.

MS (m/z) APCI AP⁺ = 364

Example 69

80

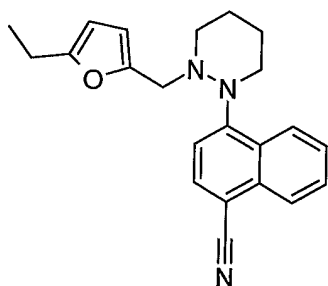


4-[2-[[3,5-bis(methoxy)phenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C69)

From **B1** and 3,5-bis(methoxy)benzaldehyde the title compound was isolated as a yellow oil.

MS (m/z) APCI AP⁺ = 388

Example 70

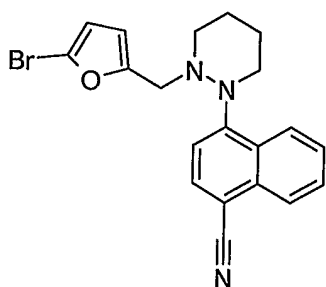


4-[2-[(5-ethyl-2-furanyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C70)

From **B1** and 5-ethyl-2-furancarbaldehyde the title compound was isolated as a yellow oil.

MS (m/z) APCI AP⁺ = 388

Example 71

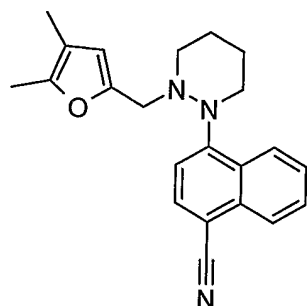


81

4-[2-[(5-bromo-2-furanyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C71)

From **B1** and 5-bromo-2-furancarbaldehyde the title compound was isolated as a yellow oil.

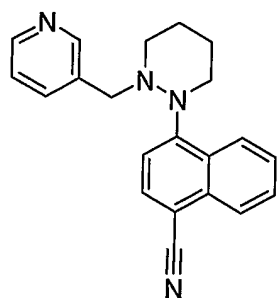
5 MS (m/z) APCI AP⁺ = 398

Example 72**4-[2-[(4,5-dimethyl-2-furanyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C72)**

10 From **B1** and 4,5-dimethyl-2-furancarbaldehyde the title compound was isolated as a yellow solid.

¹H NMR (500 MHz, DMSO-D₆) δ ppm 1.6 (s, 3 H) 1.7 (m, 2 H) 1.8 (s, 3 H) 1.8 (m, 2 H) 3.2 (m, 2 H) 3.4 (m, 2 H) 6.8 (d, J=8.3 Hz, 1 H) 7.5 (t, J=7.3 Hz, 1 H) 7.6 (t, J=7.6 Hz, 1 H) 7.8 (d, J=7.8 Hz, 1 H) 7.9 (d, J=8.3 Hz, 1 H) 8.4 (d, J=8.8 Hz, 1 H)

15 **Example 73**

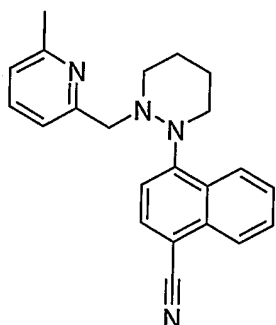
**4-[2-(3-pyridinylmethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C73)**

From **B1** and 3-pyridinecarbaldehyde the title compound was isolated as a yellow oil.

20 MS (m/z) ESI ES⁺ = 329

Example 74

82

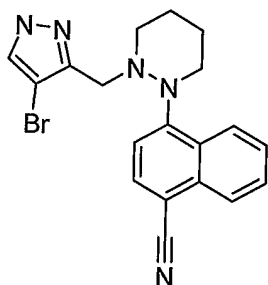


4-[2-[(6-methyl-2-pyridinyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C74)

From **B1** and 6-methyl-2-pyridinecarbaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 343

Example 75

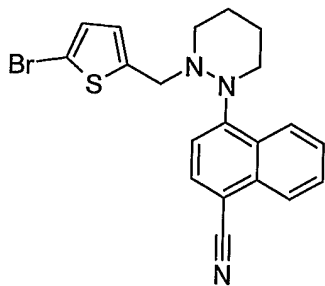


4-[2-[(4-bromo-1H-pyrazol-3-yl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C75)

From **B1** and 4-bromo-1H-pyrazol-3-carbaldehyde the title compound was isolated as a white solid.

MS (m/z) ESI ES⁺ = 397

Example 76



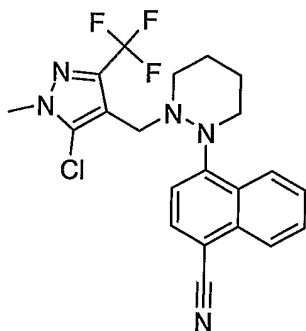
4-[2-[(5-bromo-2-thienyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C76)

83

From **B1** and 5-bromo-2-thiophenecarbaldehyde the title compound was isolated as a yellow solid.

MS (m/z) APCI AP^+ = 413

Example 77

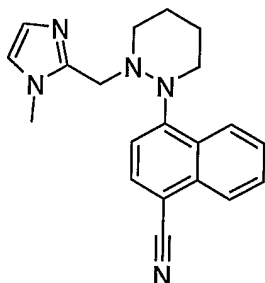


4-[2-[[5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C77)

From **B1** and 5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-carbaldehyde the title compound was isolated as a white solid.

10 MS (m/z) APCI AP^+ = 434

Example 78



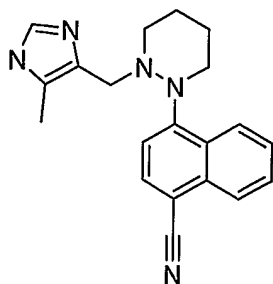
4-[2-[(1-methyl-1H-imidazol-2-yl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C78)

From **B1** and 1-methyl-1H-imidazol-2-carbaldehyde the title compound was isolated as a white solid.

MS (m/z) APCI AP^+ = 332

Example 79

84

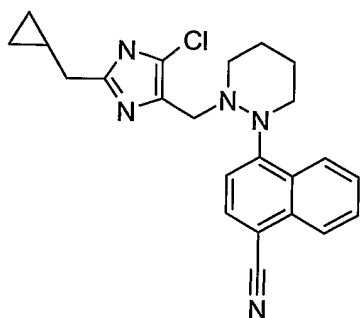


4-[2-[(4-methyl-1*H*-imidazol-5-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C79)

From **B1** and 4-methyl-1*H*-imidazol-5-carbaldehyde the title compound was isolated as a yellow solid.

MS (m/z) APCI AP⁺ = 332

Example 80

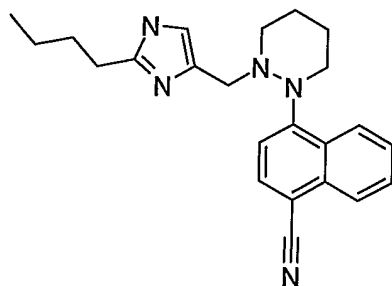


4-[2-{[4-chloro-2-(cyclopropylmethyl)-1*H*-imidazol-5-yl]methyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C80)

From **B1** and 4-chloro-2-(cyclopropylmethyl)-1*H*-imidazol-5-carbaldehyde the title compound was isolated as a yellow solid.

MS (m/z) APCI AP⁺ = 406

Example 81



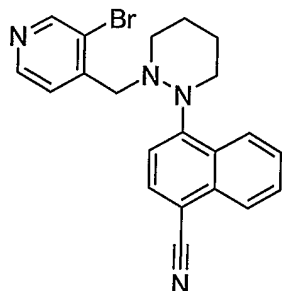
4-[2-[(2-butyl-1*H*-imidazol-4-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C81)

85

From **B1** and 2-butyl-1*H*-imidazol-4-carbaldehyde the title compound was isolated as a yellow oil.

MS (m/z) APCI AP⁺ = 374

Example 82

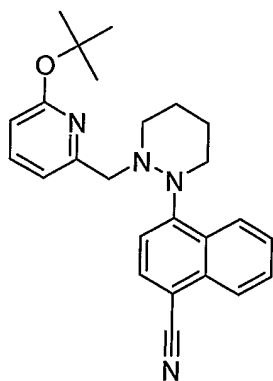


4-[2-[(3-bromo-4-pyridinyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C82)

From **B1** and 3-bromo-4-pyridinecarbaldehyde the title compound was isolated as a brown solid.

MS (m/z) APCI AP⁺ = 408

Example 83



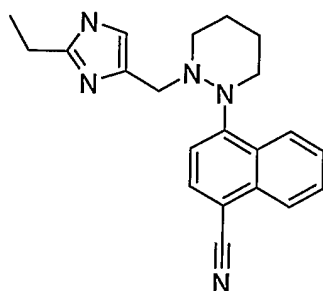
4-[2-[(6-[(1,1-dimethylethyl)oxy]-2-pyridinyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C83)

From **B1** and 6-[(1,1-dimethylethyl)oxy]-2-pyridinecarbaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 401

Example 84

86

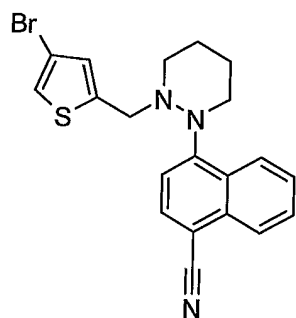


4-[2-[(2-ethyl-1*H*-imidazol-4-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C84)

From **B1** and 2-ethyl-1*H*-imidazol-4-carbaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 346

Example 85

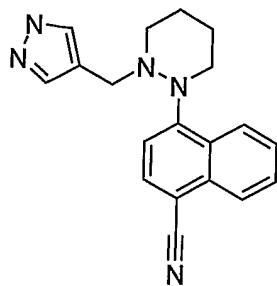


4-[2-[(4-bromo-2-thienyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C85)

From **B1** and 4-bromo-2-thiophenecarbaldehyde the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 413

Example 86



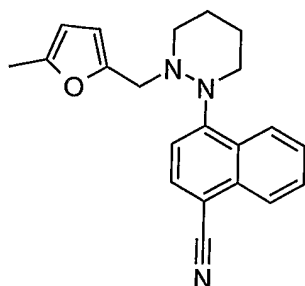
4-[2-(1*H*-pyrazol-4-ylmethyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C86)

87

From **B1** and 1*H*-pyrazol-4-carbaldehyde the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 318

Example 87



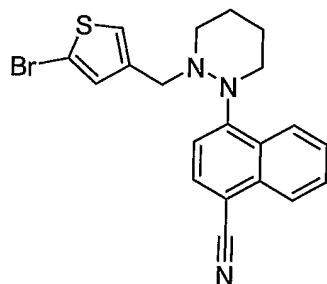
5

4-[2-[(5-methyl-2-furanyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C87)

From **B1** and 5-methyl-2-furancarbaldehyde the title compound was isolated as a yellow oil.

10 MS (m/z) ESI ES⁺ = 332

Example 88



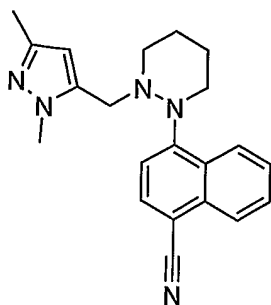
4-[2-[(5-bromo-3-thienyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C88)

15 From **B1** and 5-bromo-3-thiophenecarbaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 413

Example 89

88

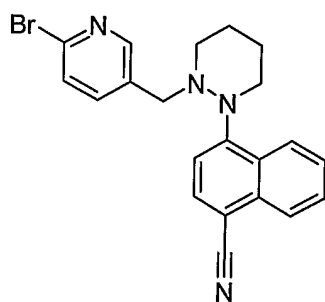


4-[2-[(1,3-dimethyl-1*H*-pyrazol-5-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C89)

From **B1** and 1,3-dimethyl-1*H*-pyrazol-5-carbaldehyde the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 346

Example 90

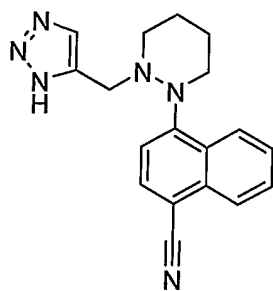


4-[2-[(6-bromo-3-pyridinyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C90)

From **B1** and 6-bromo-3-pyridinecarbaldehyde the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 408

Example 91



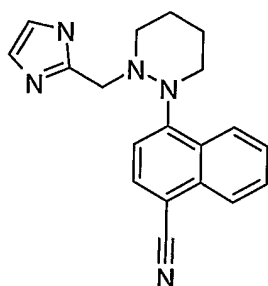
4-[2-(1*H*-1,2,3-triazol-4-ylmethyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C91)

89

From **B1** and 1*H*-1,2,3-triazol-4-carbaldehyde the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 319

Example 92



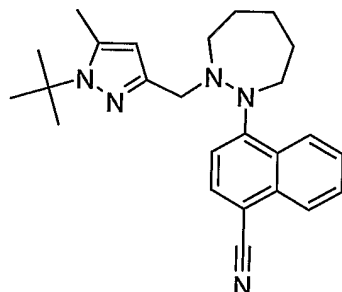
5

4-[2-(1*H*-imidazol-2-ylmethyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C92)

From **B1** and 1*H*-imidazol-2-carbaldehyde the title compound was isolated as a yellow solid.

10 MS (m/z) ESI ES⁺ = 318

Example 93



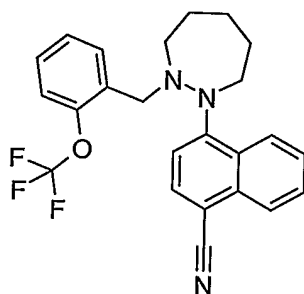
4-(2-([1-(1,1-dimethylethyl)-5-methyl-1*H*-pyrazol-3-yl]methyl)hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile (C93)

15 From **B4** and 1-(1,1-dimethylethyl)-5-methyl-1*H*-pyrazol-3-carbaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 402

Example 94

90

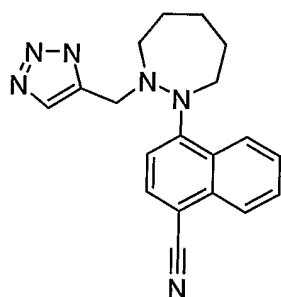


4-[2-({2-[(trifluoromethyl)oxy]phenyl}methyl)hexahydro-1H-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile (C94)

From **B4** and 2-[(trifluoromethyl)oxy]benzaldehyde the title compound was isolated as a brown oil.

MS (m/z) ESI ES⁺ = 426

Example 95

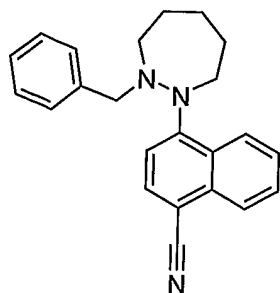


4-[2-(1H-1,2,3-triazol-4-ylmethyl)hexahydro-1H-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile (C95)

From **B4** and 1H-1,2,3-triazol-4-carbaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 333

Example 96

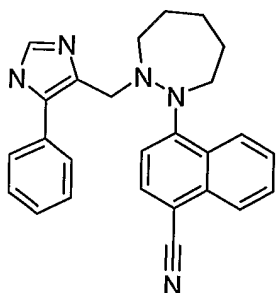


4-[2-(phenylmethyl)hexahydro-1H-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile (C138)

From **B4** and benzaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 342

Example 97

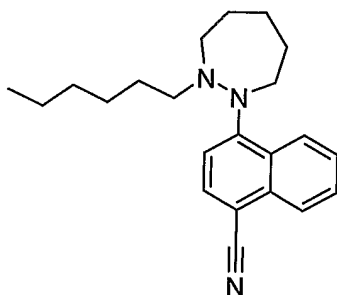


5 **4-{2-[(4-phenyl-1H-imidazol-5-yl)methyl]hexahydro-1H-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile (C97)**

From **B4** and 4-phenyl-1H-imidazol-5-carbaldehyde the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 408

10 **Example 98**

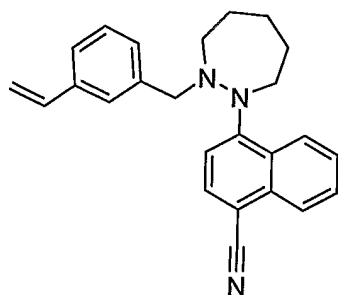


4-(2-hexylhexahydro-1H-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile (C98)

From **B4** and hexanal the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 336

15 **Example 99**



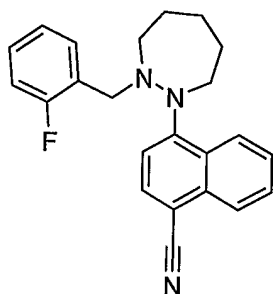
92

4-{2-[(3-ethenylphenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile (C99)

From **B4** and 3-ethenylbenzaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺= 368

5 **Example 100**

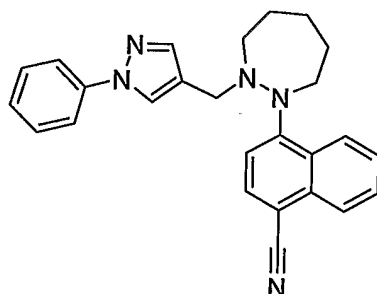


4-{2-[(2-fluorophenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile (C100)

From **B4** and 2-fluorobenzaldehyde the title compound was isolated as a yellow solid.

10 MS (m/z) ESI ES⁺= 360

Example 101

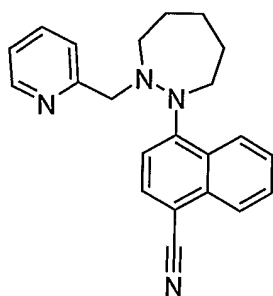


4-{2-[(1-phenyl-1*H*-pyrazol-4-yl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile (C101)

15 From **B4** and 1-phenyl-1*H*-pyrazol-4-carbaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺= 408

Example 102

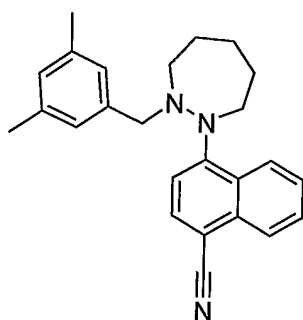


4-[2-(2-pyridinylmethyl)hexahydro-1H-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile (C102)

From **B4** and 2-pyridinecarbaldehyde the title compound was isolated as a brown oil.

5 MS (m/z) ESI ES⁺ = 343

Example 103

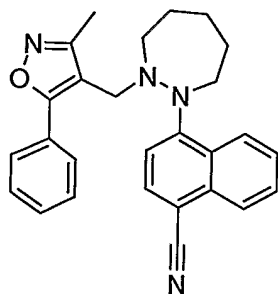


4-{2-[(3,5-dimethylphenyl)methyl]hexahydro-1H-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile (C103)

10 From **B4** and 3,5-dimethylbenzaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 370

Example 104

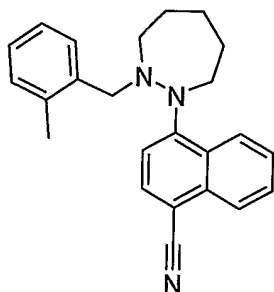


4-{2-[(3-methyl-5-phenyl-4-isoxazolyl)methyl]hexahydro-1H-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile (C104)

15 From **B4** and 3-methyl-5-phenyl-4-isoxazolecarbaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 423

Example 105

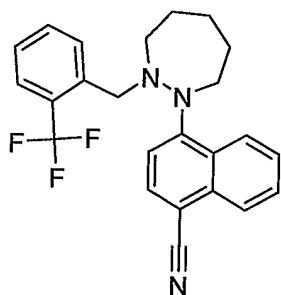


4-{2-[(2-methylphenyl)methyl]hexahydro-1H-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile (C105)

From **B4** and 2-methylbenzaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 356

Example 106

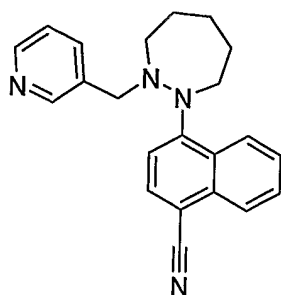


4-{2-[2-(trifluoromethyl)phenyl]methyl}hexahydro-1H-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile (C1068)

From **B4** and 2-(trifluoromethyl)benzaldehyde the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 410

Example 107

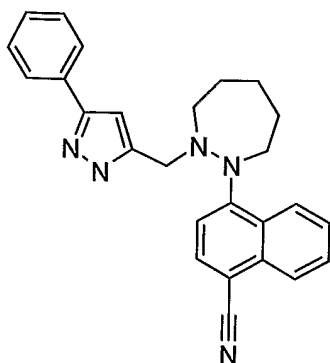


95

4-[2-(3-pyridinylmethyl)hexahydro-1*H*-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile (C107)

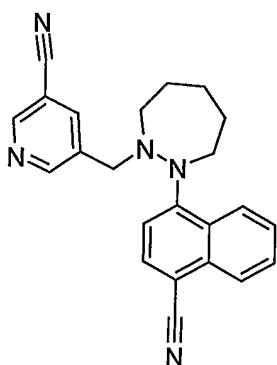
From **B4** and 3-pyridinecarbaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 343

5 Example 108**4-{2-[(3-phenyl-1*H*-pyrazol-5-yl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile (C108)**

From **B4** and 3-phenyl-1*H*-pyrazol-5-carbaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 408

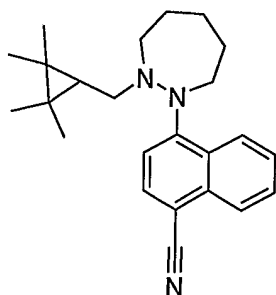
Example 109**5-{[2-(4-cyano-1-naphthalenyl)hexahydro-1*H*-1,2-diazepin-1-yl]methyl}-3-pyridinecarbonitrile (C109)**

From **B4** and 5-formyl-3-pyridinecarbonitrile the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 368

Example 110

96

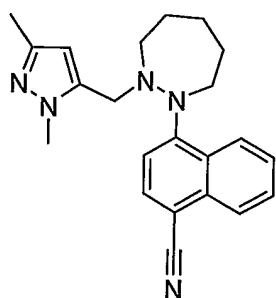


4-{2-[(2,2,3,3-tetramethylcyclopropyl)methyl]hexahydro-1H-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile (C110)

From **B4** and 2,2,3,3-tetramethylcyclopropanecarbaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 362

Example 111

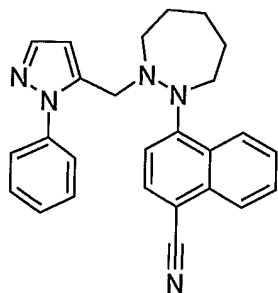


4-{2-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]hexahydro-1H-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile (C111)

From **B4** and 1,3-dimethyl-1H-pyrazol-5-carbaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 360

Example 112



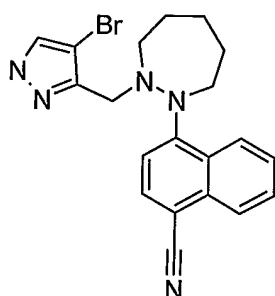
4-{2-[(1-phenyl-1H-pyrazol-5-yl)methyl]hexahydro-1H-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile (C112)

97

From **B4** and 1-phenyl-1*H*-pyrazol-5-carbaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 408

Example 113



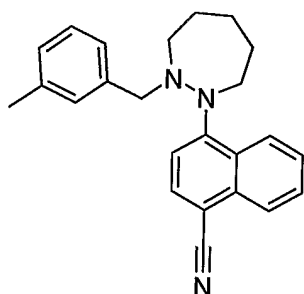
5

4-{2-[(4-bromo-1*H*-pyrazol-3-yl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile (C113)

From **B4** and 4-bromo-1*H*-pyrazol-3-carbaldehyde the title compound was isolated as a yellow oil.

10 MS (m/z) ESI ES⁺ = 411

Example 114

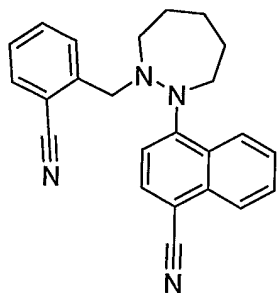


4-{2-[(3-methylphenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile (C114)

15 From **B4** and 3-methylbenzaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 356

Example 115

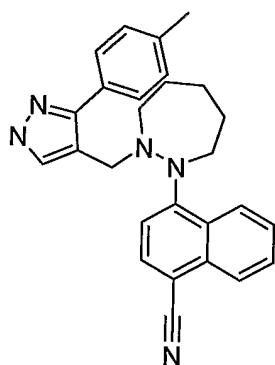


4-{2-[(2-cyanophenyl)methyl]hexahydro-1H-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile (C115)

From **B4** and 2-cyanobenzaldehyde the title compound was isolated as a green oil.

5 MS (m/z) ESI $ES^+ = 367$

Example 116

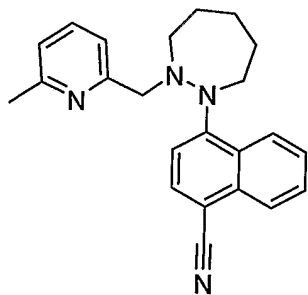


4-(2-{[3-(4-methylphenyl)-1H-pyrazol-4-yl]methyl}hexahydro-1H-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile (C116)

10 From **B4** and 3-(4-methylphenyl)-1H-pyrazol-4-carbaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI $ES^+ = 422$

Example 117



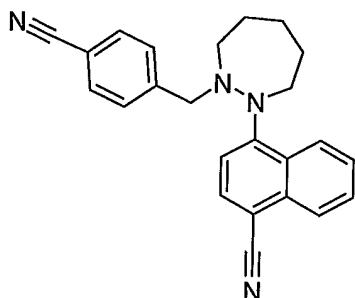
15 **4-{2-[(6-methyl-2-pyridinyl)methyl]hexahydro-1H-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile (C117)**

99

From **B4** and 6-methyl-2-pyridinecarbaldehyde the title compound was isolated as an orange oil.

MS (m/z) ESI ES⁺ = 357

Example 118



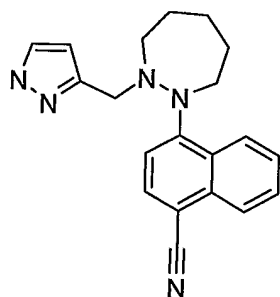
5

4-{2-[(4-cyanophenyl)methyl]hexahydro-1H-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile (C118)

From **B4** and 4-cyanobenzaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 367

10 **Example 119**



4-[2-(1H-pyrazol-3-ylmethyl)hexahydro-1H-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile (C119)

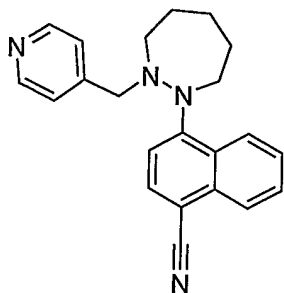
From **B4** and 1H-pyrazol-3-carbaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 332

Example 120

15

100

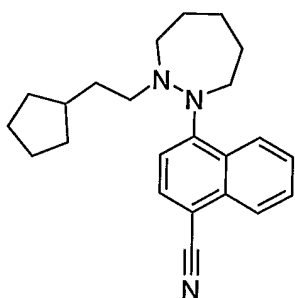


4-[2-(4-pyridinylmethyl)hexahydro-1H-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile (C120)

From **B4** and 4-pyridinecarbaldehyde the title compound was isolated as a brown solid.

5 MS (m/z) ESI $ES^+ = 343$

Example 121

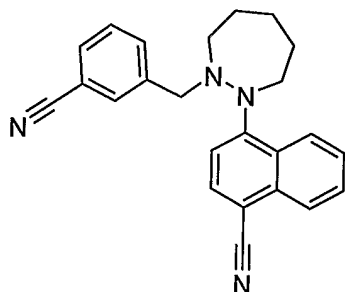


4-[2-(2-cyclopentylethyl)hexahydro-1H-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile (C121)

10 From **B4** and cyclopentylacetaldehyde the title compound was isolated as a yellow solid.

MS (m/z) ESI $ES^+ = 348$

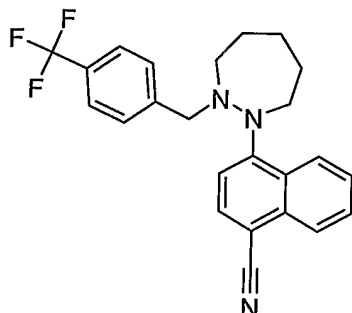
Example 122



15 **4-{2-[(3-cyanophenyl)methyl]hexahydro-1H-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile (C122)**

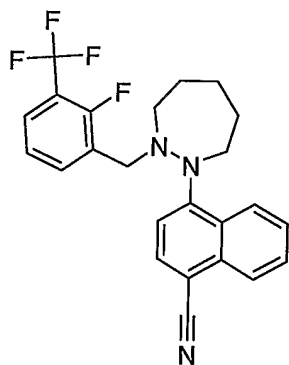
From **B4** and 3-cyanobenzaldehyde the title compound was isolated as a yellow solid.

101

MS (m/z) ESI ES⁺= 367**Example 123**

5 **4-(2-([4-(trifluoromethyl)phenyl]methyl)hexahydro-1H-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile (C123)**

From **B4** and 4-(trifluoromethyl)benzaldehyde the title compound was isolated as a yellow oil.

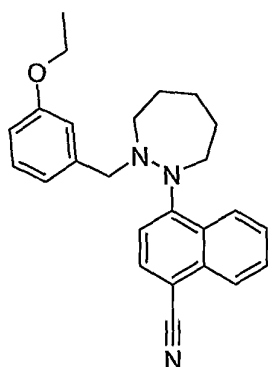
MS (m/z) ESI ES⁺= 410**Example 124**

10 **4-(2-([2-fluoro-3-(trifluoromethyl)phenyl]methyl)hexahydro-1H-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile (C124)**

From **B4** and 2-fluoro-3-(trifluoromethyl)benzaldehyde the title compound was isolated as a yellow oil.

15 MS (m/z) ESI ES⁺= 428

Example 125

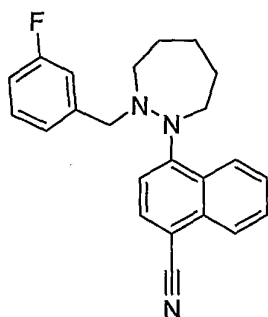


4-(2-([3-(ethoxy)phenyl]methyl)hexahydro-1H-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile (C125)

From **B4** and 3-(ethoxy)benzaldehyde the title compound was isolated as a yellow oil.

5 MS (m/z) ESI ES⁺ = 386

Example 126

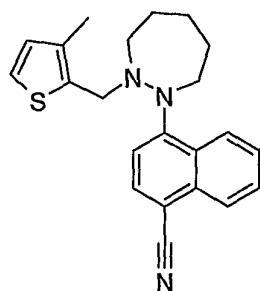


4-(2-([3-fluorophenyl]methyl)hexahydro-1H-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile (C126)

10 From **B4** and 3-fluorobenzaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 360

Example 127



4-(2-([3-methyl-2-thienyl]methyl)hexahydro-1H-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile (C127)

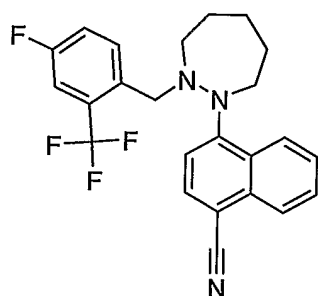
15

103

From **B4** and 3-methyl-2-thiophenecarbaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI $ES^+ = 362$

Example 128



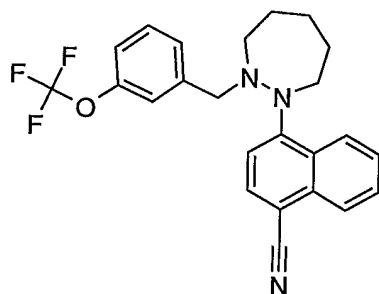
5

4-(2-([4-fluoro-2-(trifluoromethyl)phenyl]methyl)hexahydro-1H-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile (C128)

From **B4** and 4-fluoro-2-(trifluoromethyl)benzaldehyde the title compound was isolated as a yellow oil.

10 MS (m/z) ESI $ES^+ = 428$

Example 129



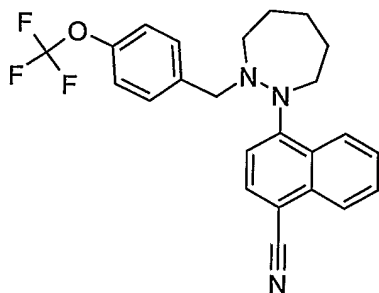
4-[2-({3-[(trifluoromethyl)oxy]phenyl}methyl)hexahydro-1H-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile (C129)

15 From **B4** and 3-[(trifluoromethyl)oxy]benzaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI $ES^+ = 426$

Example 130

104

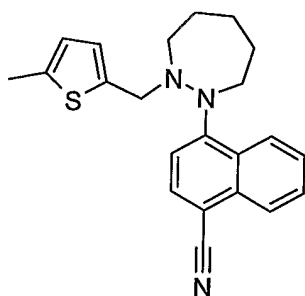


4-[2-({3-[(trifluoromethyl)oxy]phenyl}methyl)hexahydro-1H-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile (C130)

From **B4** and 4-[(trifluoromethyl)oxy]benzaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 426

Example 131

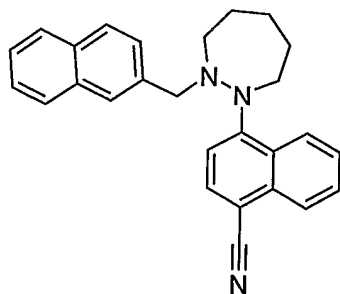


4-{2-[(5-methyl-2-thienyl)methyl]hexahydro-1H-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile (C131)

From **B4** and 5-methyl-2-thiophenecarbaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 362

Example 132



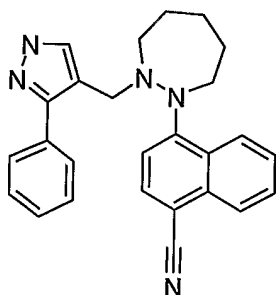
4-[2-(2-naphthalenylmethyl)hexahydro-1H-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile (C132)

105

From **B4** and 2-naphthalenecarbaldehyde the title compound was isolated as an orange oil.

MS (m/z) ESI ES⁺ = 392

Example 133



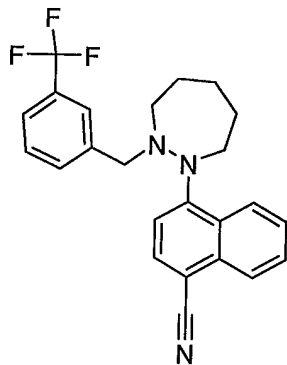
5

4-{2-[(3-phenyl-1H-pyrazol-4-yl)methyl]hexahydro-1H-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile (C133)

From **B4** and 3-phenyl-1H-pyrazol-4-carbaldehyde the title compound was isolated as a yellow oil.

10 MS (m/z) ESI ES⁺ = 408

Example 134



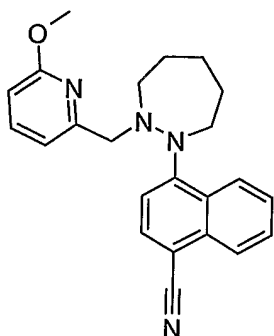
4-{2-[3-(trifluoromethyl)phenyl]methyl}hexahydro-1H-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile (C134)

15 From **B4** and 3-(trifluoromethyl)benzaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 410

Example 135

106

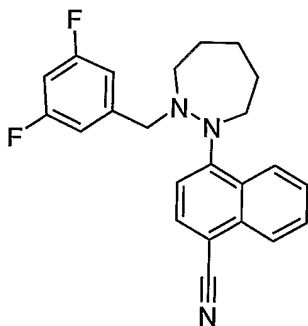


4-(2-([6-(methoxy)-2-pyridinyl]methyl)hexahydro-1H-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile (C135)

From **B4** and 6-(methoxy)-2-pyridinecarbaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI $ES^+ = 373$

Example 136

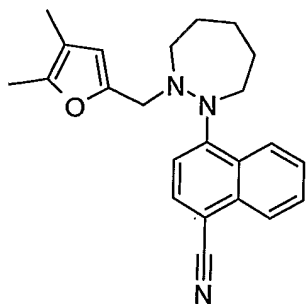


4-(2-([3,5-difluorophenyl]methyl)hexahydro-1H-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile (C136)

From **B4** and 3,5-difluorobenzaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI $ES^+ = 378$

Example 137



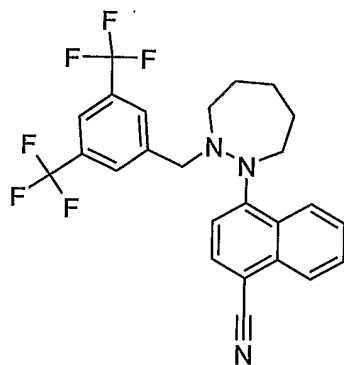
4-(2-([4,5-dimethyl-2-furanyl]methyl)hexahydro-1H-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile (C137)

107

From **B4** and 4,5-dimethyl-2-furancarbaldehyde the title compound was isolated as a brown oil.

MS (m/z) ESI ES⁺ = 360

Example 138



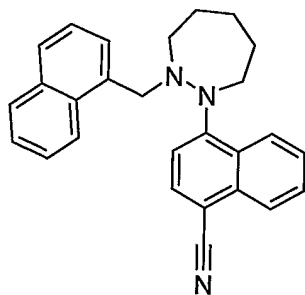
5

4-(2-([3,5-bis(trifluoromethyl)phenyl]methyl)hexahydro-1H-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile (C138)

From **B4** and 3,5-bis(trifluoromethyl)benzaldehyde the title compound was isolated as a yellow oil.

10 MS (m/z) ESI ES⁺ = 478

Example 139



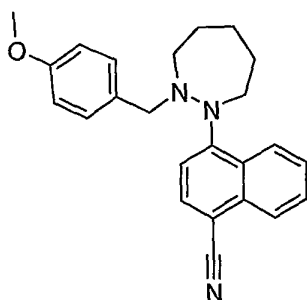
4-[2-(1-naphthalenylmethyl)hexahydro-1H-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile (C139)

15 From **B4** and 1-naphthalenecarbaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 392

Example 140

108

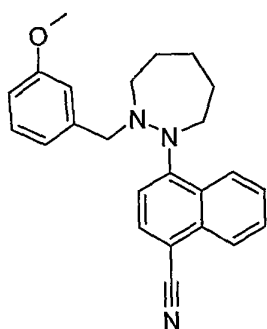


4-(2-([4-(methoxy)phenyl]methyl)hexahydro-1H-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile (C140)

From **B4** and 4-(methoxy)benzaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI $ES^+ = 372$

Example 141

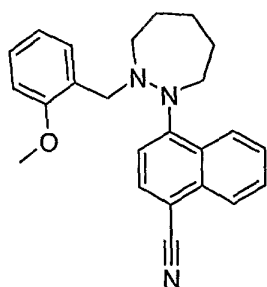


4-(2-([3-(methoxy)phenyl]methyl)hexahydro-1H-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile (C141)

From **B4** and 3-(methoxy)benzaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI $ES^+ = 372$

Example 142



15

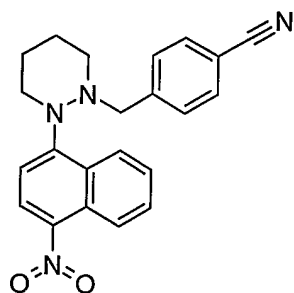
109

4-(2-{[2-(methyloxy)phenyl]methyl}hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile (C142)

From **B4** and 2-(methyloxy)benzaldehyde the title compound was isolated as a yellow oil.

5 MS (m/z) ESI ES⁺ = 372

Example 143

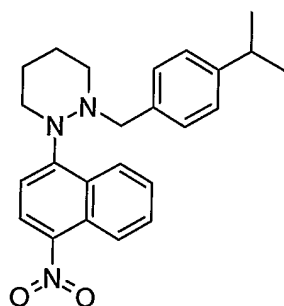


4-{[2-(4-nitro-1-naphthalenyl)tetrahydro-1(2*H*)-pyridazinyl]methyl}benzonitrile (C143)

10 From **B2** and 4-cyanobenzaldehyde the title compound was obtained.

MS (m/z) ESI ES⁺ = 373

Example 144

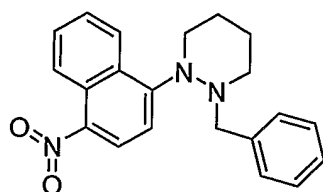


1-{[4-(1-methylethyl)phenyl]methyl}-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (C144)

15 From **B2** and 4-(1-methylethyl)benzaldehyde the title compound was obtained.

MS (m/z) ESI ES⁺ = 390

Example 145

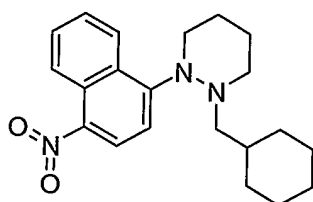


110

1-(4-nitro-1-naphthalenyl)-2-(phenylmethyl)hexahydropyridazine (C145)

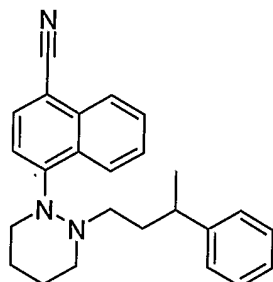
From **B2** and benzaldehyde the title compound was obtained.

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.7 (m, 2 H) 2.0 (m, 2 H) 3.2 (m, 2 H) 3.5 (m, 2 H) 4.0 (s, 2 H) 6.9 (m, 3 H) 7.1 (m, 3 H) 7.5 (m, 1 H) 7.7 (m, 1 H) 8.2 (d, $J=8.6$ Hz, 1 H) 8.4 (m, 1 H) 8.7 (m, 1 H)

Example 146**1-(cyclohexylmethyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (C146)**

From **B2** and cyclohexanecarbaldehyde the title compound was obtained.

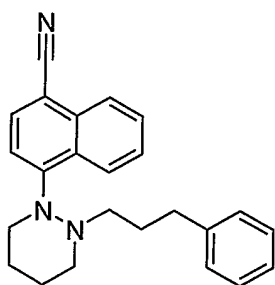
MS (m/z) ESI ES⁺ = 354

Example 147**4-[2-(3-phenylbutyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C147)**

From **B4** and 3-phenylbutanal the title compound was isolated as a yellow oil.

¹H NMR (300 MHz, METHANOL-D₄) δ ppm 1.7 (m, 8 H), 2.3 (m, 1 H), 2.7 (m, 1 H), 2.8 (m, 1 H), 3.4 (m, 5 H), 6.6 (m, 2 H), 7.0 (m, 4 H), 7.7 (m, 3 H), 8.1 (d, $J=8.3$ Hz, 1 H), 8.5 (d, $J=8.6$ Hz, 1 H)

Example 148

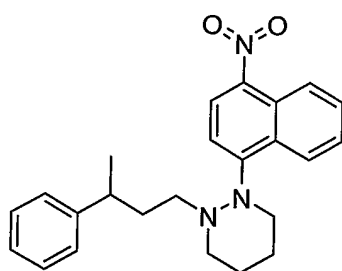


4-[2-(3-phenylpropyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C148)

From **B4** and 3-phenylpropanal the title compound was isolated as a yellow oil.

- 5 ¹H NMR (300 MHz, METHANOL-D₄) δ ppm 1.5 (m, 2 H), 1.8 (m, 4 H), 2.2 (t, $J=7.5$ Hz, 2 H), 2.9 (t, $J=6.9$ Hz, 2 H), 3.4 (m, 4 H), 6.6 (m, 2 H), 7.1 (m, 4 H), 7.6 (m, 2 H), 7.8 (d, $J=8.0$ Hz, 1 H), 8.1 (d, $J=8.3$ Hz, 1 H), 8.5 (d, $J=8.6$ Hz, 1 H)

Example 149

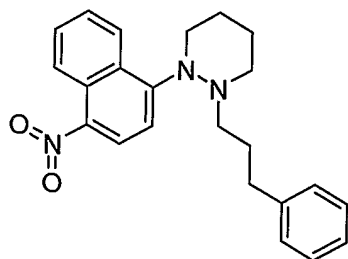


- 10 **1-(4-nitro-1-naphthalenyl)-2-(3-phenylbutyl)hexahydropyridazine (C149)**

From **B2** and 3-phenylbutanal the title compound was isolated as a red oil.

MS (m/z) APCI AP⁺ = 390

Example 150



- 15 **1-(4-nitro-1-naphthalenyl)-2-(3-phenylpropyl)hexahydropyridazine (C150)**

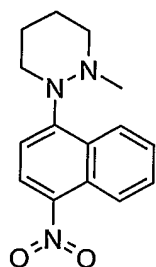
From **B2** and 3-phenylpropanal the title compound was isolated as a red oil.

112

¹H NMR (300 MHz, METHANOL-D₄) δ ppm 1.5 (m, 2 H) 1.8 (m, 4 H) 2.3 (t, $J=7.5$ Hz, 2 H) 2.9 (t, $J=6.8$ Hz, 2 H) 3.4 (m, 2 H) 3.5 (m, 2 H) 6.6 (m, 2 H) 7.1 (m, 4 H) 7.6 (m, 1 H) 7.7 (m, 1 H) 8.3 (d, $J=8.6$ Hz, 1 H) 8.4 (d, $J=9.1$ Hz, 1 H) 8.7 (d, $J=9.1$ Hz, 1 H)

Example 151

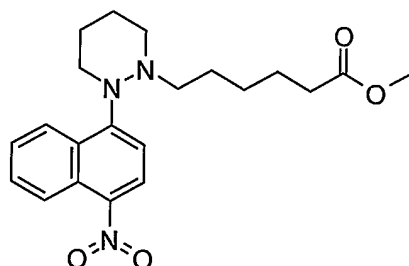
5

**1-methyl-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (C151)**

From **B2** and acetaldehyde the title compound was obtained.

MS (m/z) ESI $ES^+ = 272$

10

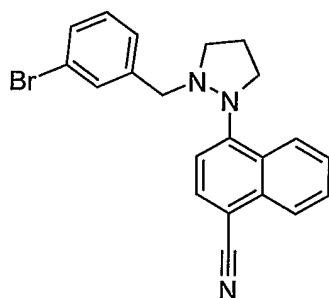
Example 152**Methyl 6-[2-(4-nitro-1-naphthalenyl)tetrahydro-1(2H)-pyridazinyl]hexanoate (C152)**

From **B2** and methyl 6-oxohexanoate the title compound was obtained.

¹H NMR (300 MHz, CHLOROFORM-D) δ ppm 1.0 (m, 2 H) 1.3 (m, 4 H) 1.8 (m, 4 H)

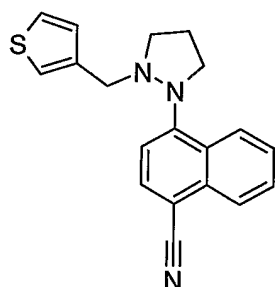
15 2.0 (m, 2 H) 2.9 (t, $J=6.9$ Hz, 2 H) 3.3 (m, 2 H) 3.5 (m, 2 H) 3.6 (s, 2 H) 7.0 (d, $J=8.8$ Hz, 1 H) 7.5 (m, 1 H) 7.7 (m, 1 H) 8.3 (d, $J=9.4$ Hz, 1 H) 8.3 (d, $J=8.6$ Hz, 1 H) 8.8 (d, $J=8.3$ Hz, 1 H)

Example 153

**4-{2-[(3-bromophenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile (C153)**

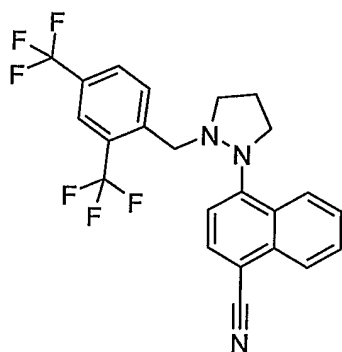
From **B5** and 3-bromobenzaldehyde the title compound was isolated as a yellow oil.

5 MS (m/z) ESI ES⁺ = 393

Example 154**4-{2-(3-thienylmethyl)-1-pyrazolidinyl}-1-naphthalenecarbonitrile (C154)**

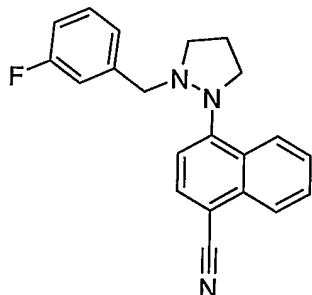
From **B5** and 3-thiophenecarbaldehyde the title compound was isolated as a yellow oil.

10 MS (m/z) ESI ES⁺ = 320

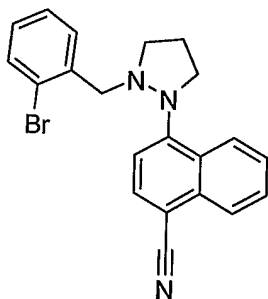
Example 155**4-{2-[[2,4-bis(trifluoromethyl)phenyl]methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile (C155)**

15 From **B5** and 2,4-bis(trifluoromethyl)benzaldehyde the title compound was isolated as a yellow solid.

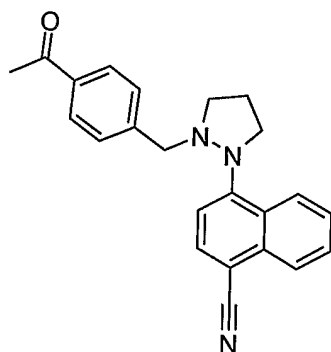
114

MS (m/z) ESI ES⁺ = 450**Example 156****4-{2-[(3-fluorophenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile (C156)**

- 5 From **B5** and 3-fluorobenzaldehyde the title compound was isolated as a yellow oil.

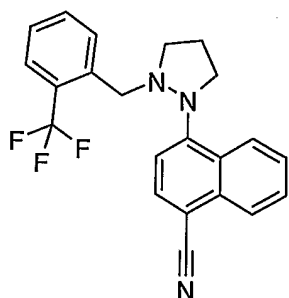
MS (m/z) ESI ES⁺ = 332**Example 157****4-{2-[(2-bromophenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile (C157)**

- 10 From **B5** and 2-bromobenzaldehyde the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 393**Example 158****4-{2-[(4-acetylphenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile (C158)**

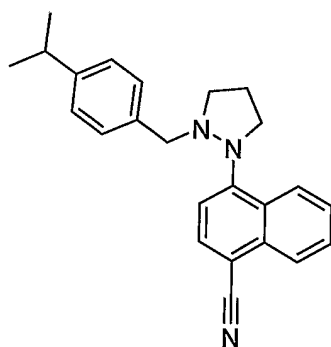
- 15 From **B5** and 4-acetylbenzaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 356

Example 159**4-(2-([2-(trifluoromethyl)phenyl]methyl)-1-pyrazolidinyl)-1-naphthalenecarbonitrile (C159)**

- 5 From **B5** and 2-(trifluoromethyl)benzaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 382

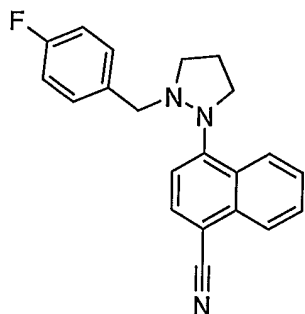
Example 160

- 10 **4-(2-([4-(1-methylethyl)phenyl]methyl)-1-pyrazolidinyl)-1-naphthalenecarbonitrile (C160)**

From **B5** and 4-(1-methylethyl)benzaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 356

- 15 **Example 161**

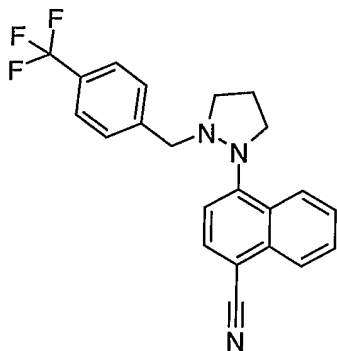


116

4-{2-[(4-fluorophenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile (C161)

From **B5** and 4-fluorobenzaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 332

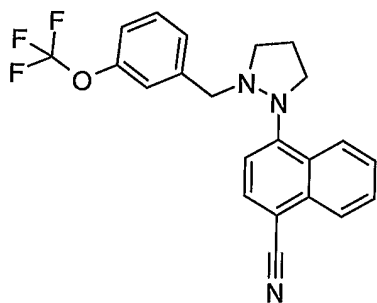
Example 162

5

4-(2-[(4-(trifluoromethyl)phenyl)methyl]-1-pyrazolidinyl)-1-naphthalenecarbonitrile (C162)

From **B5** and 4-(trifluoromethyl)benzaldehyde the title compound was isolated as a yellow oil.

10 MS (m/z) ESI ES⁺ = 382

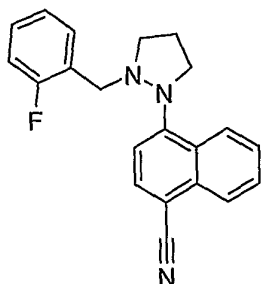
Example 163**4-[2-({3-[(trifluoromethyl)oxy]phenyl}methyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile (C163)**

15 From **B5** and 3-[(trifluoromethyl)oxy]benzaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 398

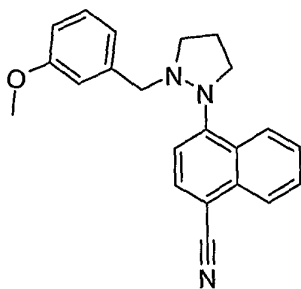
Example 164

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**4-{2-[(2-fluorophenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile (C164)**

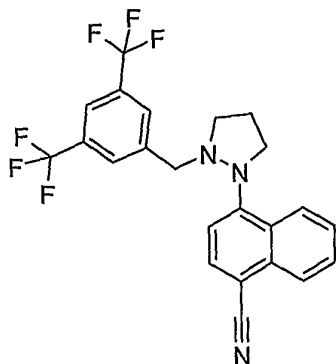
From **B5** and 3-fluorobenzaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 332

5 Example 165**4-(2-[[3-(methoxy)phenyl]methyl]-1-pyrazolidinyl)-1-naphthalenecarbonitrile (C165)**

From **B5** and 3-(methoxy)benzaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 344

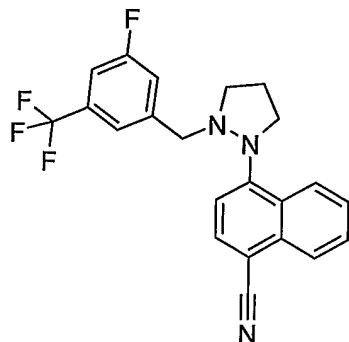
Example 166**4-(2-[[3,5-bis(trifluoromethyl)phenyl]methyl]-1-pyrazolidinyl)-1-naphthalenecarbonitrile (C166)**

118

From **B5** and 3,5-bis(trifluoromethyl)benzaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 450

Example 167



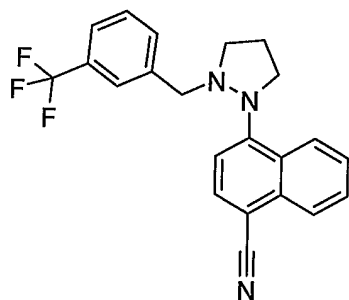
5

4-(2-([3-fluoro-5-(trifluoromethyl)phenyl]methyl)-1-pyrazolidinyl)-1-naphthalenecarbonitrile (C167)

From **B5** and 3-fluoro-5-(trifluoromethyl)benzaldehyde the title compound was isolated as a yellow oil.

10 MS (m/z) ESI ES⁺ = 400

Example 168



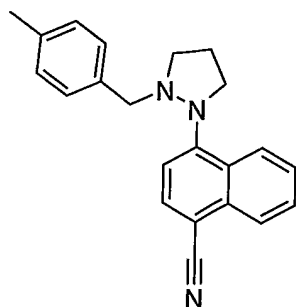
4-(2-(3-(trifluoromethyl)phenyl)methyl)-1-pyrazolidinyl)-1-naphthalenecarbonitrile (C168)

15 From **B5** and 3-(trifluoromethyl)benzaldehyde the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 382

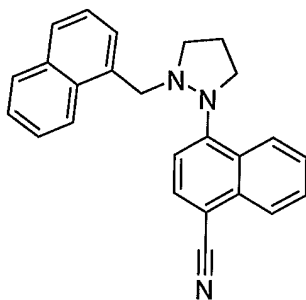
Example 169

119

**4-[2-[(4-methylphenyl)methyl]-1-pyrazolidinyl]-1-naphthalenecarbonitrile (C169)**

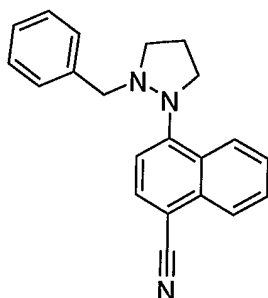
From **B5** and 4-methylbenzaldehyde the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 328

5 Example 170**4-[2-(1-naphthalenylmethyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile (C170)**

From **B5** and 1-naphthalenecarbaldehyde the title compound was isolated as a yellow solid.

10 MS (m/z) ESI ES⁺ = 364

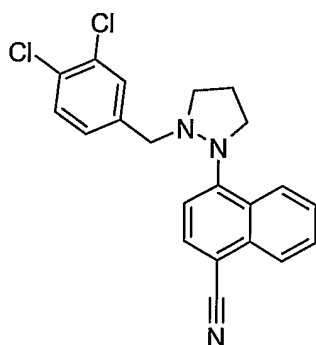
Example 171**4-[2-(phenylmethyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile (C171)**

From **B5** and benzaldehyde the title compound was isolated as a yellow oil.

15 MS (m/z) ESI ES⁺ = 314

Example 172

120

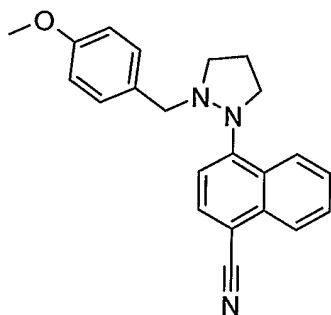


**4-{2-[(3,4-dichlorophenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile
(C172)**

From **B5** and 3,4-dichlorobenzaldehyde the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 383

Example 173

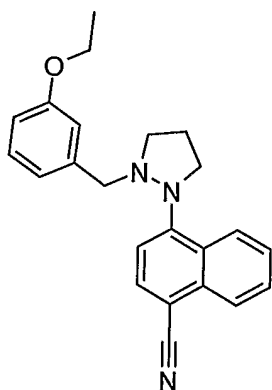


**4-{2-[4-(methoxy)phenyl]methyl}-1-pyrazolidinyl}-1-naphthalenecarbonitrile
(C173)**

From **B5** and 4-(methoxy)benzaldehyde the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 344

Example 174

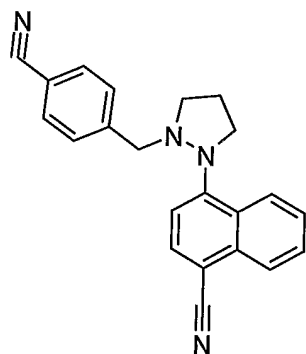


4-(2-([3-(ethoxy)phenyl]methyl)-1-pyrazolidinyl)-1-naphthalenecarbonitrile (C174)

From **B5** and 3-(ethoxy)benzaldehyde the title compound was isolated as a yellow oil.

5 MS (m/z) ESI $ES^+ = 358$

Example 175

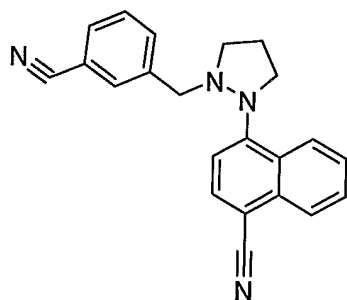


4-{2-[(4-cyanophenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile (C175)

From **B5** and 4-cyanobenzaldehyde the title compound was isolated as a yellow solid.

10 MS (m/z) ESI $ES^+ = 339$

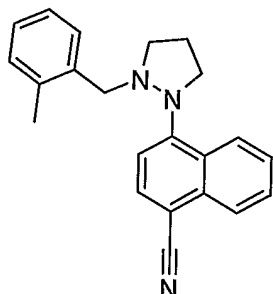
Example 176



4-{2-[(3-cyanophenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile (C176)

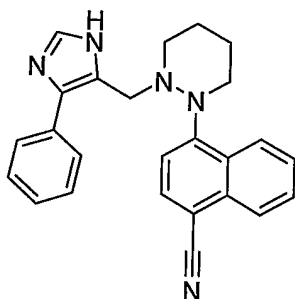
From **B5** and 3-cyanobenzaldehyde the title compound was isolated as a white solid.

122

MS (m/z) ESI ES⁺ = 339**Example 177**

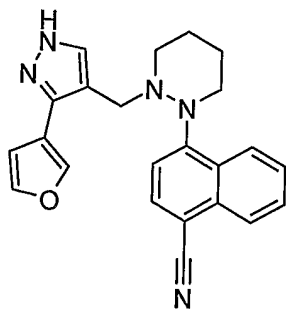
4-{2-[(2-methylphenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile (C177)

5 From **B5** and 2-methylbenzaldehyde the title compound was isolated as a white solid.

MS (m/z) ESI ES⁺ = 328**Example 178**

4-{2-[(4-phenyl-1H-imidazol-5-yl)methyl]tetrahydro-1(2H)-pyridazinyl}-1-naphthalenecarbonitrile (C178)

10 From **B1** and 4-phenyl-1H-imidazol-5-carbaldehyde the title compound was isolated as a white solid.

MS (m/z) ESI ES⁺ = 394**Example 179**

15 4-{2-[[3-(1-methylethyl)-1H-pyrazol-4-yl]methyl]tetrahydro-1(2H)-pyridazinyl}-1-naphthalenecarbonitrile (C179)

123

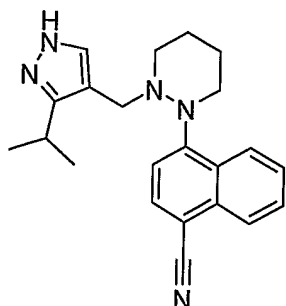
To a 250-ml round bottom flask equipped with a magnetic stir bar and nitrogen inlet was added ethyl 3-(3-furanyl)-3-oxopropanoate (1g, 5.5mmoles) followed by [bis(methyloxy)methyl]dimethylamine (10ml). The reaction was allowed to stir at room temperature overnight. The volatiles were removed *in vacuo*. The crude product (5.5 mmoles) was used without characterization or purification. To this crude product was added acetic acid (10ml) and hydrazine hydrate (0.83g, 3eq) and heated at 100 °C overnight. After cooling to room temperature, the volatiles were removed under reduced pressure. The residue was partitioned between ethyl acetate and 0.1N NaOH (pH ~10). The phases were separated and the organic fraction was washed twice with water, once with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to yield quantitative yield of crude pyrazole ester. This crude product was used without purification. The pyrazole ester (5.5 mmoles) in diethyl ether (5ml) was added dropwise to a precooled (0 °C) suspension of lithium aluminumhydride (330mg, 1.5eq) in diethyl ether (10ml). The reaction mixture was allowed to stir for 1hr at room temperature at which point 0.4ml of water was added **very slowly**, 0.4ml of 5N NaOH, and 1.2ml of water. This mixture was allowed to stir for 2hrs resulting in the precipitation of a white solid. The reaction mixture was filtered through Celite and the salts were washed with copious amounts of ethyl acetate and methanol. The filtrate was concentrated to yield 540mg (60% yield) of crude pyrazole alcohol. To the crude pyrazole alcohol was added acetone (10ml) followed by manganese dioxide (2.9g, 10eq) and the reaction was stirred at 50 °C for 4hrs. After cooling to room temperature the reaction was filtered through Celite and washed with acetone. The filtrate was concentrated to yield 300mg (56% yield) of the pyrazole aldehyde. The above aldehyde (100mg, 2eq) was coupled with **B1** (75mg, 1eq) via the reductive amination procedure outlined in Example 1 (**C1**) to yield 45mg of the title compound. MS(m/z) ESI ES⁺ = 384

The following compounds were synthesized according to a similar general procedure as used for **C179** with the following exceptions: minimal amounts of anhydrous THF were used as the co-solvent in the LiAlH₄ reaction when solubility in Et₂O was low, with certain less-reactive substrates the LiAlH₄ reduction was allowed to proceed up to 48hrs at 0 °C, and, in certain cases,

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varying amounts of over-reduction of the ester to the Me analog was observed during the LiAlH_4 reaction:

Example 180

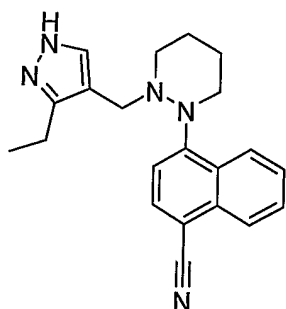


- 5 **4-[2-([3-(1-methylethyl)-1H-pyrazol-4-yl]methyl)]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C180)**

From **B1** and ethyl 4-methyl-3-oxopentanoate the title compound was obtained.

MS(m/z) ESI $\text{ES}^+ = 360$

Example 181



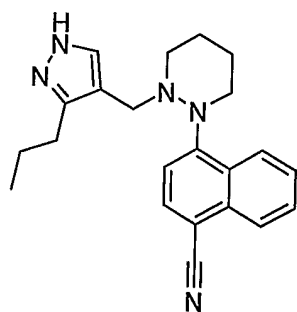
10

- 4-[2-([3-ethyl-1H-pyrazol-4-yl]methyl)]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C181)**

From **B1** and ethyl 3-oxopentanoate the title compound was obtained.

MS(m/z) ESI $\text{ES}^+ = 346$

- 15 **Example 182**



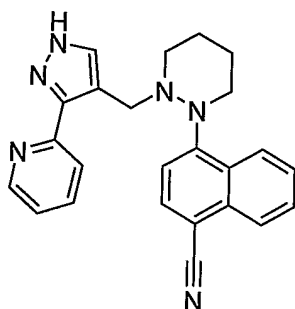
125

4-[2-[(3-propyl-1*H*-pyrazol-4-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C182)

From **B1** and ethyl 3-oxohexanoate the title compound was obtained.

MS(*m/z*) ESI ES^+ = 360

5 **Example 183**

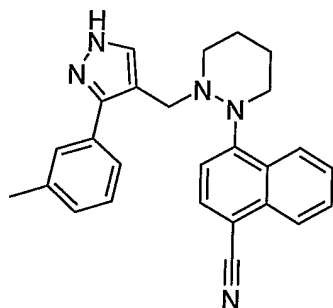


4-[2-[(3-(2-pyridinyl)-1*H*-pyrazol-4-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C183)

From **B1** and ethyl 3-oxo-3-(2-pyridinyl)propanoate the title compound was obtained.

10 MS(*m/z*) ESI ES^+ = 395

Example 184



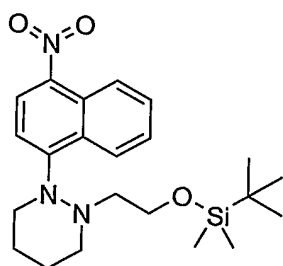
4-[2-[(3-(3-methylphenyl)-1*H*-pyrazol-4-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (C184)

15 From **B1** and ethyl 3-(3-methylphenyl)-3-oxopropanoate the title compound was obtained.

MS(*m/z*) ESI ES^+ = 408

The following compounds were synthesized according to a similar general procedure as used for Example 1 (**C1**):

20 **Example 185**



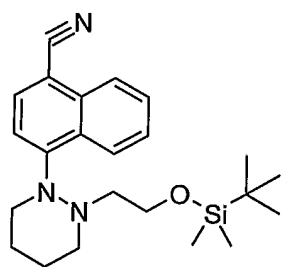
E. 1-(2-(((1,1-dimethylethyl)(dimethyl)silyl)oxy)ethyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (E1)

From **B2** and {[(1,1-dimethylethyl)(dimethyl)silyl]oxy}acetaldehyde the title compound

5 was obtained.

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm -0.1 (s, 6 H) 0.8 (s, 9 H) 1.8 (m, 4 H) 3.0 (t, $J=6.6$ Hz, 2 H) 3.3 (m, 2 H) 3.4 (t, $J=6.5$ Hz, 2 H) 3.5 (m, 2 H) 7.0 (d, $J=8.6$ Hz, 1 H) 7.5 (t, $J=7.7$ Hz, 1 H) 7.6 (t, $J=7.8$ Hz, 1 H) 8.3 (d, $J=8.6$ Hz, 2 H) 8.7 (d, $J=8.8$ Hz, 1 H)

10 **Example 186**



4-[2-(2-(((1,1-dimethylethyl)(dimethyl)silyl)oxy)ethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (E2)

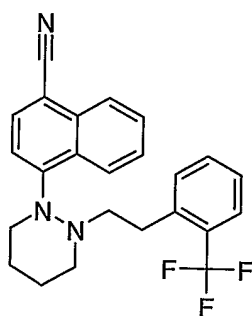
From **B1** and {[(1,1-dimethylethyl)(dimethyl)silyl]oxy}acetaldehyde the title compound

15 was obtained.

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm -0.2 (s, 6 H) 0.7 (s, 9 H) 1.8 (m, 4 H) 2.9 (t, $J=6.6$ Hz, 2 H) 3.3 (t, $J=6.6$ Hz, 2 H) 3.3 (m, 2 H) 3.4 (m, 2 H) 6.9 (d, $J=7.9$ Hz, 1 H) 7.5 (m, 1 H) 7.6 (t, $J=8.0$ Hz, 1 H) 7.8 (d, $J=8.1$ Hz, 1 H) 8.1 (d, $J=8.3$ Hz, 1 H) 8.3 (d, $J=8.8$ Hz, 1 H)

20 **Cyclic Hydrazine Reductive Amination Using Phenylacetaldehydes**

Example 187



4-[2-{2-[2-(trifluoromethyl)phenyl]ethyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C185)

To a 40ml scintillation vial was added 0.067ml of 2-[(trifluoromethyl)phenyl]ethanol (0.42 mmoles, 1eq) and 5ml dichloromethane. Then 3g of 21 wt% pyridinium chlorochromate/silica gel (Silicycle, 21wt%, 4eq) was added and the reaction was shaken on an orbital shaker overnight. The reaction was filtered, washed with 3ml diethyl ether and concentrated at room temperature at 200 mBar until approximately 3ml of volume remained. The resulting aldehyde was neither isolated nor analyzed the crude product was used in the next step below. (100% yield was assumed.)

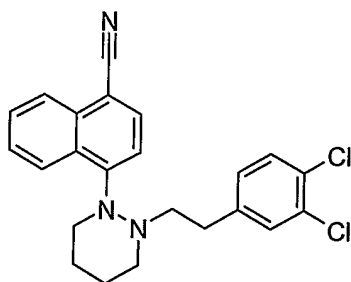
To a 40ml scintillation vial was added 66mg 4-(tetrahydro-1(2H)-pyridazinyl)-1-naphthalenecarbonitrile (**B1**) (0.278 mmoles, 1eq), 3ml ethanol, 1ml acetic acid, and the above aldehyde solution, which contains a solution of the above aldehyde in 3ml dichloromethane (0.42mmoles, 1.5eq). Then 400mg (polystyrylmethyl)trimethylammoniumcyanoborohydride resin (Novabiochem, 4.3mmol/g, 5eq) was added and the reaction was shaken on an orbital shaker overnight. The reaction was filtered and concentrated *in vacuo*. The residue was purified via preparative HPLC (Phenomenex column Luna C18, 75mm x 30mm, 5 micron), 50% acetonitrile/water (0.01% TFA) to 100% acetonitrile, to yield 36mg of the title compound as a yellow oil.

¹H NMR (400 MHz, METHANOL-D₄) δ ppm 1.8 (m, 4 H), 2.6 (t, *J*=7.2 Hz, 2 H), 3.1 (t, *J*=7.2 Hz, 2 H), 3.4 (m, 2 H), 3.4 (m, 2 H), 7.0 (m, 1 H), 7.0 (m, *J*=8.1 Hz, 1 H), 7.1 (m, 2 H), 7.4 (m, 1 H), 7.4 (m, 1 H), 7.6 (m, 1 H), 7.8 (d, *J*=7.9 Hz, 1 H), 8.0 (d, *J*=8.6 Hz, 1 H), 8.3 (d, *J*=8.8 Hz, 1 H)

The following compounds were synthesized according to the same general procedure as used to synthesize Example 187 (**C185**):

Example 188

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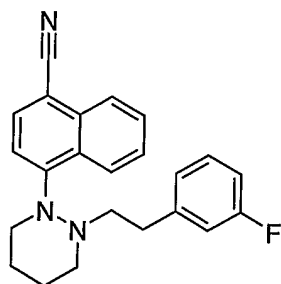


4-[2-[2-(3,4-dichlorophenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C186)

From **B1** and 2-(3,4-dichlorophenyl)ethanol the title compound was isolated as an orange solid.

MS (m/z) APCI AP^+ = 410

Example 189

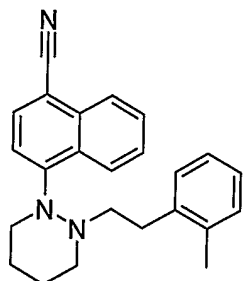


4-[2-[2-(3-fluorophenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C187)

From **B1** and 2-(3-fluorophenyl)ethanol the title compound was isolated as an orange oil.

MS (m/z) APCI AP^+ = 360

Example 190



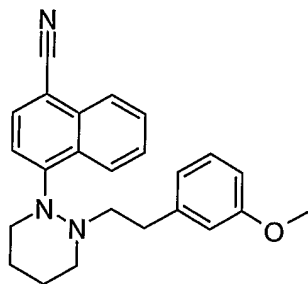
4-[2-[2-(2-methylphenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C188)

129

From **B1** and 2-(2-methylphenyl)ethanol the title compound was isolated as an orange oil.

MS (m/z) APCI AP⁺ = 356

Example 191

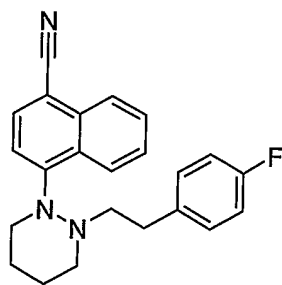


4-[2-{2-[3-(methoxy)phenyl]ethyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C189)

From **B1** and 2-[3-(methoxy)phenyl]ethanol the title compound was isolated as an orange oil.

- 10 ¹H NMR (400 MHz, METHANOL-D₄) δ ppm 1.8 (m, 4 H), 2.4 (m, 2 H), 3.2 (t, $J=7.5$ Hz, 2 H), 3.5 (t, $J=7.5$ Hz, 2 H), 3.6 (m, 3 H), 6.2 (m, 1 H), 6.3 (m, 1 H), 6.5 (m, 1 H), 6.9 (t, $J=8.0$ Hz, 1 H), 7.1 (m, 1 H), 7.4 (m, 1 H), 7.6 (m, 1 H), 7.8 (d, $J=7.7$ Hz, 1 H), 8.0 (d, $J=8.1$ Hz, 1 H), 8.3 (d, $J=9.7$ Hz, 1 H)

Example 192

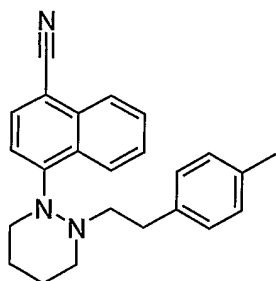


4-[2-{2-(4-fluorophenyl)ethyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C190)

From **B1** and 2-(4-fluorophenyl)ethanol the title compound was isolated as an orange oil.

- 20 ¹H NMR (400 MHz, METHANOL-D₄) δ ppm 1.8 (m, 4 H), 2.4 (m, 2 H), 3.1 (t, $J=7.0$ Hz, 2 H), 3.3 (m, 2 H), 3.4 (t, $J=7.0$ Hz, 2 H), 6.6 (m, 2 H), 6.7 (m, 2 H), 7.0 (m, 1 H), 7.4 (m,

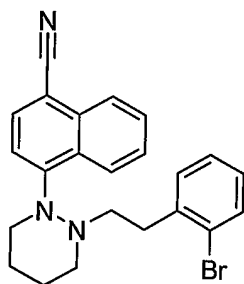
130
1 H), 7.6 (t, $J=7.2$ Hz, 1 H), 7.8 (d, $J=7.9$ Hz, 1 H), 8.0 (d, $J=8.1$ Hz, 1 H), 8.2 (d, $J=8.4$ Hz, 1 H)

Example 193

5 **4-[2-[2-(4-methylphenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C191)**

From **B1** and 2-(4-methylphenyl)ethanol the title compound was isolated as an orange oil.

1H NMR (400 MHz, METHANOL-D₄) δ ppm 1.8 (m, 4 H), 2.2 (m, 3 H), 2.4 (m, 2 H),
10 3.1 (t, $J=7.0$ Hz, 2 H), 3.3 (m, 2 H), 3.4 (t, $J=7.1$ Hz, 2 H), 6.6 (d, $J=7.9$ Hz, 2 H),
6.7 (d, $J=7.5$ Hz, 2 H), 7.0 (m, 1 H), 7.4 (m, 1 H), 7.6 (t, $J=7.5$ Hz, 1 H), 7.8 (d,
 $J=8.6$ Hz, 1 H), 8.0 (d, $J=9.5$ Hz, 1 H), 8.2 (d, $J=8.8$ Hz, 1 H)

Example 194

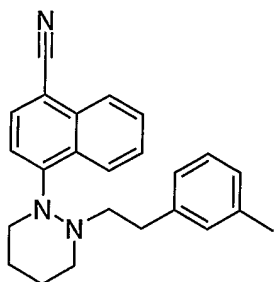
15 **4-[2-[2-(2-bromophenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C192)**

From **B1** and 2-(2-bromophenyl)ethanol the title compound was isolated as a yellow oil.

1H NMR (400 MHz, METHANOL-D₄) δ ppm 1.8 (m, 4 H) 2.5 (t, $J=7.3$ Hz, 2 H) 3.1 (t,
 $J=7.2$ Hz, 2 H) 3.4 (m, 2 H) 3.4 (m, 2 H) 6.8 (m, 2 H) 6.9 (m, 1 H) 7.0 (d, $J=7.9$ Hz, 1 H)
20 7.2 (m, 1 H) 7.4 (m, 1 H) 7.6 (m, 1 H) 7.8 (d, $J=7.9$ Hz, 1 H) 8.0 (d, $J=8.4$ Hz, 1 H) 8.3
(d, $J=8.8$ Hz, 1 H)

Example 195

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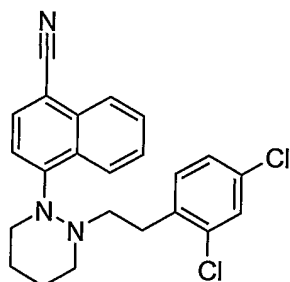


4-[2-[2-(3-methylphenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C193)

From **B1** and 2-(3-methylphenyl)ethanol the title compound was isolated as an orange oil.

¹H NMR (400 MHz, METHANOL-D₄) δ ppm 1.8 (m, 4 H), 2.1 (m, 3 H), 2.4 (m, 2 H), 3.1 (t, $J=7.3$ Hz, 2 H), 3.4 (m, 2 H), 3.5 (t, $J=7.3$ Hz, 2 H), 6.5 (m, 1 H), 6.6 (m, 1 H), 6.7 (m, 1 H), 6.8 (t, $J=7.4$ Hz, 1 H), 7.1 (m, 1 H), 7.4 (m, 1 H), 7.6 (m, 1 H), 7.8 (d, $J=6.6$ Hz, 1 H), 8.0 (d, $J=8.4$ Hz, 1 H), 8.3 (d, $J=9.0$ Hz, 1 H)

Example 196

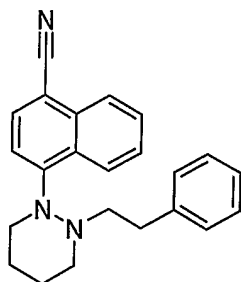


4-[2-[2-(2,4-dichlorophenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C194)

From **B1** and 2-(2,4-dichlorophenyl)ethanol the title compound was isolated as a yellow oil.

¹H NMR (400 MHz, METHANOL-D₄) δ ppm 1.8 (m, 4 H), 2.5 (t, $J=6.6$ Hz, 2 H), 3.1 (t, $J=6.5$ Hz, 2 H), 3.4 (m, 4 H), 6.7 (m, 2 H), 6.8 (d, $J=1.8$ Hz, 1 H), 6.9 (m, $J=8.1$ Hz, 1 H), 7.3 (m, 1 H), 7.6 (m, 1 H), 7.7 (d, $J=7.9$ Hz, 1 H), 8.0 (d, $J=8.2$ Hz, 1 H), 8.1 (d, $J=8.2$ Hz, 1 H)

Example 197

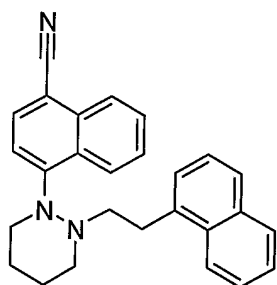


4-[2-(2-phenylethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C195)

From **B1** and 2-(phenyl)ethanol the title compound was isolated as an orange oil.

¹H NMR (400 MHz, METHANOL-D₄) δ ppm 1.8 (m, 4 H) 2.5 (m, 2 H) 3.2 (t, $J=7.3$ Hz, 2 H) 3.4 (m, 2 H) 3.5 (m, 2 H) 6.8 (m, 2 H) 7.0 (m, 3 H) 7.1 (m, 1 H) 7.5 (m, 1 H) 7.6 (m, 1 H) 7.8 (d, $J=8.4$ Hz, 1 H) 8.0 (d, $J=8.6$ Hz, 1 H) 8.3 (d, $J=8.2$ Hz, 1 H)

Example 198

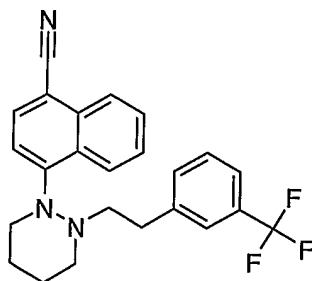


4-[2-[2-(1-naphthalenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C196)

From **B1** and 2-(1-naphthalenyl)ethanol the title compound was isolated as a red oil.

MS (m/z) APCI AP⁺ = 392

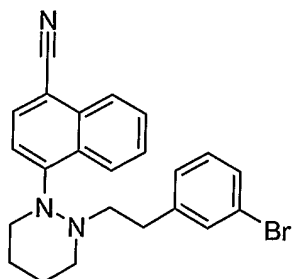
Example 199



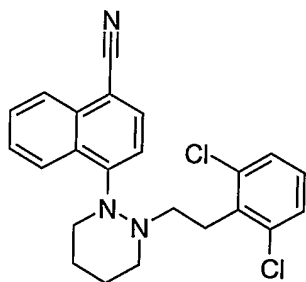
4-[2-[2-[3-(trifluoromethyl)phenyl]ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C197)

From **B1** and 2-[3-(trifluoromethyl)phenyl]ethanol the title compound was isolated as a red oil.

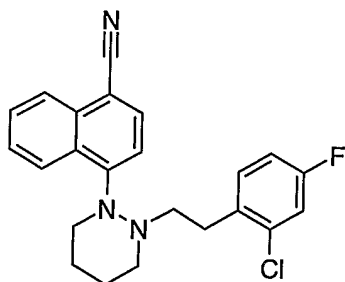
133

MS (m/z) APCI AP⁺ = 410**Example 200****4-[2-[2-(3-bromophenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C198)**

From **B1** and 2-(3-bromophenyl)ethanol the title compound was isolated as an orange oil.

MS (m/z) APCI AP⁺ = 421**Example 201****4-[2-[2-(2,6-dichlorophenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C199)**

From **B1** and 2-(2,6-dichlorophenyl)ethanol the title compound was isolated as a yellow oil.

MS (m/z) APCI AP⁺ = 410**Example 202**

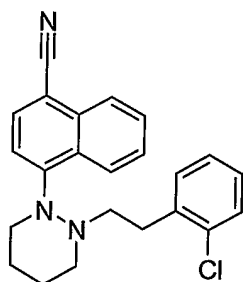
134

4-[2-[2-(2-chloro-4-fluorophenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C200)

From **B1** and 2-(2-chloro-4-fluorophenyl)ethanol the title compound was isolated as a red oil.

5 MS (m/z) APCI AP⁺ = 394

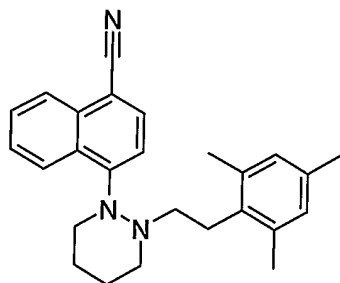
Example 203



4-[2-[2-(2-chlorophenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C201)

10 From **B1** and 2-(2-chlorophenyl)ethanol the title compound was isolated as a red oil.
MS (m/z) APCI AP⁺ = 376

Example 204



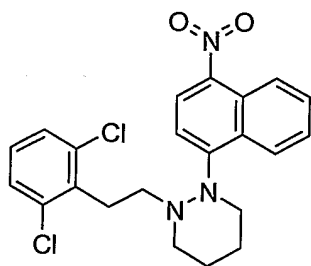
4-[2-[2-(2,4,6-trimethylphenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C202)

15 From **B1** and 2-(2,4,6-trimethylphenyl)ethanol the title compound was isolated as an orange oil.

MS (m/z) APCI AP⁺ = 384

Example 205

135

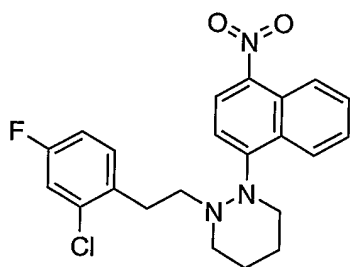


1-[2-(2,6-dichlorophenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (C203)

From **B2** and 2-(2,6-dichlorophenyl)ethanol the title compound was isolated as a red oil.

5 MS (m/z) APCI AP⁺ = 430

Example 206

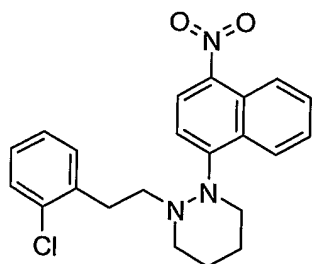


1-[2-(2-chloro-4-fluorophenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (C204)

10 From **B2** and 2-(2-chloro-4-fluorophenyl)ethanol the title compound was isolated as a red oil.

MS (m/z) APCI AP⁺ = 414

Example 207



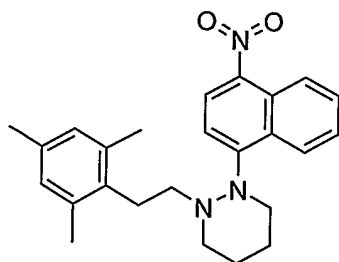
15 **1-[2-(2-chlorophenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (C205)**

From **B2** and 2-(2-chlorophenyl)ethanol the title compound was isolated as a red oil.

MS (m/z) APCI AP⁺ = 396

Example 208

136

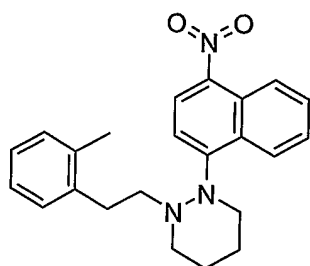


1-(4-nitro-1-naphthalenyl)-2-[2-(2,4,6-trimethylphenyl)ethyl]hexahydropyridazine (C206)

From **B2** and 2-(2,4,6-trimethylphenyl)ethanol the title compound was isolated as a red oil.

MS (m/z) APCI AP⁺ = 404

Example 209

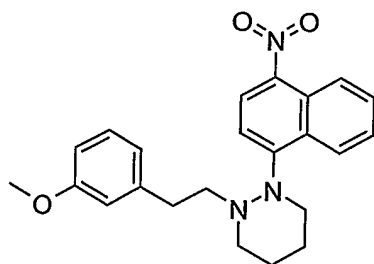


1-[2-(2-methylphenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (C207)

From **B2** and 2-(2-methylphenyl)ethanol the title compound was isolated as a red oil.

MS (m/z) APCI AP⁺ = 376

Example 210



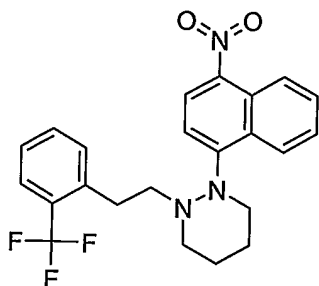
1-{2-[3-(methoxy)phenyl]ethyl}-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (C208)

From **B2** and 2-[3-(methoxy)phenyl]ethanol the title compound was isolated as a red oil.

MS (m/z) APCI AP⁺ = 392

Example 211

137

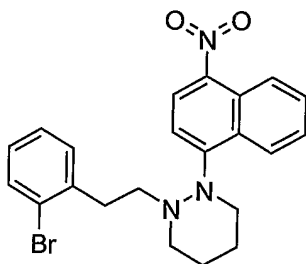


1-(4-nitro-1-naphthalenyl)-2-{2-[2-(trifluoromethyl)phenyl]ethyl}hexahydropyridazine (C209)

From **B2** and 2-[2-(trifluoromethyl)phenyl]ethanol the title compound was isolated as a red oil.

MS (m/z) APCI AP⁺ = 430

Example 212

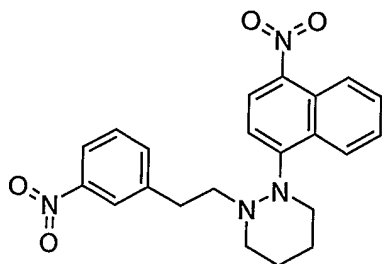


1-[2-(2-bromophenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (C210)

From **B2** and 2-(2-bromophenyl)ethanol the title compound was isolated as a red oil.

MS (m/z) APCI AP⁺ = 441

Example 213



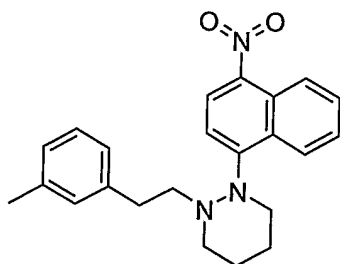
1-(4-nitro-1-naphthalenyl)-2-[2-(3-nitrophenyl)ethyl]hexahydropyridazine (C211)

From **B2** and 2-(3-nitrophenyl)ethanol the title compound was isolated as a red oil.

MS (m/z) APCI AP⁺ = 407

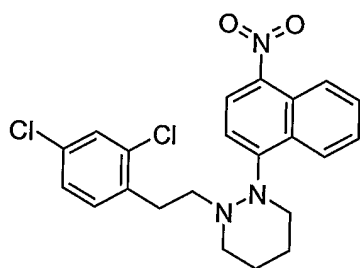
Example 214

138

**1-[2-(3-methylphenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (C212)**

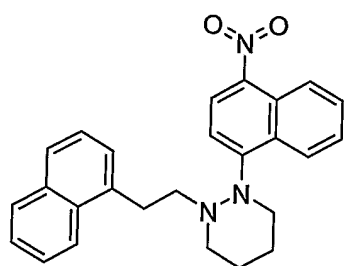
From **B2** and 2-(3-methylphenyl)ethanol the title compound was isolated as a red oil.

MS (m/z) APCI AP⁺ = 376

5 Example 215**1-[2-(2,4-dichlorophenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (C213)**

From **B2** and 2-(2,4-dichlorophenyl)ethanol the title compound was isolated as a red oil.

10 MS (m/z) APCI AP⁺ = 430

Example 216**1-[2-(1-naphthalenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (C214)**

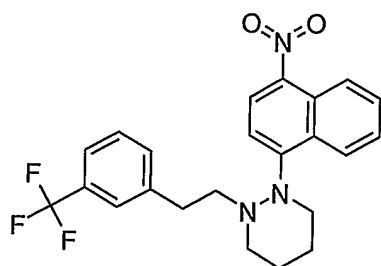
From **B2** and 2-(1-naphthalenyl)ethanol the title compound was isolated as an orange solid.

15

MS (m/z) APCI AP⁺ = 412

Example 217

139

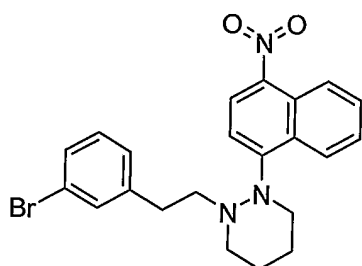


1-(4-nitro-1-naphthalenyl)-2-{2-[3-(trifluoromethyl)phenyl]ethyl}hexahydropyridazine (C215)

From **B2** and 2-[3-(trifluoromethyl)phenyl]ethanol the title compound was isolated as an orange oil.

MS (m/z) APCI AP⁺ = 430

Example 218

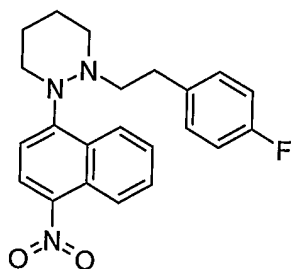


1-[2-(3-bromophenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (C216)

From **B2** and 2-(3-bromophenyl)ethanol the title compound was isolated as an orange oil.

MS (m/z) APCI AP⁺ = 441

Example 219

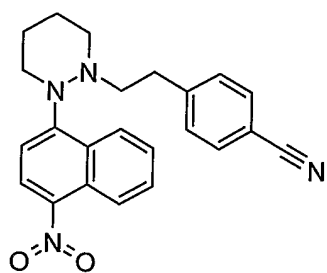


1-[2-(4-fluorophenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (C217)

From **B2** and 2-(4-fluorophenyl)ethanol the title compound was obtained.

140

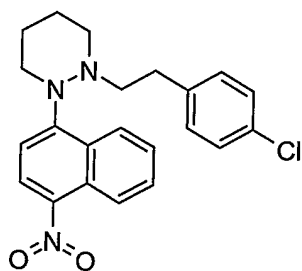
¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 2.0 (m, 4 H) 2.8 (m, 2 H) 3.2 (m, 2 H) 3.6 (m, 4 H) 6.6 (dd, $J=8.4, 5.3$ Hz, 2 H) 6.8 (m, 2 H) 7.7 (m, 1 H) 7.8 (m, 1 H) 7.9 (m, 1 H) 8.4 (d, $J=8.4$ Hz, 1 H) 8.6 (d, $J=8.6$ Hz, 1 H)

Example 220

4-{2-[2-(4-nitro-1-naphthalenyl)tetrahydro-1(2H)-pyridazinyl]ethyl}benzonitrile (C218)

From **B2** and 2-(4-cyanophenyl)ethanol the title compound was obtained.

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 2.1 (m, 4 H) 2.9 (m, 2 H) 3.3 (m, 2 H) 3.5 (m, 2 H) 3.7 (m, 2 H) 6.8 (d, $J=8.3$ Hz, 2 H) 7.3 (d, $J=8.1$ Hz, 2 H) 7.6 (t, $J=7.6$ Hz, 1 H) 7.8 (m, 1 H) 7.9 (m, 1 H) 8.3 (d, $J=8.3$ Hz, 1 H) 8.3 (d, $J=8.4$ Hz, 1 H) 8.6 (d, $J=8.6$ Hz, 1 H)

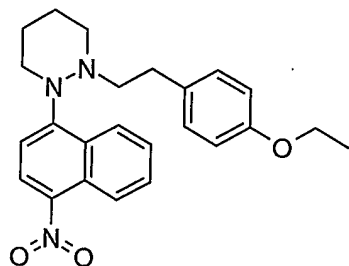
Example 221

1-[2-(4-chlorophenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (C219)

From **B2** and 2-(4-chlorophenyl)ethanol the title compound was obtained.

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 2.0 (m, 4 H) 2.7 (m, 2 H) 3.2 (m, 2 H) 3.6 (m, 4 H) 6.6 (d, $J=8.3$ Hz, 2 H) 7.0 (m, 2 H) 7.6 (m, 1 H) 7.7 (m, 2 H) 8.3 (m, 2 H) 8.6 (d, $J=8.8$ Hz, 1 H)

Example 222

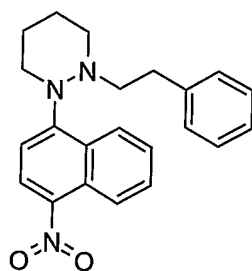


1-{2-[4-(ethyloxy)phenyl]ethyl}-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (C220)

From **B2** and 2-[4-(ethyloxy)phenyl]ethanol the title compound was obtained.

- 5 ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.4 (t, $J=7.0$ Hz, 3 H) 1.8 (m, 4 H) 2.5 (m, 2 H) 3.1 (m, 2 H) 3.3 (m, 2 H) 3.6 (m, 2 H) 3.9 (q, $J=7.1$ Hz, 2 H) 6.6 (m, 2 H) 6.8 (m, 2 H) 7.0 (d, $J=8.8$ Hz, 1 H) 7.4 (m, 1 H) 7.6 (m, 1 H) 8.2 (dd, $J=8.7, 0.8$ Hz, 1 H) 8.3 (d, $J=8.8$ Hz, 1 H) 8.8 (d, $J=8.3$ Hz, 1 H)

Example 223



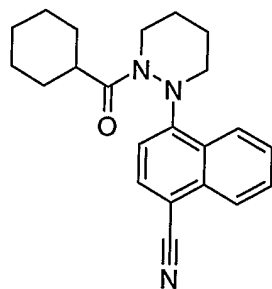
1-(4-nitro-1-naphthalenyl)-2-(2-phenylethyl)hexahydropyridazine (C221)

From **B2** and 2-(phenyl)ethanol the title compound was obtained.

- 10 ¹H NMR (300 MHz, CHLOROFORM-D) δ ppm 1.8 (m, 4 H) 2.6 (m, 2 H) 3.2 (m, 2 H) 3.3 (m, 2 H) 3.6 (m, 2 H) 6.9 (m, 2 H) 7.0 (d, $J=8.8$ Hz, 1 H) 7.1 (m, 3 H) 7.5 (m, 1 H) 7.7 (m, 1 H) 8.2 (d, $J=8.0$ Hz, 1 H) 8.3 (d, $J=8.6$ Hz, 1 H) 8.8 (d, $J=8.3$ Hz, 1 H)

Cyclic Hydrazine Acylations

Example 224



142

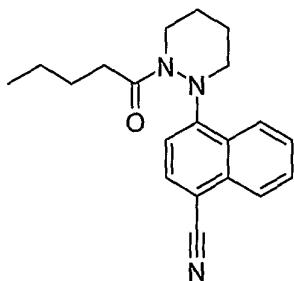
D. 4-[2-(cyclohexylcarbonyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D1)

To a 40ml scintillation vial was added 73mg 4-(tetrahydro-1(2H)-pyridazinyl)-1-naphthalenecarbonitrile (**B1**) (0.31 mmol, 1eq) and 2ml dichloromethane. Then
5 0.055 ml cyclohexanecarbonyl chloride (0.339mmol, 1.1eq) was added followed by 0.064ml triethylamine (0.462mmol, 1.5eq). The reaction was shaken on an orbital shaker overnight. The reaction mixture was concentrated *in vacuo* and the residue was purified via preparative HPLC (Phenomenex column Luna C18, 75mm x 30mm, 5 micron), 30% acetonitrile/water (0.01% TFA) to 100% acetonitrile, to yield 25mg of the
10 title compound as a yellow solid.

MS (m/z) ESI ES⁺ = 348

The following compounds were synthesized according to a similar general procedure as shown for **D1**:

15 **Example 225**

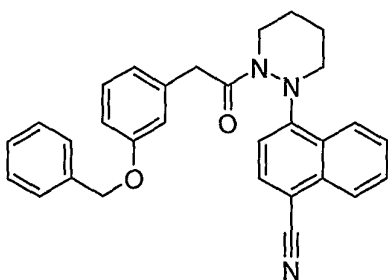


4-(2-pentanoyltetrahydro-1(2H)-pyridazinyl)-1-naphthalenecarbonitrile (D2)

From **B1** and pentanoyl chloride the title compound was isolated as an orange oil.

MS (m/z) ESI ES⁺ = 322

20 **Example 226**

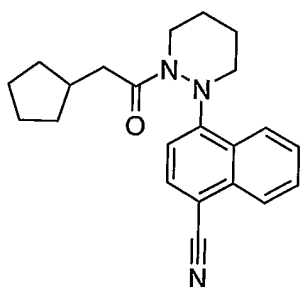


143

4-[2-({3-[(phenylmethyl)oxy]phenyl}acetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D3)

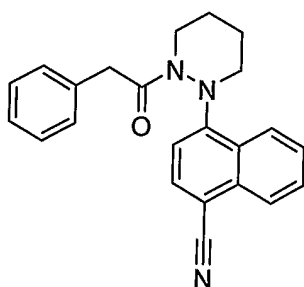
From **B1** and {3-[(phenylmethyl)oxy]phenyl}acetyl chloride the title compound was isolated as a yellow oil.

5 MS (m/z) ESI ES⁺ = 462

Example 227**4-[2-(cyclopentylacetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D4)**

10 From **B1** and cyclopentylacetyl chloride the title compound was isolated as an orange oil.

MS (m/z) ESI ES⁺ = 348

Example 228

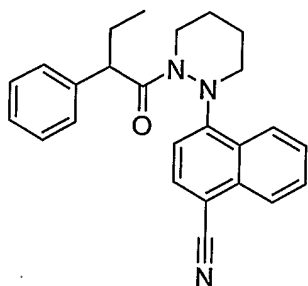
15 **4-[2-(phenylacetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D5)**

From **B1** and phenylacetyl chloride the title compound was isolated as an orange oil.

MS (m/z) ESI ES⁺ = 356

Example 229

144

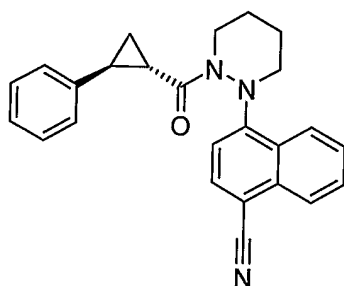


4-[2-(2-phenylbutanoyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D6)

5 From **B1** and 2-phenylbutanoyl chloride the title compound was isolated as an orange oil.

MS (m/z) ESI ES⁺ = 384

Example 230

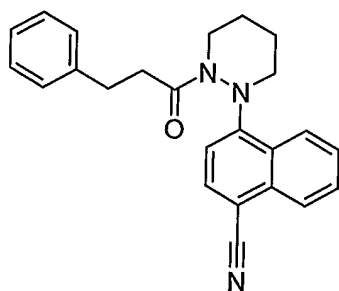


10 **4-[2-[(1S,2S)-2-phenylcyclopropyl]carbonyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D8)**

From **B1** and (1S,2S)-2-phenylcyclopropylcarbonyl chloride the title compound was isolated as an orange oil.

MS (m/z) ESI ES⁺ = 382

Example 231



15

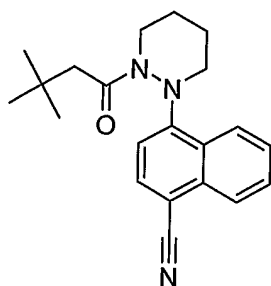
4-[2-(3-phenylpropanoyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D9)

145

From **B1** and phenylpropanoyl chloride the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 370

Example 232



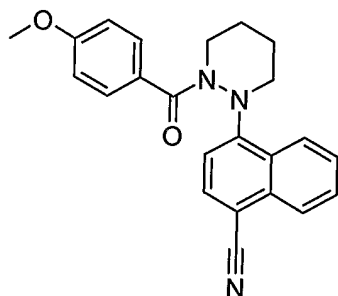
5

4-[2-(3,3-dimethylbutanoyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D10)

From **B1** and 2-3,3-dimethylbutanoyl chloride the title compound was isolated as a white solid.

10 MS (m/z) ESI ES⁺ = 336

Example 233

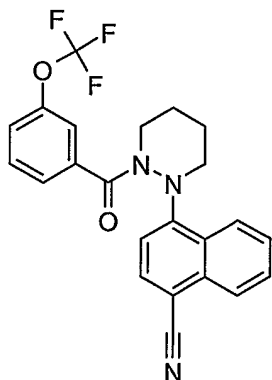


4-[2-{[4-(methyloxy)phenyl]carbonyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D11)

15 From **B1** and 4-(methyloxy)benzoyl chloride the title compound was isolated as a white solid.

MS (m/z) APCI AP⁺ = 372

Example 234

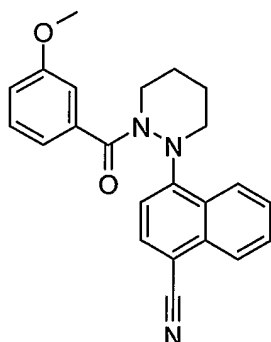


4-[2-({3-[(trifluoromethyl)oxy]phenyl}carbonyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D12)

From **B1** and 3-[(trifluoromethyl)oxy]benzoyl chloride the title compound was isolated as a white solid.

MS (m/z) APCI AP⁺ = 426

Example 235



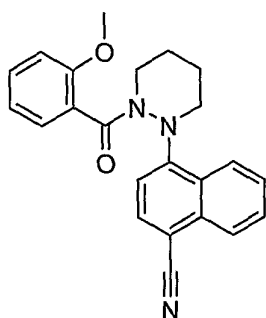
4-[2-({3-(methyloxy)phenyl}carbonyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D13)

From **B1** and 3-(methyloxy)benzoyl chloride the title compound was isolated as a white solid.

MS (m/z) APCI AP⁺ = 372

Example 236

147

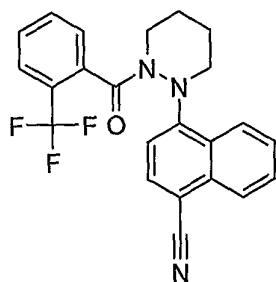


4-[2-[[2-(methoxy)phenyl]carbonyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D14)

From **B1** and 2-(methoxy)benzoyl chloride the title compound was isolated as a white solid.

MS (m/z) APCI AP⁺ = 372

Example 237

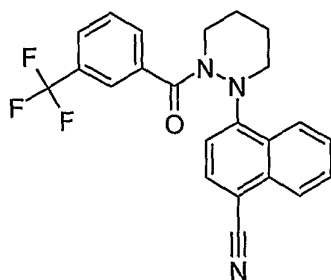


4-[2-[[2-(trifluoromethyl)phenyl]carbonyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D15)

From **B1** and 2-(trifluoromethyl)benzoyl chloride the title compound was isolated as a white solid.

MS (m/z) APCI AP⁺ = 410

Example 238



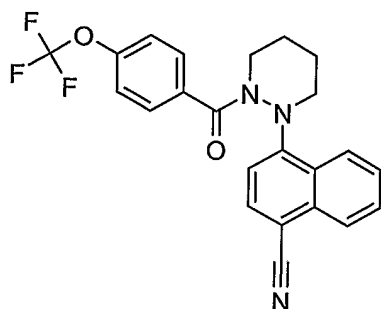
4-[2-[[3-(trifluoromethyl)phenyl]carbonyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D16)

148

From **B1** and 3-(trifluoromethyl)benzoyl chloride the title compound was isolated as a white solid.

MS (m/z) APCI AP⁺ = 410

Example 239



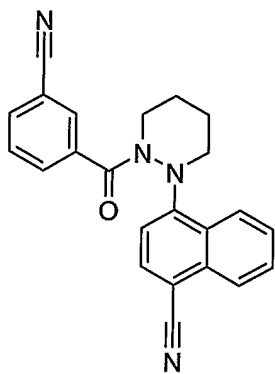
5

4-[2-({4-[(trifluoromethyl)oxy]phenyl}carbonyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D17)

From **B1** and 4-[(trifluoromethyl)oxy]benzoyl chloride the title compound was isolated as a white solid.

10 MS (m/z) APCI AP⁺ = 426

Example 240



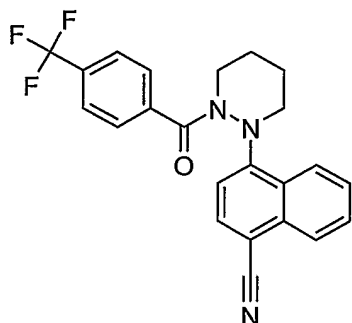
4-[2-[(3-cyanophenyl)carbonyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D18)

15 From **B1** and 3-cyanobenzoyl chloride the title compound was isolated as a white solid.

MS (m/z) APCI AP⁺ = 367

Example 241

149

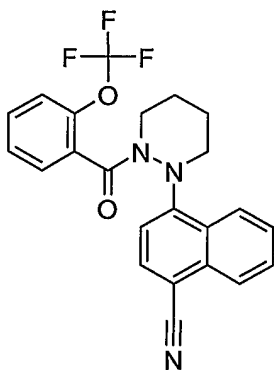


4-[2-[[4-(trifluoromethyl)phenyl]carbonyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D19)

From **B1** and 4-(trifluoromethyl)benzoyl chloride the title compound was isolated as a white solid.

MS (m/z) APCI $AP^+ = 410$

Example 242

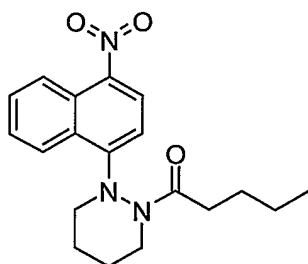


4-[2-[[2-[(trifluoromethyl)oxy]phenyl]carbonyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D20)

From **B1** and 2-[(trifluoromethyl)oxy]benzoyl chloride the title compound was isolated as a white solid.

MS (m/z) APCI $AP^+ = 426$

Example 243



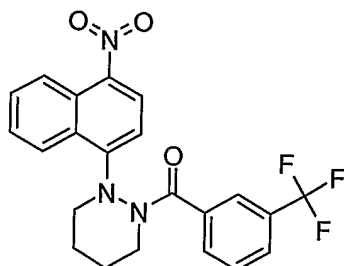
1-(4-nitro-1-naphthalenyl)-2-pentanoylhexahydropyridazine (D21)

150

From **B2** and pentanoyl chloride the title compound was isolated as a yellow solid.

MS (m/z) APCI AP⁺ = 342

Example 244

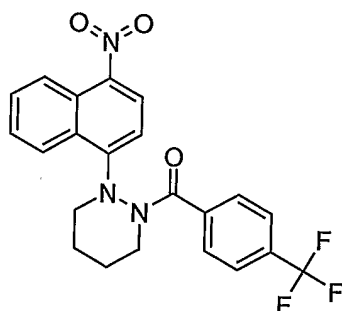


5 **1-(4-nitro-1-naphthalenyl)-2-([3-(trifluoromethyl)phenyl]carbonyl)hexahydropyridazine (D22)**

From **B2** and 3-(trifluoromethyl)benzoyl chloride the title compound was isolated as a yellow solid.

MS (m/z) APCI AP⁺ = 430

10 **Example 245**



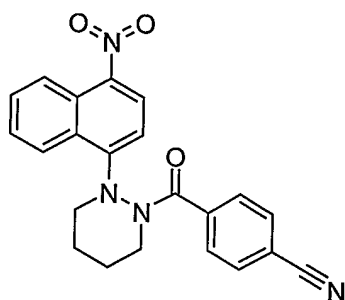
1-(4-nitro-1-naphthalenyl)-2-([4-(trifluoromethyl)phenyl]carbonyl)hexahydropyridazine (D23)

From **B2** and 4-(trifluoromethyl)benzoyl chloride the title compound was isolated as a yellow solid.

MS (m/z) APCI AP⁺ = 430

Example 246

151

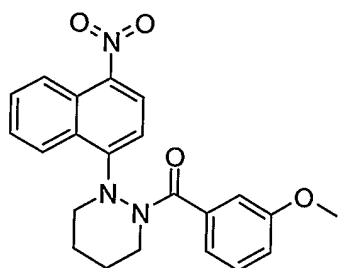


4-([2-(4-nitro-1-naphthalenyl)tetrahydro-1(2H)-pyridazinyl]carbonyl)benzonitrile (D24)

5 From **B2** and 4-cyanobenzoyl chloride the title compound was isolated as a yellow solid.

MS (m/z) APCI AP⁺ = 387

Example 247

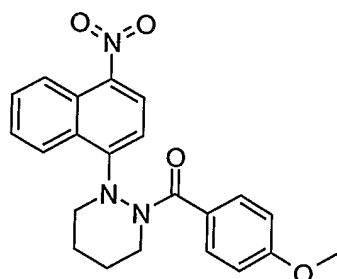


10 **1-([3-(methoxy)phenyl]carbonyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D25)**

From **B2** and 3-(methoxy)benzoyl chloride the title compound was isolated as a yellow solid.

MS (m/z) APCI AP⁺ = 392

Example 248



15

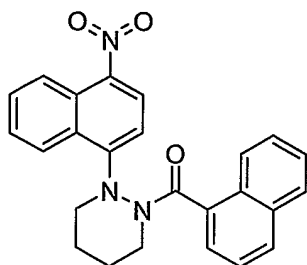
1-([4-(methoxy)phenyl]carbonyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D26)

152

From **B2** and 4-(methyloxy)benzoyl chloride the title compound was isolated as a yellow solid.

MS (m/z) APCI AP⁺ = 392

Example 249



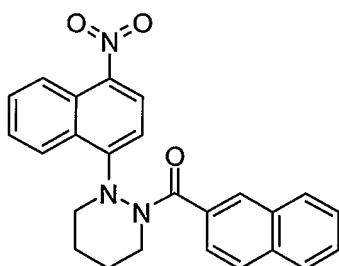
5

1-(1-naphthalenylcarbonyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D27)

From **B2** and 1-naphthalenecarbonyl chloride the title compound was isolated as a green solid.

MS (m/z) APCI AP⁺ = 412

10 **Example 250**

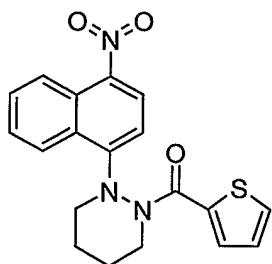


1-(2-naphthalenylcarbonyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D28)

From **B2** and 2-naphthalenecarbonyl chloride the title compound was isolated as a yellow solid.

15 MS (m/z) APCI AP⁺ = 412

Example 251



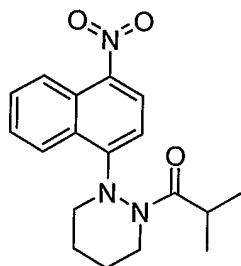
1-(4-nitro-1-naphthalenyl)-2-(2-thienylcarbonyl)hexahydropyridazine (D29)

153

From **B2** and 2-thiophenecarbonyl chloride the title compound was isolated as a yellow solid.

MS (m/z) APCI AP⁺ = 368

Example 252



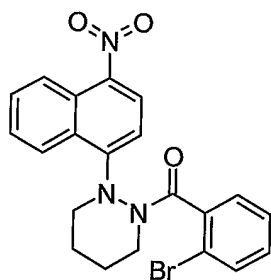
5

1-(2-methylpropanoyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D30)

From **B2** and isobutyryl chloride the title compound was isolated as a yellow solid.

MS (m/z) APCI AP⁺ = 328

Example 253



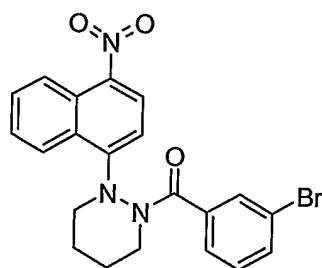
10

1-[(2-bromophenyl)carbonyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D31)

From **B2** and 2-bromobenzoyl chloride the title compound was isolated as a green solid.

MS (m/z) APCI AP⁺ = 441

Example 254



15

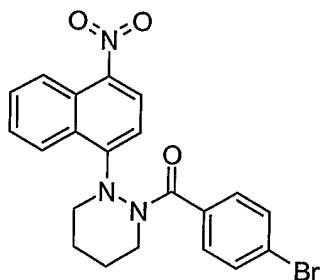
1-[(3-bromophenyl)carbonyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D32)

154

From **B2** and 3-bromobenzoyl chloride the title compound was isolated as a yellow solid.

MS (m/z) APCI AP⁺ = 441

Example 255

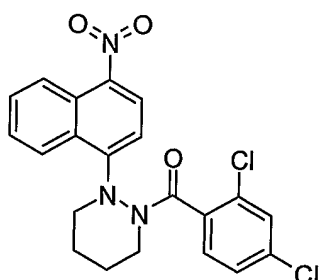


1-[(4-bromophenyl)carbonyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D33)

From **B2** and 4-bromobenzoyl chloride the title compound was isolated as a yellow solid.

MS (m/z) APCI AP⁺ = 441

Example 256

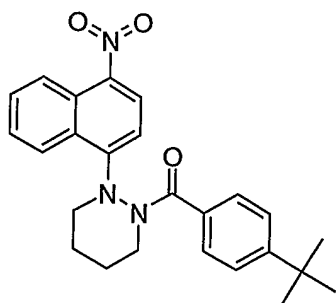


1-[(2,4-dichlorophenyl)carbonyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D34)

From **B2** and 2,4-dichlorobenzoyl chloride the title compound was isolated as a yellow solid.

MS (m/z) APCI AP⁺ = 430

Example 257



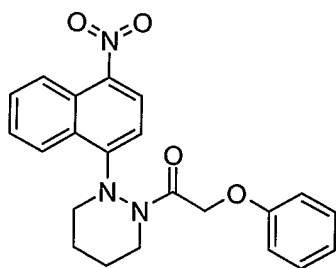
155

1-[[4-(1,1-dimethylethyl)phenyl]carbonyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D35)

From **B2** and 4-(1,1-dimethylethyl)benzoyl chloride the title compound was isolated as a yellow solid.

5 MS (m/z) APCI AP⁺ = 418

Example 258



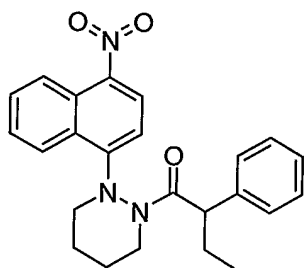
1-(4-nitro-1-naphthalenyl)-2-[(phenyloxy)acetyl]hexahydropyridazine (D36)

From **B2** and (phenyloxy)acetyl chloride the title compound was isolated as a yellow solid.

10

MS (m/z) APCI AP⁺ = 392

Example 259

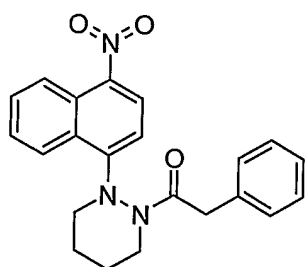


1-(4-nitro-1-naphthalenyl)-2-(2-phenylbutanoyl)hexahydropyridazine (D37)

15 From **B2** and 2-phenylbutanoyl chloride the title compound was isolated as a yellow solid.

MS (m/z) APCI AP⁺ = 404

Example 260

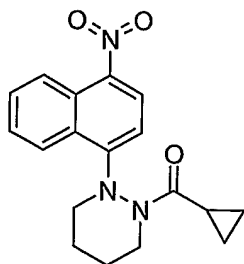


156

1-(4-nitro-1-naphthalenyl)-2-(phenylacetyl)hexahydropyridazine (D38)

From **B2** and phenylacetyl chloride the title compound was isolated as a yellow solid.

MS (m/z) APCI AP⁺ = 376

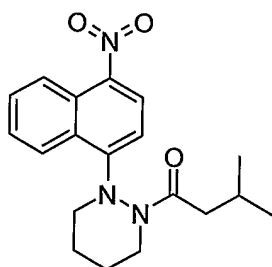
Example 261

5

1-(cyclopropylcarbonyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D39)

From **B2** and cyclopropanecarbonyl chloride the title compound was isolated as an orange solid.

MS (m/z) APCI AP⁺ = 326

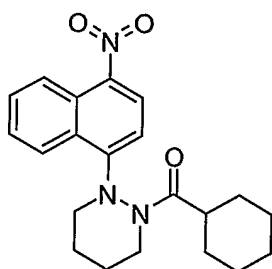
Example 262

10

1-(3-methylbutanoyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D40)

From **B2** and 3-methylbutanoyl chloride the title compound was isolated as a yellow solid.

15 MS (m/z) APCI AP⁺ = 342

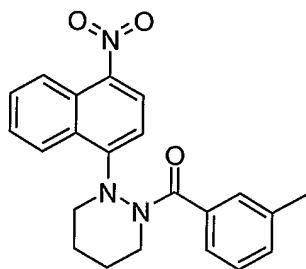
Example 263**1-(cyclohexylcarbonyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D41)**

157

From **B2** and cyclohexanecarbonyl chloride the title compound was isolated as a yellow solid.

MS (m/z) APCI AP⁺ = 368

Example 264



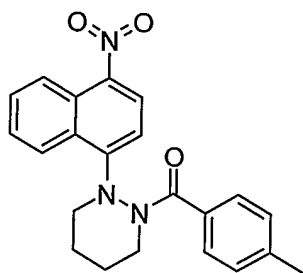
5

1-[(3-methylphenyl)carbonyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D42)

From **B2** and 3-methylbenzoyl chloride the title compound was isolated as a yellow solid.

10 MS (m/z) APCI AP⁺ = 376

Example 265

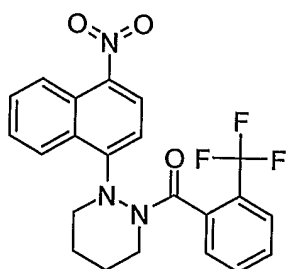


1-[(4-methylphenyl)carbonyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D43)

15 From **B2** and 4-methylbenzoyl chloride the title compound was isolated as a yellow solid.

MS (m/z) APCI AP⁺ = 376

Example 266

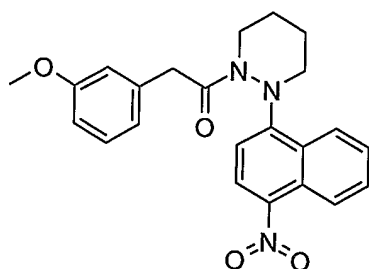


1-(4-nitro-1-naphthalenyl)-2-([2-(trifluoromethyl)phenyl]carbonyl)hexahydropyridazine (D44)

From **B2** and 2-(trifluoromethyl)benzoyl chloride the title compound was isolated as a green solid.

5 MS (m/z) APCI AP⁺ = 430

Example 267

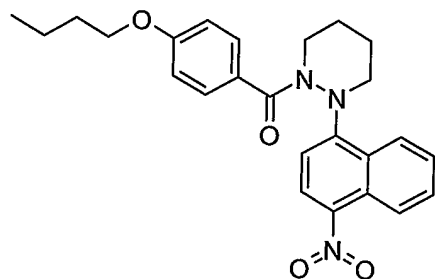


1-([3-(methyloxy)phenyl]acetyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D45)

10 From **B2** and 3-(methyloxy)phenylacetyl chloride the title compound was isolated as a yellow solid.

MS (m/z) ES⁺ = 406

Example 268

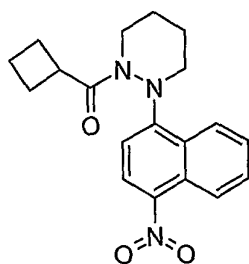


15 **1-([4-(butyloxy)phenyl]carbonyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D46)**

From **B2** and 4-(butyloxy)benzoyl chloride the title compound was isolated as a yellow oil.

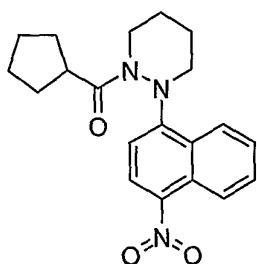
MS (m/z) ES⁺ = 434

20 **Example 269**

**1-(cyclobutylcarbonyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D47)**

From **B2** and cyclobutanecarbonyl chloride the title compound was isolated as an orange solid.

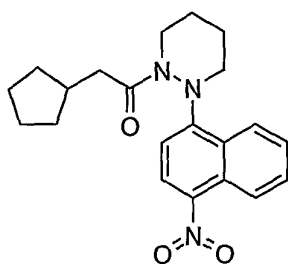
5 MS (m/z) ES^+ = 340

Example 270**1-(cyclopentylcarbonyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D48)**

From **B2** and cyclopentanecarbonyl chloride the title compound was isolated as a

10 yellow solid.

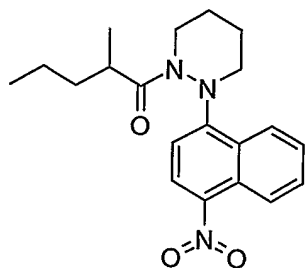
MS (m/z) ES^+ = 354

Example 271**1-(cyclopentylacetyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D49)**

15 From **B2** and cyclopentylacetyl chloride the title compound was isolated as a yellow solid.

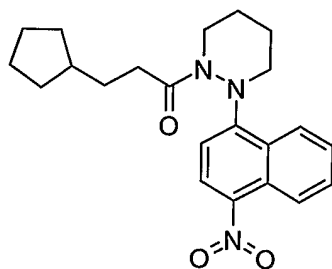
MS (m/z) ES^+ = 368

Example 272

**1-(2-methylpentanoyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D50)**

From **B2** and 2-methylpentanoyl chloride the title compound was isolated as a yellow oil.

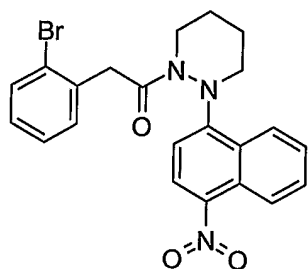
5 MS (m/z) ES^+ = 356

Example 273**1-(3-cyclopentylpropanoyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D51)**

From **B2** and cyclopentylpropanoyl chloride the title compound was isolated as a yellow oil.

10

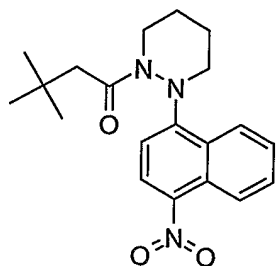
MS (m/z) ES^+ = 382

Example 274**1-[(2-bromophenyl)acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D52)**

15 From **B2** and 2-(bromophenyl)acetyl chloride the title compound was isolated as an orange oil.

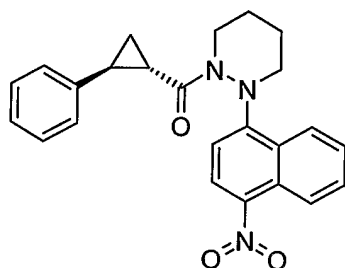
MS (m/z) ES^+ = 455

Example 275

**1-(3,3-dimethylbutanoyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D53)**

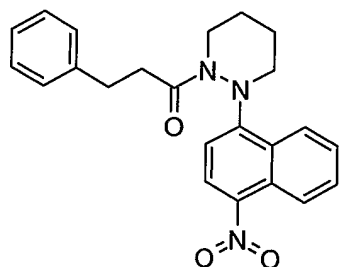
From **B2** and 3,3-dimethylbutanoyl chloride the title compound was isolated as a yellow solid.

5 MS (m/z) ES⁺ = 356

Example 276**1-(4-nitro-1-naphthalenyl)-2-([(1S,2S)-2-phenylcyclopropyl]carbonyl)hexahydropyridazine (D54)**

10 From **B2** and (1S,2S)-2-phenylcyclopropylcarbonyl chloride the title compound was isolated as an orange oil.

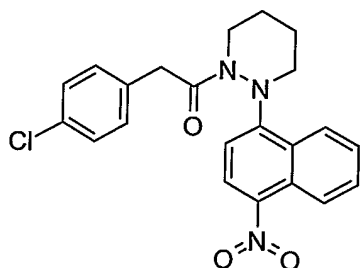
MS (m/z) ES⁺ = 402

Example 277**15 1-(4-nitro-1-naphthalenyl)-2-(3-phenylpropanoyl)hexahydropyridazine (D55)**

From **B2** and 3-phenylpropanoyl chloride the title compound was isolated as a yellow oil.

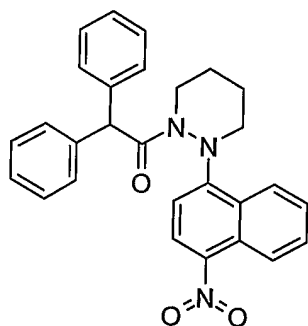
MS (m/z) ES⁺ = 390

162

Example 278**1-[(4-chlorophenyl)acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D56)**

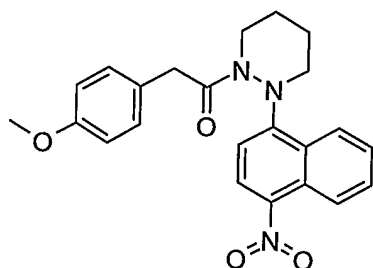
5 From **B2** and 4-(chlorophenyl)acetyl chloride the title compound was isolated as a yellow solid.

MS (m/z) ES^+ = 410

Example 279**1-(diphenylacetyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D57)**

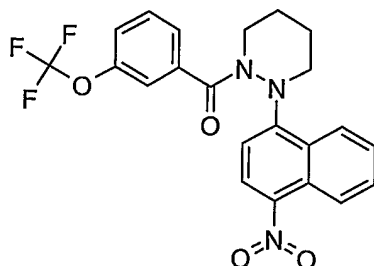
10 From **B2** and diphenylacetyl chloride the title compound was isolated as a yellow solid.

MS (m/z) ES^+ = 452

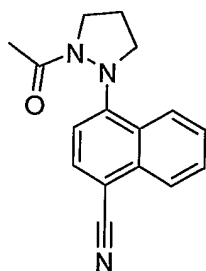
Example 280**1-[(4-(methoxy)phenyl)acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D58)**

15 From **B2** and 4-(methoxy)phenylacetyl chloride the title compound was isolated as a yellow solid.

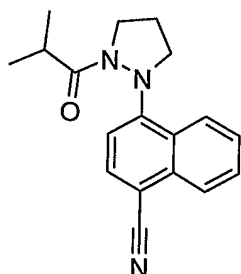
163

MS (m/z) ES⁺ = 406**Example 281****1-(4-nitro-1-naphthalenyl)-2-({3-****5 [(trifluoromethyl)oxy]phenyl}carbonyl)hexahydropyridazine (D59)**

From **B2** and 3-[(trifluoromethyl)oxy]benzoyl chloride the title compound was isolated as a yellow solid.

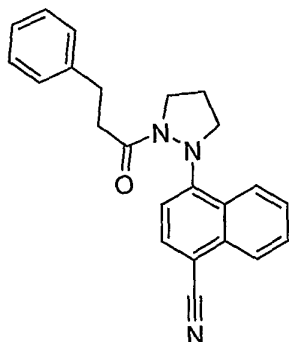
MS (m/z) ES⁺ = 446**Example 282****4-(2-acetyl-1-pyrazolidinyl)-1-naphthalenecarbonitrile (D60)**

From **B5** and acetic anhydride the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 266**Example 283****4-[2-(2-methylpropanoyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile (D61)**

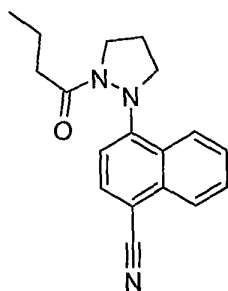
From **B5** and isobutyryl chloride the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 294

Example 284**4-[2-(3-phenylpropanoyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile (D62)**

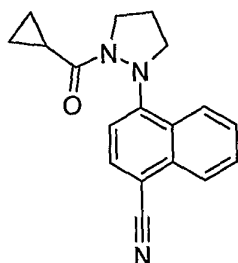
From **B5** and 3-phenylpropanoyl chloride the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 356

Example 285**4-(2-butanoyl-1-pyrazolidinyl)-1-naphthalenecarbonitrile (D63)**

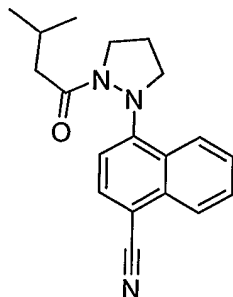
From **B5** and butanoyl chloride the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 294

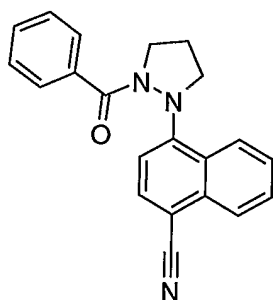
Example 286**4-[2-(cyclopropylcarbonyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile (D64)**

From **B5** and cyclopropanecarbonyl chloride the title compound was isolated as a yellow solid.

165

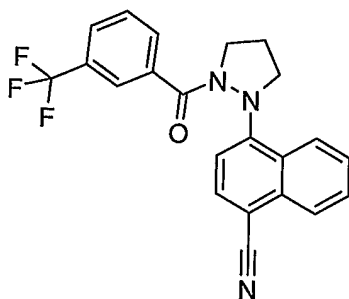
MS (m/z) ESI ES⁺ = 292**Example 287****4-[2-(3-methylbutanoyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile (D65)**

- 5 From **B5** and 3-methylbutanoyl chloride the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 308**Example 288**

10 **4-[2-(phenylcarbonyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile (D66)**

From **B5** and benzoyl chloride the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 328**Example 289**

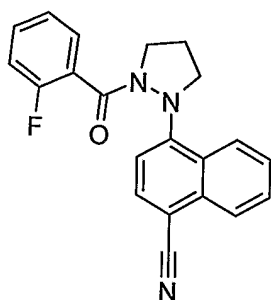
- 15 **4-(2-{{3-(trifluoromethyl)phenyl}carbonyl}-1-pyrazolidinyl)-1-naphthalenecarbonitrile (D67)**

166

From **B5** and 3-(trifluoromethyl)benzoyl chloride the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 396

Example 290



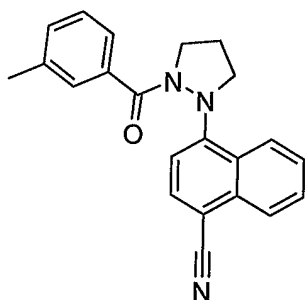
5

4-{2-[(2-fluorophenyl)carbonyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile (D68)

From **B5** and 2-fluorobenzoyl chloride the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 346

Example 291



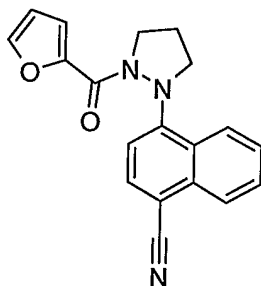
10

4-{2-[(3-methylphenyl)carbonyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile (D69)

From **B5** and 3-methylbenzoyl chloride the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 342

15 **Example 292**



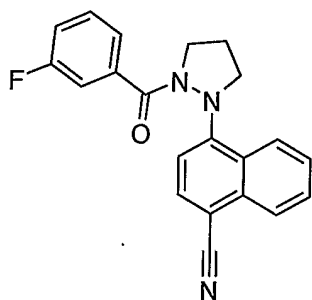
4-{2-[(2-furanylcarbonyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile (D70)

167

From **B5** and 2-furancarbonyl chloride the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 318

Example 293



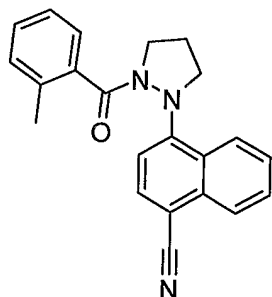
5

4-{2-[(3-fluorophenyl)carbonyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile (D71)

From **B5** and 3-fluorobenzoyl chloride the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 346

Example 294



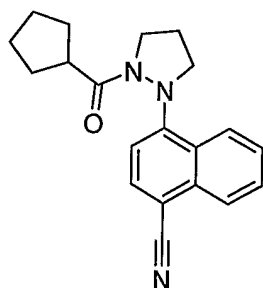
10

4-{2-[(2-methylphenyl)carbonyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile (D72)

From **B5** and 2-methylbenzoyl chloride the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 342

Example 295



15

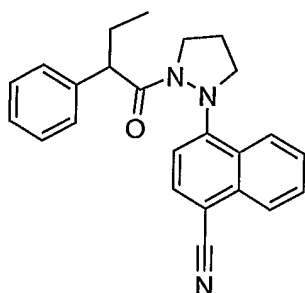
4-{2-(cyclopentylcarbonyl)-1-pyrazolidinyl}-1-naphthalenecarbonitrile (D73)

168

From **B5** and cyclopentanecarbonyl chloride the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 320

Example 296



5

4-[2-(2-phenylbutanoyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile (D74)

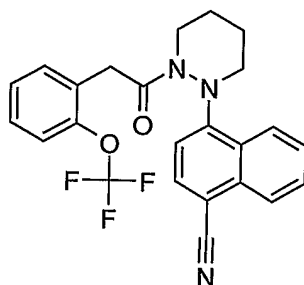
From **B5** and 2-phenylbutanoyl chloride the title compound was isolated as a white solid.

MS (m/z) ESI ES⁺ = 370

10

Hexahydropyridazine HATU-mediated Amide Couplings

Example 297



4-[2-({2-[(trifluoromethyl)oxy]phenyl}acetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D75)

- 15 To a 40ml scintillation vial was added 82mg {2-[(trifluoromethyl)oxy]phenyl}acetic acid (0.371mmoles, 1.1eq), 2ml dimethylformamide, and 0.065ml diisopropylethyl amine (0.371mmoles, 1.1eq) followed by the addition of 141mg O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 0.371mmoles, 1.1eq). The reaction mixture was shaken for 15 minutes on an orbital shaker at room temperature.
- 20 Then 80mg 4-(tetrahydro-1(2H)-pyridazinyl)-1-naphthalenecarbonitrile (**B1**) (0.337mmoles, 1eq) was added and the reaction was shaken on an orbital shaker overnight. The reaction mixture was partitioned between ethyl acetate and 1N NaOH

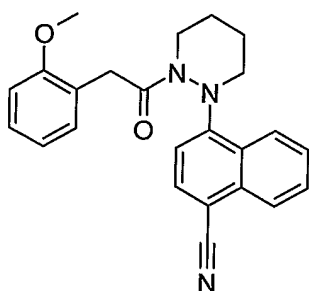
169

and the organic fraction was concentrated *in vacuo*. The residue was purified via preparative HPLC (Phenomenex column Luna C18, 75mm x 30mm, 5 micron), 30% acetonitrile/water (0.01% TFA) to 100% acetonitrile, to yield 66mg of the title compound as a white solid.

5 MS (m/z) APCI AP⁺ = 440

The following compounds were synthesized according to a similar general procedure as described for **D75**:

Example 298

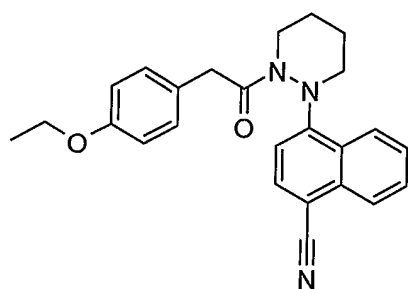


10 **4-[2-{{2-(methyloxy)phenyl}acetyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D76)**

From **B1** and [2-(methyloxy)phenyl]acetic acid the title compound was isolated as a white solid.

MS (m/z) APCI AP⁺ = 386

15 **Example 299**



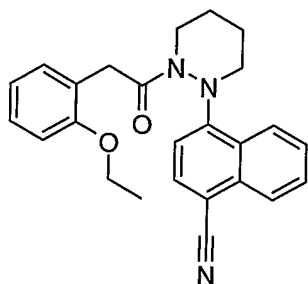
4-[2-{{4-(ethyloxy)phenyl}acetyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D77)

20 From **B1** and [4-(ethyloxy)phenyl]acetic acid the title compound was isolated as a yellow solid.

MS (m/z) APCI AP⁺ = 400

Example 300

170

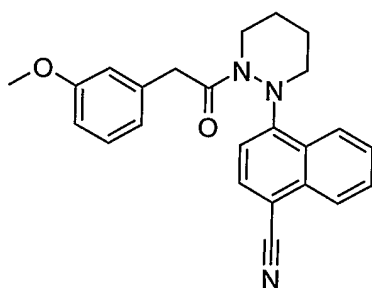


4-[2-{[2-(ethyloxy)phenyl]acetyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D78)

From **B1** and [2-(ethyloxy)phenyl]acetic acid the title compound was isolated as a yellow oil.

MS (m/z) APCI AP⁺ = 400

Example 301

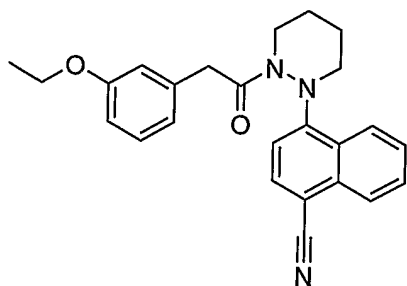


4-[2-{[3-(methyloxy)phenyl]acetyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D79)

From **B1** and [3-(methyloxy)phenyl]acetic acid the title compound was isolated as a yellow oil.

MS (m/z) APCI AP⁺ = 386

Example 302



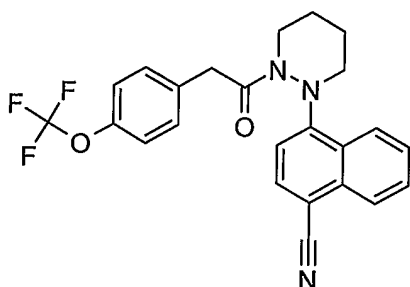
4-[2-{[3-(ethyloxy)phenyl]acetyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D80)

171

From **B1** and [3-(ethyloxy)phenyl]acetic acid the title compound was isolated as a yellow oil.

MS (m/z) APCI AP⁺ = 400

Example 303



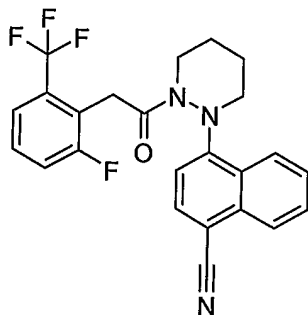
5

4-[2-({4-[(trifluoromethyl)oxy]phenyl}acetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D81)

From **B1** and {4-[(trifluoromethyl)oxy]phenyl}acetic acid the title compound was isolated as a yellow oil.

10 MS (m/z) APCI AP⁺ = 440

Example 304



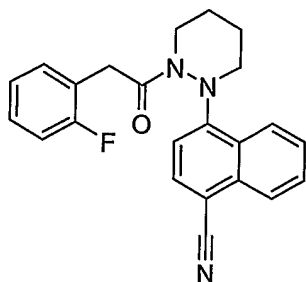
4-[2-{{2-fluoro-6-(trifluoromethyl)phenyl}acetyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D82)

15 From **B1** and [2-fluoro-6-(trifluoromethyl)phenyl]acetic acid the title compound was isolated as a yellow oil.

MS (m/z) APCI AP⁺ = 442

Example 305

172

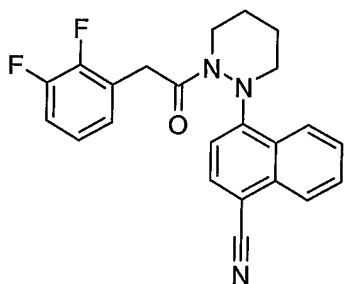


4-[2-[(2-fluorophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D83)

From **B1** and (2-fluorophenyl)acetic acid the title compound was isolated as a white solid.

MS (m/z) APCI AP⁺ = 374

Example 306

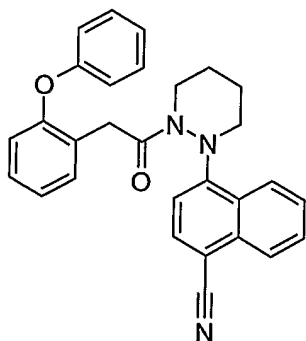


4-[2-[(2,3-difluorophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D84)

From **B1** and (2,3-difluorophenyl)acetic acid the title compound was isolated as a white solid.

MS (m/z) APCI AP⁺ = 392

Example 307

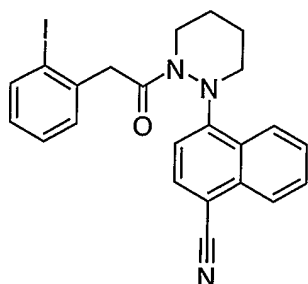


173

4-[2-[[2-(phenyloxy)phenyl]acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D85)

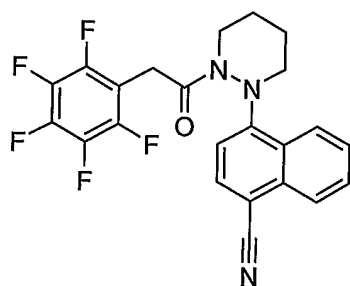
From **B1** and [2-(phenyloxy)phenyl]acetic acid the title compound was isolated as a white solid.

5 MS (m/z) APCI AP⁺ = 448

Example 308**4-[2-[(2-iodophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D86)**

10 From **B1** and (2-iodophenyl)acetic acid the title compound was isolated as a white solid.

MS (m/z) APCI AP⁺ = 482

Example 309

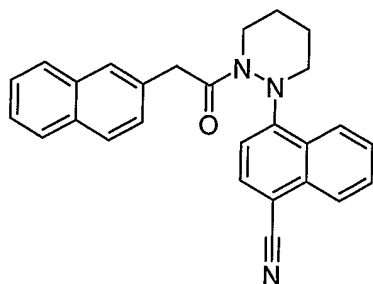
15 **4-[2-[(pentafluorophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D87)**

From **B1** and (pentafluorophenyl)acetic acid the title compound was isolated as a clear oil.

MS (m/z) APCI AP⁺ = 446

20 **Example 310**

174

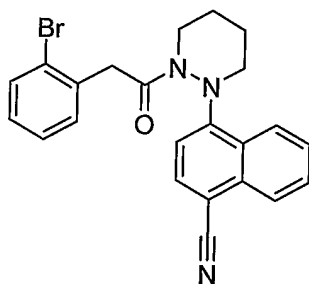


4-[2-(2-naphthalenylacetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D88)

From **B1** and (2-naphthalenyl)acetic acid the title compound was isolated as a white solid.

MS (m/z) APCI AP⁺ = 406

Example 311

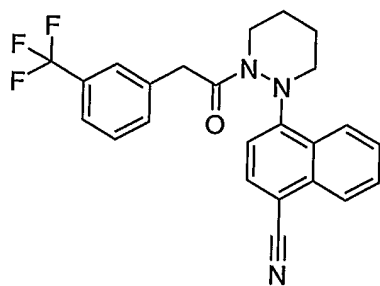


4-[2-[(2-bromophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D89)

From **B1** and (2-bromophenyl)acetic acid the title compound was isolated as a white solid.

MS (m/z) APCI AP⁺ = 435

Example 312



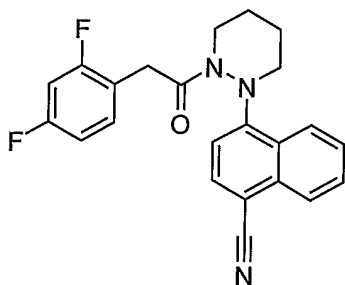
4-[2-[[3-(trifluoromethyl)phenyl]acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D90)

175

From **B1** and [3-(trifluoromethyl)phenyl]acetic acid the title compound was isolated as a white solid.

MS (m/z) APCI AP⁺ = 424

Example 313



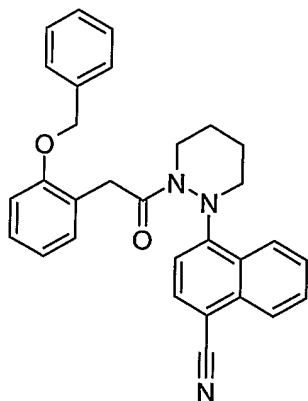
5

4-[2-[(2,4-difluorophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D91)

From **B1** and (2,4-difluorophenyl)acetic acid the title compound was isolated as a white solid.

10 MS (m/z) APCI AP⁺ = 392

Example 314



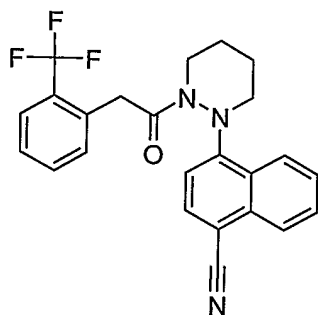
4-[2-[(2-{[phenylmethyl]oxy}phenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D92)

15 From **B1** and {2-[phenylmethyl(oxy)]phenyl}acetic acid the title compound was isolated as a yellow oil.

MS (m/z) APCI AP⁺ = 462

Example 315

176

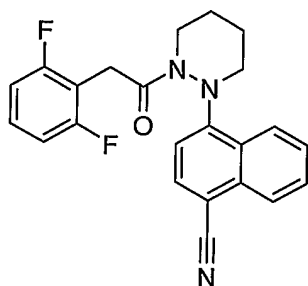


4-[2-[(2,4,6-trifluorophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D93)

From **B1** and [2-(trifluoromethyl)phenyl]acetic acid the title compound was isolated as a white solid.

MS (m/z) APCI AP⁺ = 424

Example 316

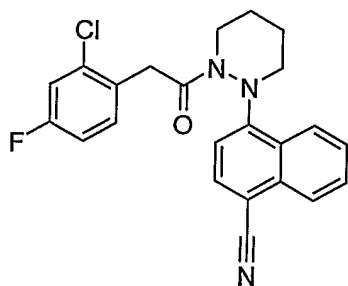


4-[2-[(2,6-difluorophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D94)

From **B1** and (2,6-difluorophenyl)acetic acid the title compound was isolated as a white solid.

MS (m/z) APCI AP⁺ = 392

Example 317



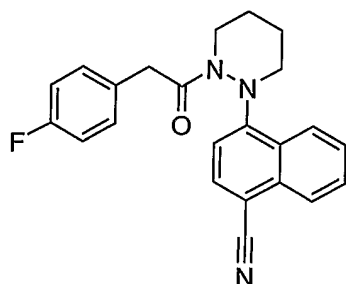
4-[2-[(2-chloro-4-fluorophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D95)

177

From **B1** and (2-chloro-4-fluorophenyl)acetic acid the title compound was isolated as a white solid.

MS (m/z) APCI AP⁺ = 408

Example 318



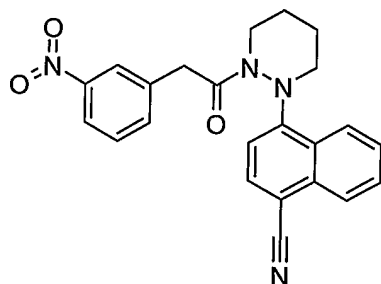
5

4-[2-[(4-fluorophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D96)

From **B1** and (4-fluorophenyl)acetic acid the title compound was isolated as a white solid.

10 MS (m/z) APCI AP⁺ = 374

Example 319



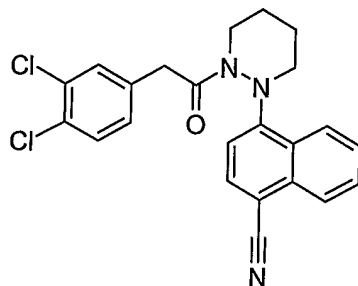
4-[2-[(3-nitrophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D97)

15 From **B1** and (3-nitrophenyl)acetic acid the title compound was isolated as a yellow solid.

MS (m/z) APCI AP⁺ = 401

Example 320

178

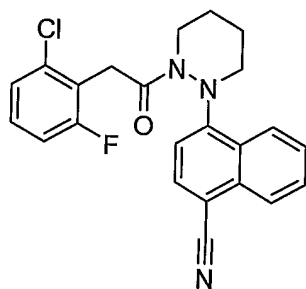


4-[2-[(3,4-dichlorophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D98)

From **B1** and (3,4-dichlorophenyl)acetic acid the title compound was isolated as a white solid.

MS (m/z) APCI AP⁺ = 424

Example 322

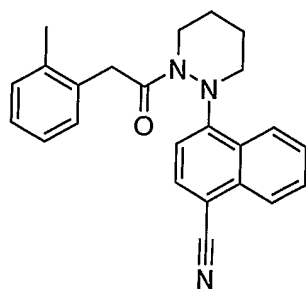


4-[2-[(2-chloro-6-fluorophenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D99)

From **B1** and (2-chloro-6-fluorophenyl)acetic acid the title compound was isolated as a white solid.

MS (m/z) APCI AP⁺ = 408

Example 323



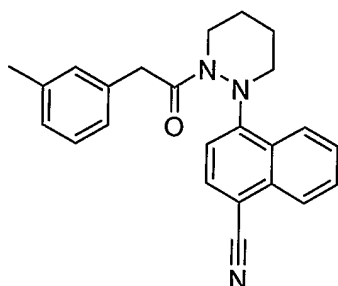
4-[2-[(2-methylphenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D100)

179

From **B1** and (2-methylphenyl)acetic acid the title compound was isolated as a white solid.

MS (m/z) APCI $AP^+ = 370$

Example 324



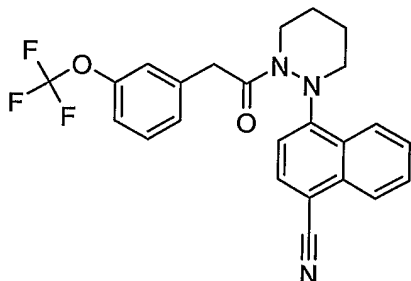
5

4-[2-[(3-methylphenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D101)

From **B1** and (3-methylphenyl)acetic acid the title compound was isolated as a white solid.

10 MS (m/z) APCI $AP^+ = 370$

Example 325



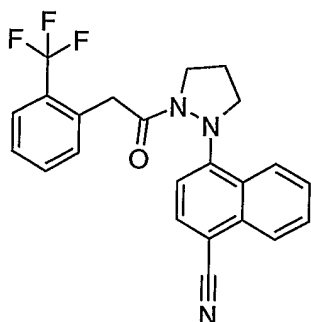
4-[2-[(3-[(trifluoromethyl)oxy]phenyl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D102)

15 From **B1** and {3-[(trifluoromethyl)oxy]phenyl}acetic acid the title compound was isolated as a white solid.

MS (m/z) APCI $AP^+ = 440$

Example 326

180

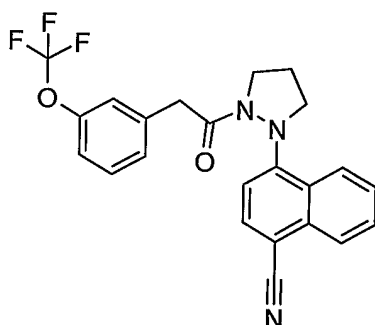


4-[2-({3-[(trifluoromethyl)oxy]phenyl}acetyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile (D103)

From **B5** and [2-(trifluoromethyl)phenyl]acetic acid the title compound was isolated as a yellow solid.

MS (m/z) ESI $ES^+ = 410$

Example 327

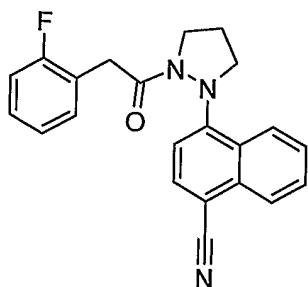


4-[2-({3-[(trifluoromethyl)oxy]phenyl}acetyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile (D104)

From **B5** and {3-[(trifluoromethyl)oxy]phenyl}acetic acid the title compound was isolated as a yellow oil.

MS (m/z) ESI $ES^+ = 426$

Example 328



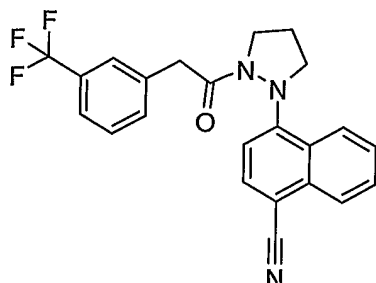
4-{2-[(2-fluorophenyl)acetyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile (D105)

181

From **B5** and (2-fluorophenyl)acetic acid the title compound was isolated as a clear oil.

MS (m/z) ESI ES⁺ = 360

Example 329

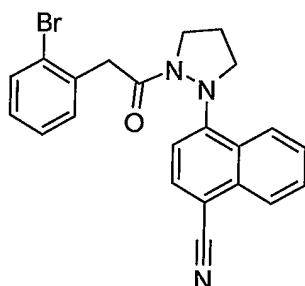


5 **4-(2-([3-(trifluoromethyl)phenyl]acetyl)-1-pyrazolidinyl)-1-naphthalenecarbonitrile (D106)**

From **B5** and [3-(trifluoromethyl)phenyl]acetic acid the title compound was isolated as a clear oil.

MS (m/z) ESI ES⁺ = 410

10 **Example 330**

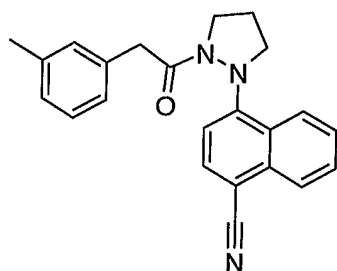


4-(2-([2-bromophenyl]acetyl)-1-pyrazolidinyl)-1-naphthalenecarbonitrile (D107)

From **B5** and (2-bromophenyl)acetic acid the title compound was isolated as a white solid.

15 MS (m/z) ESI ES⁺ = 421

Example 331



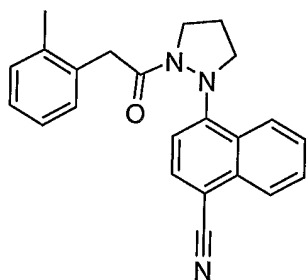
4-(2-([3-methylphenyl]acetyl)-1-pyrazolidinyl)-1-naphthalenecarbonitrile (D108)

182

From **B5** and (3-methylphenyl)acetic acid the title compound was isolated as a yellow oil.

MS (m/z) ESI $ES^+ = 356$

Example 332



5

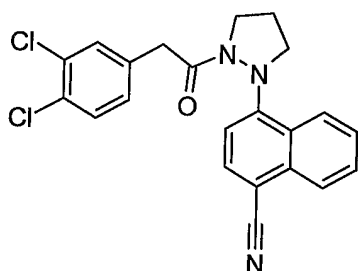
4-{2-[(2-methylphenyl)acetyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile (D109)

From **B5** and (2-methylphenyl)acetic acid the title compound was isolated as a yellow oil.

MS (m/z) ESI $ES^+ = 356$

10

Example 333



4-{2-[(3,4-dichlorophenyl)acetyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile (D110)

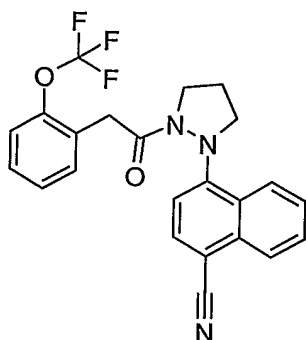
From **B5** and (3,4-dichlorophenyl)acetic acid the title compound was isolated as a clear oil.

15

MS (m/z) ESI $ES^+ = 411$

Example 334

183

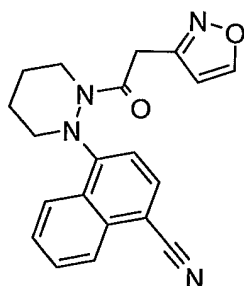


4-[2-({2-[(trifluoromethyl)oxy]phenyl}acetyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile (D111)

From **B5** and {2-[(trifluoromethyl)oxy]phenyl}acetic acid the title compound was isolated as a white solid.

MS (m/z) ESI ES^+ = 426

Example 335

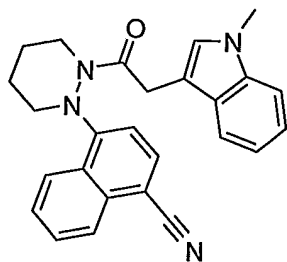


4-[2-(3-isoxazolylacetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D112)

From **B1** and (3-isoxazolyl)acetic acid the title compound was obtained.

MS (m/z) ESI ES^+ = 347

Example 336



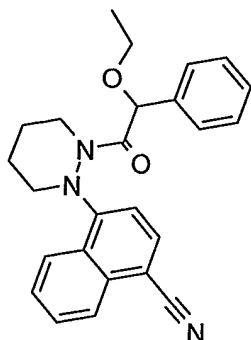
4-[2-[(1-methyl-1H-indol-3-yl)acetyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D113)

184

From **B1** and (1-methyl-1*H*-indol-3-yl)acetic acid the title compound was obtained.

MS (m/z) ESI ES⁺ = 409

Example 337

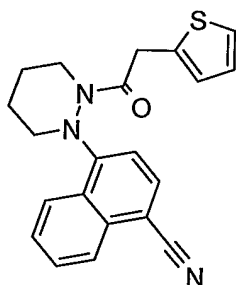


5 **4-[2-[(ethyloxy)(phenyl)acetyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (D114)**

From **B1** and (ethyloxy)(phenyl)acetic acid the title compound was obtained.

MS (m/z) ESI ES⁺ = 400

Example 338



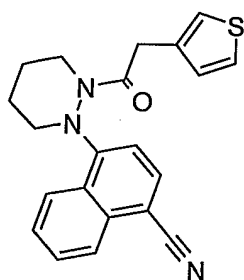
10

4-[2-(2-thienylacetyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (D115)

From **B1** and (2-thienyl)acetic acid the title compound was obtained.

MS (m/z) ESI ES⁺ = 362

15 **Example 339**



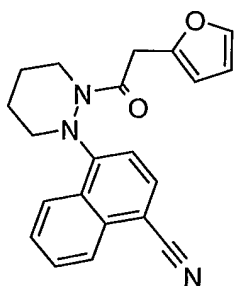
185

4-[2-(3-thienylacetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D116)

From **B1** and (3-thienyl)acetic acid the title compound was obtained.

MS (m/z) ESI ES⁺ = 362

5 **Example 340**



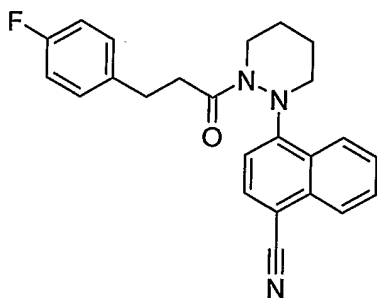
4-[2-(2-furanylacetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D117)

From **B1** and (2-furanyl)acetic acid the title compound was obtained.

10 MS (m/z) ESI ES⁺ = 346

Hexahydropyridazine Amide Couplings: Mixed Anhydride Route

Example 341



4-[2-[3-(4-fluorophenyl)propanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D118)

15 To a 40ml scintillation vial was added 106mg 3-(4-fluorophenyl)propanoic acid (0.695mmoles, 1.0eq), 1ml dichloromethane, and 0.1ml triethylamine (0.695mmoles, 2.2eq). This was followed by the addition of 0.083ml isobutylchloroformate (0.695mmoles, 2.2eq). The reaction mixture was shaken for 15 minutes on an orbital shaker at room temperature. Then 75mg 4-(tetrahydro-1(2H)-pyridazinyl)-1-naphthalenecarbonitrile (**B1**) (0.316mmoles, 1eq) in 1ml dichloromethane was added
20 and the reaction was shaken on an orbital shaker overnight. The reaction mixture was

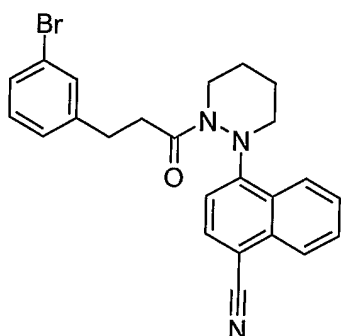
186

concentrated *in vacuo*. The residue was purified via preparative HPLC (Phenomenex column Luna C18, 75mm x 30mm, 5 micron), 30% acetonitrile/water (0.01% TFA) to 100% acetonitrile, to yield 19mg of the title compound as a clear oil.

MS (m/z) APCI AP⁺ = 388

- 5 The following compounds were synthesized according to a similar general procedure as described for **D118**:

Example 342

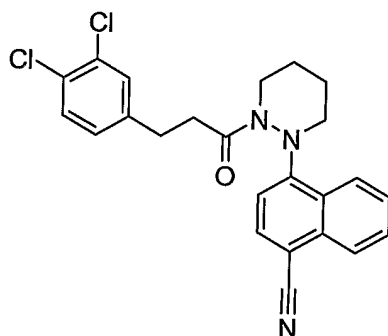


- 10 **4-[2-[3-(3-bromophenyl)propanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D119)**

From **B1** and 3-(3-bromophenyl)propanoic acid the title compound was isolated as a white solid.

MS (m/z) APCI AP⁺ = 449

Example 343



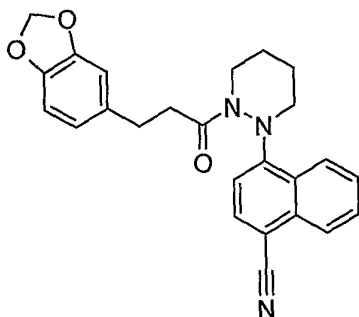
- 15 **4-[2-[3-(3,4-dichlorophenyl)propanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D120)**

From **B1** and 3-(3,4-dichlorophenyl)propanoic acid the title compound was isolated as a white solid.

- 20 MS (m/z) APCI AP⁺ = 438

Example 342

187

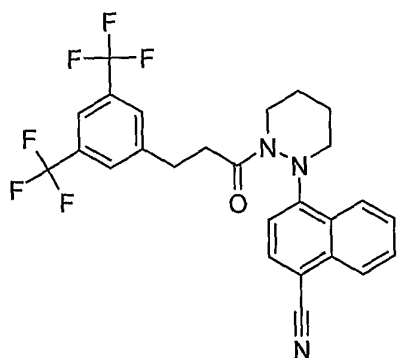


4-[2-[3-(1,3-benzodioxol-5-yl)propanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D121)

From **B1** and 3-(1,3-benzodioxol-5-yl)propanoic acid the title compound was isolated as a clear oil.

MS (m/z) APCI AP⁺ = 414

Example 343

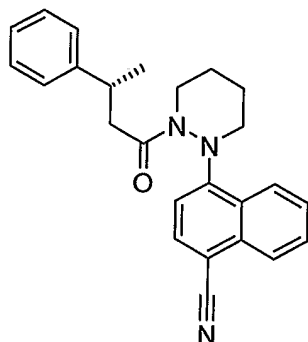


4-[2-[3-[3,5-bis(trifluoromethyl)phenyl]propanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D122)

From **B1** and 3-[3,5-bis(trifluoromethyl)phenyl]propanoic acid the title compound was isolated as a clear oil.

MS (m/z) APCI AP⁺ = 506

Example 344

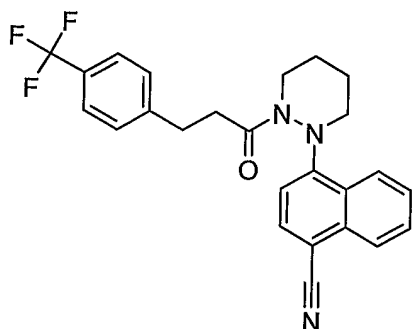


4-[2-[(3R)-3-phenylbutanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D123)

From **B1** and (3R)-3-phenylbutanoic acid the title compound was isolated as a clear oil.

5 MS (m/z) APCI AP⁺ = 384

Example 345

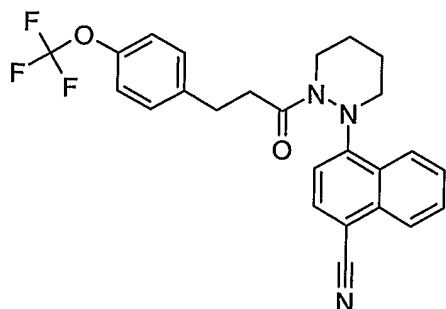


4-[2-{3-[4-(trifluoromethyl)phenyl]propanoyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D124)

10 From **B1** and 3-[4-(trifluoromethyl)phenyl]propanoic acid the title compound was isolated as a clear oil.

MS (m/z) APCI AP⁺ = 438

Example 346



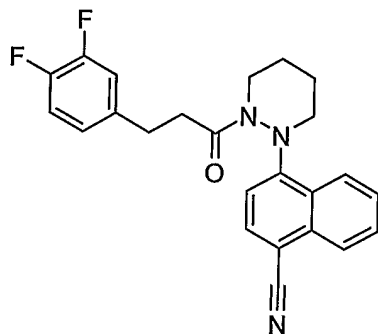
15 **4-[2-{3-[4-((trifluoromethyl)oxy)phenyl]propanoyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D125)**

189

From **B1** and 3-[[4-(trifluoromethyl)oxy]phenyl]propanoic acid the title compound was isolated as a clear oil.

MS (m/z) APCI AP⁺ = 454

Example 347



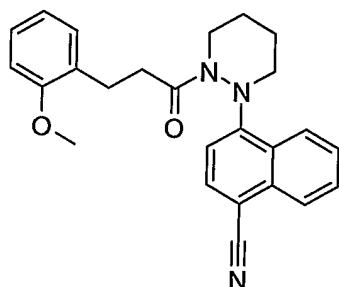
5

4-[2-[3-(3,4-difluorophenyl)propanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D126)

From **B1** and 3-(3,4-difluorophenyl)propanoic acid the title compound was isolated as a white solid.

10 MS (m/z) APCI AP⁺ = 406

Example 348



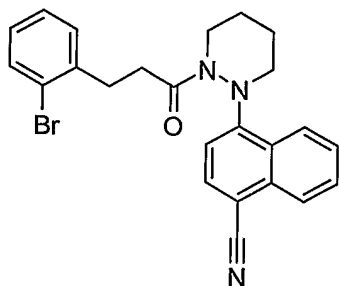
4-[2-[3-[2-(methoxy)phenyl]propanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D127)

15 From **B1** and 3-[2-(methoxy)phenyl]propanoic acid the title compound was isolated as a clear oil.

MS (m/z) APCI AP⁺ = 400

Example 349

190

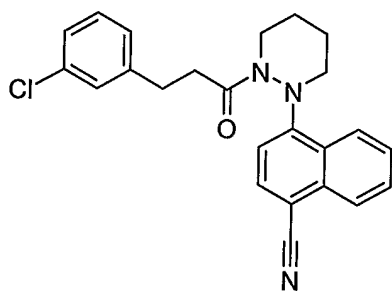


4-[2-[3-(2-bromophenyl)propanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D128)

From **B1** and 3-(2-bromophenyl)propanoic acid the title compound was isolated as a clear oil.

MS (m/z) APCI AP⁺ = 449

Example 350

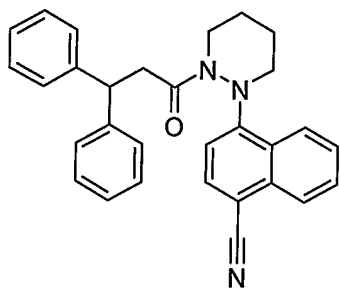


4-[2-[3-(3-chlorophenyl)propanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D129)

From **B1** and 3-(3-chlorophenyl)propanoic acid the title compound was isolated as a white solid.

MS (m/z) APCI AP⁺ = 404

Example 351



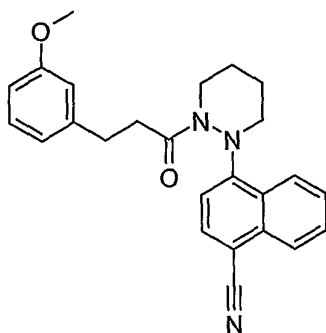
4-[2-(3,3-diphenylpropanoyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D130)

191

From **B1** and 3,3-diphenylpropanoic acid the title compound was isolated as a white solid.

MS (m/z) APCI AP^+ = 446

Example 352



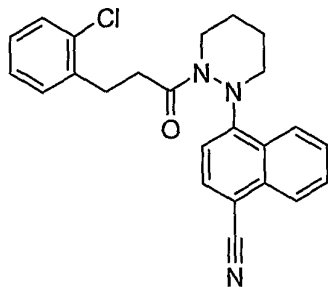
5

4-[2-{3-[3-(methoxy)phenyl]propanoyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D131)

From **B1** and 3-[3-(methoxy)phenyl]propanoic acid the title compound was isolated as a clear oil.

10 MS (m/z) APCI AP^+ = 400

Example 353



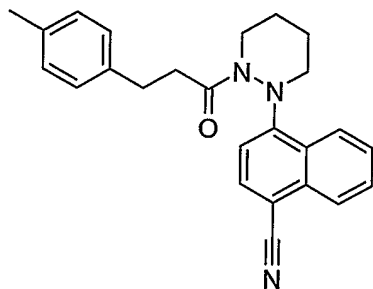
4-[2-{3-(2-chlorophenyl)propanoyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D132)

15 From **B1** and 3-(2-chlorophenyl)propanoic acid the title compound was isolated as a white solid.

MS (m/z) APCI AP^+ = 404

Example 354

192

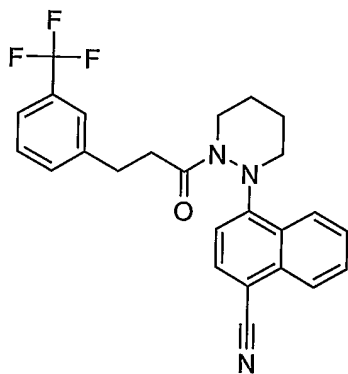


4-[2-[3-(4-methylphenyl)propanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D133)

From **B1** and 3-(4-methylphenyl)propanoic acid the title compound was isolated as a clear oil.

MS (m/z) APCI AP⁺ = 384

Example 355

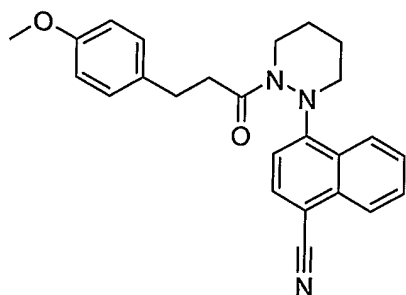


4-[2-[3-[3-(trifluoromethyl)phenyl]propanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D134)

From **B1** and 3-[3-(trifluoromethyl)phenyl]propanoic acid the title compound was isolated as a clear oil.

MS (m/z) APCI AP⁺ = 438

Example 356

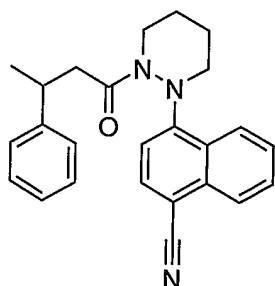


193

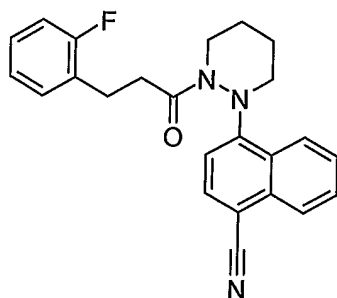
4-[2-{3-[4-(methyloxy)phenyl]propanoyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D135)

From **B1** and 3-[4-(methyloxy)phenyl]propanoic acid the title compound was isolated as a clear oil.

5 MS (m/z) APCI AP⁺ = 400

Example 357**4-[2-(3-phenylbutanoyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D136)**

10 From **B1** and 3-phenylbutanoic acid the title compound was isolated as a white solid.
MS (m/z) APCI AP⁺ = 384

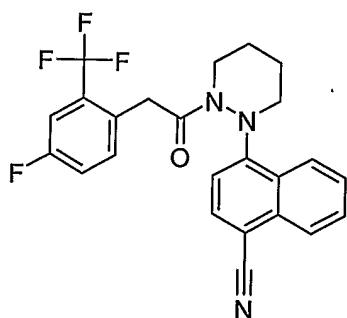
Example 358**4-[2-[3-(2-fluorophenyl)propanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D137)**

15 From **B1** and 3-(2-fluorophenyl)propanoic acid the title compound was isolated as a clear oil.

MS (m/z) APCI AP⁺ = 388

Example 359

194

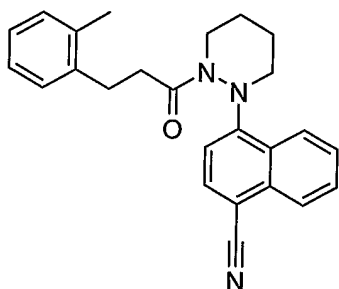


4-[2-{[4-fluoro-2-(trifluoromethyl)phenyl]acetyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D138)

From **B1** and [4-fluoro-2-(trifluoromethyl)phenyl]acetic acid the title compound was isolated as a white solid.

MS (m/z) APCI AP⁺ = 442

Example 360

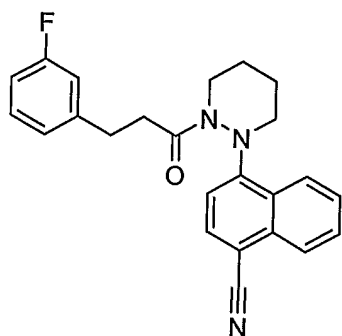


4-[2-[3-(2-methylphenyl)propanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D139)

From **B1** and 3-(2-methylphenyl)propanoic acid the title compound was isolated as a clear oil.

MS (m/z) APCI AP⁺ = 384

Example 361



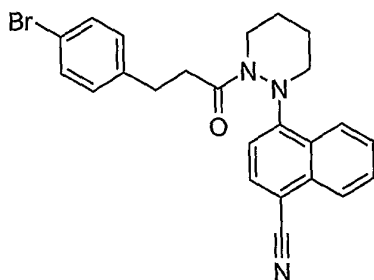
195

4-[2-[3-(3-fluorophenyl)propanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D140)

From **B1** and 3-(3-fluorophenyl)propanoic acid the title compound was isolated as a white solid.

5 MS (m/z) APCI AP⁺ = 388

Example 362

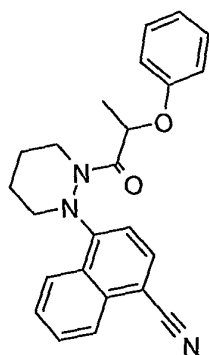


4-[2-[3-(4-bromophenyl)propanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D141)

10 From **B1** and 3-(4-bromophenyl)propanoic acid the title compound was isolated as a clear oil.

MS (m/z) APCI AP⁺ = 449

Example 363

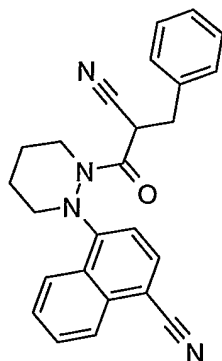


15 **4-[2-[2-(phenyloxy)propanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D142)**

From **B1** and 2-(phenyloxy)propanoic acid the title compound was obtained.

MS(m/z) ESI ES⁺ = 386

Example 364

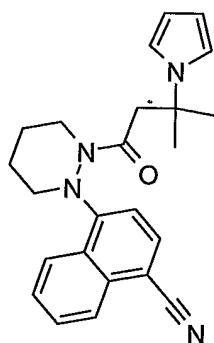


4-[2-(2-cyano-3-phenylpropanoyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D143)

From **B1** and 2-cyano-3-phenylpropanoic acid the title compound was obtained.

5 MS(m/z) ESI ES⁺ = 395

Example 365

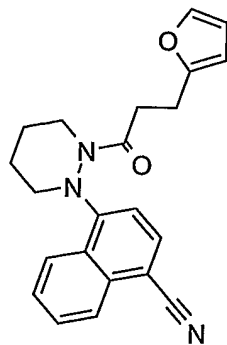


4-[2-[3-methyl-3-(1H-pyrrol-1-yl)butanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (D144)

10 From **B1** and 3-methyl-3-(1H-pyrrol-1-yl)butanoic acid the title compound was obtained.

MS(m/z) APCI AP⁺ = 385

Example 366



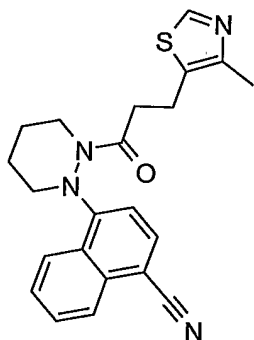
197

4-[2-[3-(2-furanyl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (D145)

From **B1** and 3-(2-furanyl)propanoic acid the title compound was obtained.

MS(m/z) ESI ES⁺ = 360

5 **Example 367**

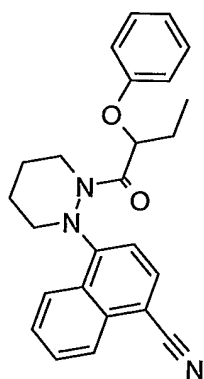


4-[2-[3-(4-methyl-1,3-thiazol-5-yl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (D146)

From **B1** and 3-(4-methyl-1,3-thiazol-5-yl)propanoic acid the title compound was obtained.

MS(m/z) ESI ES⁺ = 391

Example 368



4-[2-[2-(phenyloxy)butanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile (D147)

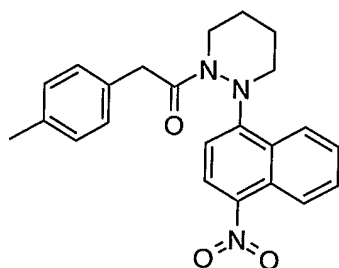
From **B1** and 2-phenoxybutanoic acid the title compound was obtained.

MS(m/z) ESI ES⁺ = 400

Hexahydropyridazine Amide Couplings: Polystyrene-Linked Carbodiimide

Method

Example 369



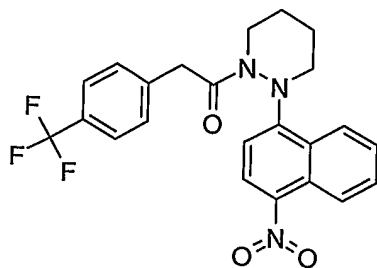
5 **1-[(4-methylphenyl)acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D147)**

To a 40ml scintillation vial was added 73mg 1-(4-nitro-1-naphthalenyl)hexahydropyridazine (**B2**) (0.28 mmoles, 1eq), 3ml chloroform, and 55mg (4-methylphenyl)acetic acid (0.37mmoles, 1.3eq). Then 410mg polystyrene-linked carbodiimide resin (Argonaut Technologies, 1.28mmol/g, 2eq) was added and the reaction was heated at 60 °C on an orbital shaker overnight. After cooling to room temperature the reaction was filtered and concentrated *in vacuo*. The residue was purified via preparative HPLC (Phenomenex column Luna C18, 75mm x 30mm, 5 micron), 30% acetonitrile/water (0.01% TFA) to 100% acetonitrile, to yield 69mg of the title compound as a yellow solid.

15 MS (m/z) ES⁺ = 390

The following compounds were synthesized according to a similar general procedure as described for **D147**:

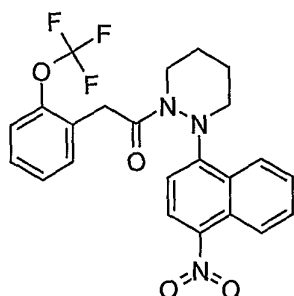
Example 370



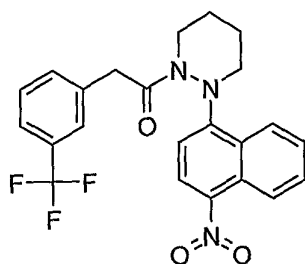
20 **1-(4-nitro-1-naphthalenyl)-2-[(4-(trifluoromethyl)phenyl)acetyl]hexahydropyridazine (D148)**

From **B2** and [4-(trifluoromethyl)phenyl]acetic acid the title compound was isolated as a yellow solid.

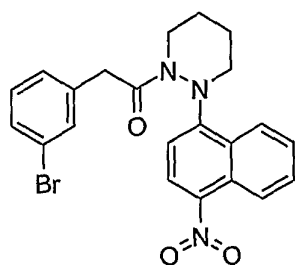
199

MS (m/z) ESI ES⁺ = 444**Example 371****1-(4-nitro-1-naphthalenyl)-2-({2-****5 [(trifluoromethyl)oxy]phenyl}acetyl)hexahydropyridazine (D149)**

From **B2** and {2-[(trifluoromethyl)oxy]phenyl}acetic acid the title compound was isolated as an orange oil.

MS (m/z) ESI ES⁺ = 460**Example 372****1-(4-nitro-1-naphthalenyl)-2-({3-****10 (trifluoromethyl)phenyl}acetyl)hexahydropyridazine (D150)**

From **B2** and [3-(trifluoromethyl)phenyl]acetic acid the title compound was isolated as a yellow oil.

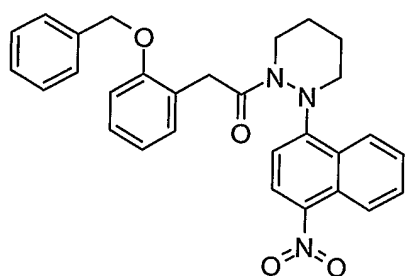
15 MS (m/z) ESI ES⁺ = 444**Example 373****1-[(3-bromophenyl)acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D151)**

200

From **B2** and (3-bromophenyl)acetic acid the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 455

Example 374

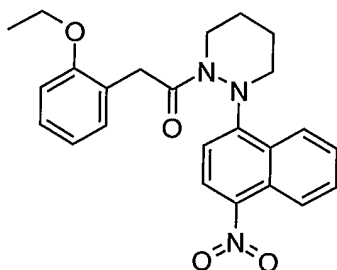


**1-((4-nitro-1-naphthalenyl)-2-({2-
[(phenylmethoxy)phenyl]acetyl})hexahydropyridazine (D152)**

From **B2** and {2-[(phenylmethoxy)phenyl]acetic acid the title compound was isolated as a yellow oil.

MS (m/z) ESI ES⁺ = 482

Example 375



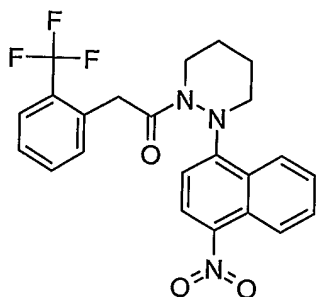
1-([2-(ethoxy)phenyl]acetyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D153)

From **B2** and [2-(ethoxy)phenyl]acetic acid the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 420

Example 376

201

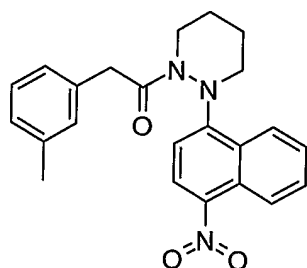


1-(4-nitro-1-naphthalenyl)-2-([2-(trifluoromethyl)phenyl]acetyl)hexahydropyridazine (D154)

From **B2** and [2-(trifluoromethyl)phenyl]acetic acid the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 444

Example 377

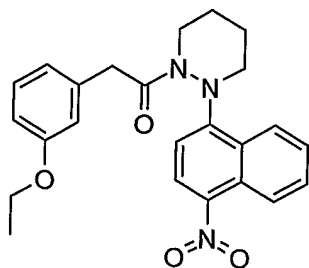


1-[(3-methylphenyl)acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D155)

From **B2** and (3-methylphenyl)acetic acid the title compound was isolated as an orange oil.

MS (m/z) ESI ES⁺ = 390

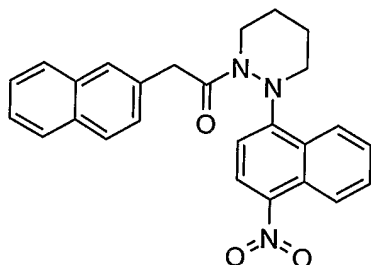
Example 378



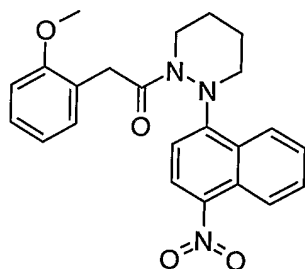
1-[(3-(ethyloxy)phenyl)acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D156)

From **B2** and [3-(ethyloxy)phenyl]acetic acid the title compound was isolated as a yellow oil.

202

MS (m/z) ESI ES⁺ = 420**Example 379****1-(2-naphthalenylacetyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D157)**

- 5 From **B2** and (2-naphthalenyl)acetic acid the title compound was isolated as a yellow oil.

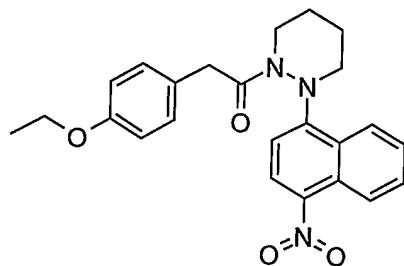
MS (m/z) ESI ES⁺ = 426**Example 380**

- 10 **1-([2-(methyloxy)phenyl]acetyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D158)**

From **B2** and [2-(methyloxy)phenyl]acetic acid the title compound was isolated as an orange oil.

MS (m/z) ESI ES⁺ = 406

- 15 **Example 381**

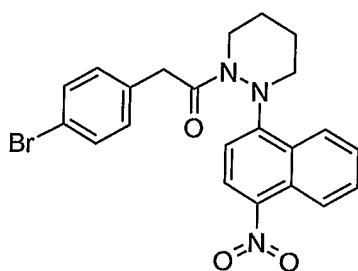
**1-[4-(ethyloxy)phenyl]acetyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D159)**

203

From **B2** and [4-(ethyloxy)phenyl]acetic acid the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 420

Example 382



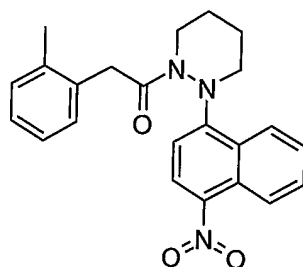
5

1-[(4-bromophenyl)acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D160)

From **B2** and (4-bromophenyl)acetic acid the title compound was isolated as a yellow solid.

MS (m/z) ESI ES⁺ = 455

10 **Example 383**

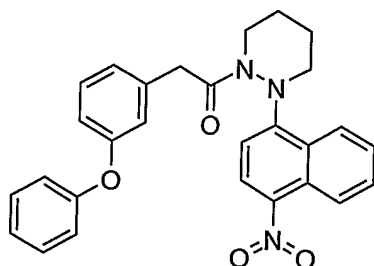


1-[(2-methylphenyl)acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D161)

From **B2** and (2-methylphenyl)acetic acid the title compound was isolated as a yellow oil.

15 MS (m/z) ESI ES⁺ = 390

Example 384



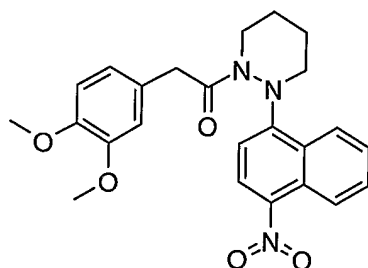
204

1-(4-nitro-1-naphthalenyl)-2-[[3-(phenyloxy)phenyl]acetyl]hexahydropyridazine (D162)

From **B2** and [3-(phenyloxy)phenyl]acetic acid the title compound was isolated as a yellow oil.

5 MS (m/z) ESI $ES^+ = 468$

Example 385



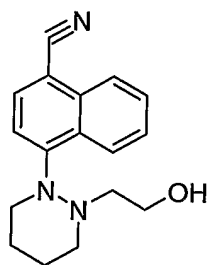
1-[[3,4-bis(methoxy)phenyl]acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (D163)

10 From **B2** and [3,4-(dimethyloxy)phenyl]acetic acid the title compound was isolated as a yellow solid.

MS (m/z) $ES^+ = 436$

tert-Butyldimethylsilyl ether Deprotection

Example 386



F. 4-[2-(2-hydroxyethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (F1)

To a 40ml scintillation vial was added 670mg 4-[2-(2-[[[(1,1-

dimethylethyl)(dimethyl)silyl]oxy}ethyl)tetrahydro-1(2H)-pyridazinyl]-1-

20 naphthalenecarbonitrile (**C186**) (1.69 mmoles, 1eq), 10ml ethanol, and 450mg pyridinium *p*-toluenesulfonate (1.69mmoles, 1eq). The reaction mixture was heated at 70 °C overnight and, after cooling to room temperature, was concentrated *in vacuo*.

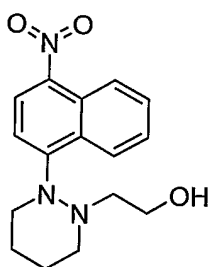
205

The residue was purified via flash chromatography (20% ethyl acetate/hexanes to 50% ethyl acetate/hexanes) to yield 161mg of the title compound.

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.6 (m, 1 H) 1.7 (m, 2 H) 1.9 (m, 2 H) 3.0 (m, 2 H) 3.3 (m, 4 H) 3.4 (m, 2 H) 7.0 (d, $J=8.1$ Hz, 1 H) 7.5 (m, 1 H) 7.6 (t, $J=7.1$ Hz, 1 H) 7.8 (d, $J=7.9$ Hz, 1 H) 8.2 (d, $J=8.4$ Hz, 1 H) 8.3 (d, $J=8.2$ Hz, 1 H)

The following compounds were synthesized according to a similar general procedure as described for F1:

Example 387



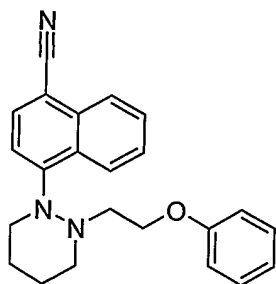
10 **2-[2-(4-nitro-1-naphthalenyl)tetrahydro-1(2H)-pyridazinyl]ethanol (F3)**

From **C185** the title compound was obtained.

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.6 (m, 1 H) 1.8 (m, 4 H) 3.0 (m, 2 H) 3.3 (m, 4 H) 3.5 (m, 2 H) 7.0 (d, $J=8.4$ Hz, 1 H) 7.5 (t, $J=7.6$ Hz, 1 H) 7.7 (t, $J=7.9$ Hz, 1 H) 8.2 (d, $J=8.4$ Hz, 1 H) 8.3 (d, $J=8.6$ Hz, 1 H) 8.7 (d, $J=8.8$ Hz, 1 H)

15 **Mitsunobu Reaction**

Example 388



G. 4-[2-[2-(phenyloxy)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (G1)

20 To a 40ml scintillation vial was added 47mg 4-[2-(2-hydroxyethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (**F1**) (0.166 mmoles, 1eq), 2ml dichloromethane, 62mg triphenylphosphine (0.199mmoles, 1.2eq), and 20mg phenol (0.183mmoles, 1.1eq). This was followed by the addition of 0.050ml diisopropylazodicarboxylate

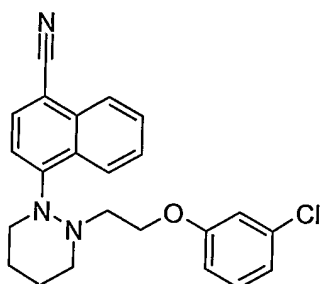
206

(0.199mmoles, 1.22eq). The reaction mixture was shaken on an orbital shaker overnight at room temperature and then was concentrated *in vacuo*. The residue was purified via preparative HPLC (Phenomenex column Luna C18, 75mm x 30mm, 5 micron), 50% acetonitrile/water (0.01% TFA) to 100% acetonitrile, to yield 16mg of the title compound as a yellow oil.

¹H NMR (400 MHz, METHANOL-D₄) δ ppm 1.9 (m, 4 H), 3.3 (t, *J*=5.7 Hz, 2 H), 3.5 (m, 4 H), 3.7 (t, *J*=5.5 Hz, 2 H), 6.4 (d, *J*=7.9 Hz, 2 H), 6.8 (m, 1 H), 7.1 (m, 3 H), 7.5 (m, 1 H), 7.6 (m, 1 H), 7.8 (d, *J*=8.1 Hz, 1 H), 8.0 (d, *J*=8.4 Hz, 1 H), 8.5 (d, *J*=8.6 Hz, 1 H)

The following compounds were synthesized according to a similar general procedure as described for **G1**:

Example 389

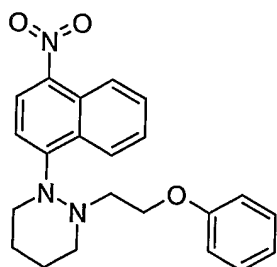


4-[2-{2-[(3-chlorophenyl)oxy]ethyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (G2)

From **F1** and 3-chlorophenol the title compound was isolated as a yellow oil.

MS (*m/z*) APCI AP⁺ = 392

Example 390

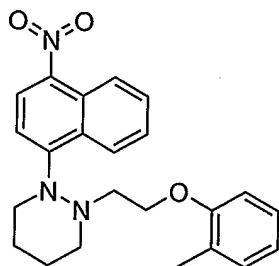


1-(4-nitro-1-naphthalenyl)-2-[2-(phenyloxy)ethyl]hexahydropyridazine (G3)

From **F2** and phenol the title compound was isolated as a red oil.

MS (*m/z*) APCI AP⁺ = 378

Example 391

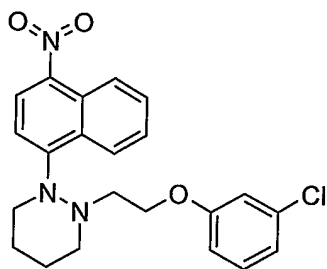


1-{2-[(2-methylphenyl)oxy]ethyl}-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (G4)

From **F2** and *o*-cresol the title compound was isolated as a red oil.

5 MS (m/z) APCI AP⁺ = 392

Example 392

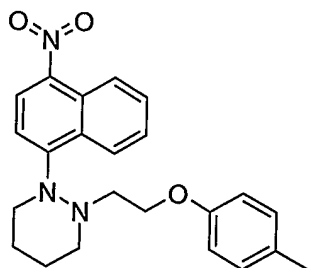


1-{2-[(3-chlorophenyl)oxy]ethyl}-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (G5)

10 From **F2** and 3-chlorophenol the title compound was isolated as a red oil.

MS (m/z) APCI AP⁺ = 412

Example 393



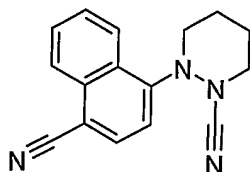
1-{2-[(4-methylphenyl)oxy]ethyl}-2-(4-nitro-1-naphthalenyl)hexahydropyridazine (G6)

15

From **F2** and *p*-cresol the title compound was isolated as a red oil.

MS (m/z) APCI AP⁺ = 392

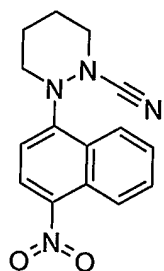
Cyanation of Hexahydropyridazine

Example 394**2-(4-cyano-1-naphthalenyl)tetrahydro-1(2H)-pyridazinecarbonitrile**

- To a 100ml round bottom flask equipped with a magnetic stirbar and nitrogen flow was added 250mg 4-(tetrahydro-1(2H)-pyridazinyl)-1-naphthalenecarbonitrile (**B1**) (1 mmole, 1.0eq) in 20ml acetonitrile, 0.375ml diisopropylethyl amine (2mmoles, 2eq), then cooled to 0 °C via an ice bath, at which point, 112mg cyanogen bromide (1mmole, 1eq) was added. The reaction was allowed to warm gently to room temperature and stirred at rt for 18 hours. The solvent was removed under reduced and the resulting residue was purified by flash chromatography (eluted with 100% dichloromethane) to yield desired compound.

¹H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.0 (m, 2 H) 2.1 (m, 2 H) 3.6 (m, 2 H) 3.7 (m, 2 H) 7.2 (d, $J=7.7$ Hz, 61 H) 7.7 (m, 2 H) 7.9 (d, $J=7.7$ Hz, 1 H) 8.1 (m, $J=7.6$, 1.0 Hz, 1 H) 8.3 (m, $J=7.5$, 0.8 Hz, 1 H)

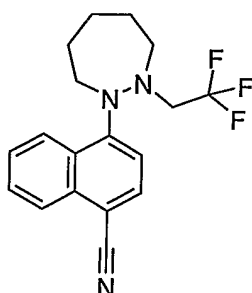
- The following compounds were synthesized according to a similar general procedure as described for **Example 394**:

Example 395**2-(4-nitro-1-naphthalenyl)tetrahydro-1(2H)-pyridazinecarbonitrile**

- From **B2** the title compound was obtained.

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 2.0 (m, 4 H) 3.6 (m, 2 H) 3.7 (m, 2 H) 7.2 (d, $J=8.2$ Hz, 1 H) 7.6 (m, 1 H) 7.7 (m, 1 H) 8.1 (d, $J=8.6$ Hz, 1 H) 8.2 (d, $J=8.4$ Hz, 1 H) 8.6 (d, $J=8.8$ Hz, 1 H)

Trifluoroethylation of Hexahydrodiazepine

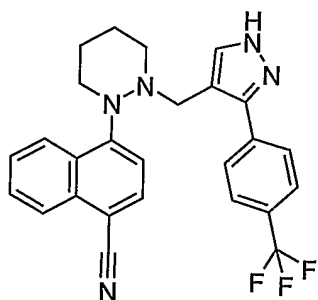
Example 396**4-[2-(2,2,2-trifluoroethyl)hexahydro-1H-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile**

- 5 To a 50ml round bottom flask equipped with a magnetic stirbar, an addition funnel, and nitrogen flow was added 250mg 4-(hexahydro-1H-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile (**B4**) (1 mmoles, 1.0eq) in 5ml 1,2-dichloroethane, then added 187mg sodium cyanoborohydride (3 mmoles, 3.0eq). The reaction mixture was cooled to 0 °C via an ice bath, at which point, 5ml trifluoroacetic acid was added. Then
- 10 trifluoroacetaldehyde hydrate was added dropwise and the reaction was allowed to warm gently to room temperature and stirred at rt for two days. To the reaction mixture was added 10ml water and 20ml dichloromethane. The phases were then separated and the organic phase was concentrated under reduced pressure to yield desired compound.
- 15 MS (m/z) ES⁺ = 334

The following compounds were synthesized according to a similar general procedure as used for **C179** with the following exceptions: minimal amounts of anhydrous THF were used as the co-solvent in the LiAlH₄ reaction when solubility in Et₂O was low, with certain less-reactive substrates the LiAlH₄ reduction was allowed to proceed up to 48hrs at 0 °C, and, in certain cases, varying amounts of over-reduction of the ester to the Me analog was observed during the LiAlH₄ reaction:

Example 397

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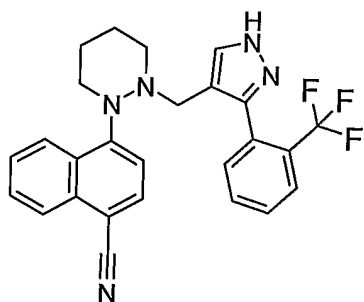


4-[2-({3-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C222)

From (B1) and methyl 3-oxo-3-[4-(trifluoromethyl)phenyl]propanoate the title compound was obtained.

MS (m/z) APCI AP⁺ = 462

Example 398

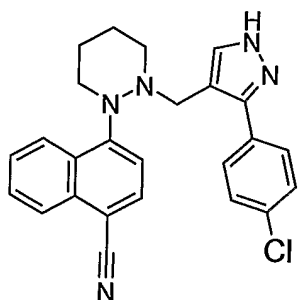


4-[2-({3-[2-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C223)

From (B1) and methyl 3-oxo-3-[2-(trifluoromethyl)phenyl]propanoate the title compound was obtained.

MS (m/z) APCI AP⁺ = 462

Example 399



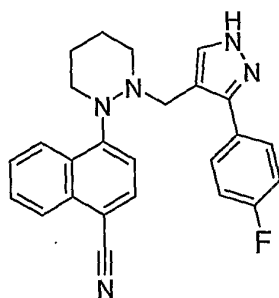
4-[2-({3-[4-chlorophenyl]-1H-pyrazol-4-yl}methyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C224)

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From (B1) and ethyl 3-oxo-3-[4-chlorophenyl]propanoate the title compound was obtained.

MS (m/z) APCI AP⁺ = 428

Example 400

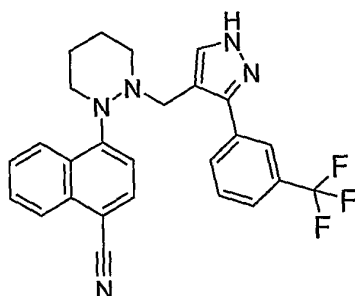


4-[2-({3-(4-fluorophenyl)-1H-pyrazol-4-yl}methyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C225)

From (B1) and methyl 3-oxo-3-[4-fluorophenyl]propanoate the title compound was obtained.

MS (m/z) ESI ES⁺ = 412

Example 401



4-[2-({3-[3-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile (C226)

From (B1) and methyl 3-oxo-3-[3-(trifluoromethyl)phenyl]propanoate the title compound was obtained.

MS (m/z) ESI ES⁺ = 462

BIOLOGICAL SECTION

Compounds of the current invention are preferably modulators of the glucocorticoid receptor. Activity mediated through oxosteroid nuclear receptors was determined using the following in vitro and in vivo assays.

In Vitro Assays:

The following abbreviations and sources of materials are used

Fluormone PL Red – a commercially available PR fluorophore (PanVera Corp, Product No P2965)

Fluormone GS Red – a commercially available GR fluorophore (PanVera Corp, Product No P2894)

Fluormone AL Green - a commercially available AR fluorophore (PanVera Corp, Product No P3010)

PR-LBD - Purified human progesterone ligand binding domain tagged with Glutathione Transferase (PanVera Corp, Product No P2900)

GR – purified human glucocorticoid receptor (PanVera Corp, Product No P2812)

AR-LBD- Purified rat androgen ligand binding domain tagged with Glutathione Transferase (PanVera Corp, Product No P3009)

PR Screening Buffer - 100 mM potassium phosphate (pH 7.4), 100 μ G/ml bovine gamma globulin, 15% ethylene glycol, 0.02% NaN₃, 10% glycerol (PanVera Corp Product No P2967) with 0.1% w/v CHAPS

AR Screening Buffer - pH 7.5 containing protein stabilizing agents and glycerol (PanVera Corp Product No P3011)

GR Screening Buffer - 100 mM potassium phosphate (pH 7.4), 200 mM Na₂MoO₄, 1 mM EDTA, 20% DMSO (PanVera Corp Product No P2814) with GR stabilizing peptide (100 μ M) (PanVera Corp Product No P2815)

DTT – dithiothreitol (PanVera Corp Product No P2325)

Discovery Analyst – is an FP reader

DMSO – dimethylsulphoxide

Glucocorticoid Receptor Fluorescence Polarization Assay (GR – FPA):

The glucocorticoid receptor fluorescence polarization assay is used to investigate the interaction of the compounds with the glucocorticoid receptor.

Compounds are added to the 384 well black plates to a final volume of 0.5 μ L. Sufficient Fluormone GS Red and GR are defrosted on ice to give a final concentration of 1 nM and 4 nM, respectively. GR screening buffer is chilled to 4 °C prior to addition of DTT to give a final concentration of 1mM. The Fluormone GS Red, and GR in GR Screening Buffer are added to compound plates to give a final volume of 10 μ L. The

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assay is allowed to incubate at 4°C for 12 hours. The plates are counted in a Discovery Analyst with suitable 535 nM excitation and 590 nM emission interference filters. Compounds that interact with the GR result in a lower fluorescence polarization reading. Test compounds are dissolved and diluted in DMSO. Compounds are assayed in singlicate, a four parameter curve fit of the following form being applied

$$y = \frac{a - d}{1 + \left(\frac{x}{c}\right)^b} + d$$

where a is the minimum, b is the Hill slope, c is the EC₅₀ and d is the maximum. Maximum and minimum values are compared to adhesion in the absence of compound and in the presence of 10⁻⁵M dexamethasone. Data is presented as the mean pIC₅₀ with the standard error of the mean of n experiments. Compounds with pIC₅₀ greater than 6.0 and a % max greater than 50 are preferred.

Example Number	pIC ₅₀ in GR – FPA (as described above)
1-401	≥ 5.8

Progesterone Receptor Fluorescence Polarization Assay (PR – FPA):

The progesterone receptor fluorescence polarization assay is used to investigate the interaction of the compounds with the progesterone receptor.

Compounds are added to the 384 well black plates to a final volume of 0.5 μL. Sufficient Fluormone PL Red and PR-LBD are defrosted on ice to give a final concentration of 2 nM and 40 nM, respectively. PR screening buffer is chilled to 4°C prior to addition of DTT to give a final concentration of 1 mM. The Fluormone PL Red and PR-LBD in PR Screening Buffer are added to compound plates to give a final volume of 10 μL. The assay is allowed to incubate at 20-22°C for 2 hours. The plates are counted in a Discovery Analyst with suitable 535 nM excitation and 590 nM emission interference filters. Compounds that interact with the PR result in a lower fluorescence polarization reading. Test compounds are dissolved and diluted in DMSO. Compounds are assayed in singlicate, a four parameter curve fit of the following form being applied

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$$y = \frac{a - d}{1 + \left(\frac{x}{c}\right)^b} + d$$

where a is the minimum, b is the Hill slope, c is the IC₅₀ and d is the maximum. Maximum and minimum values are compared to adhesion in the absence of compound and in the presence of 10⁻⁵M progesterone. Data is presented as the mean pIC₅₀ with the standard error of the mean of n experiments.

Androgen Receptor Fluorescence Polarization Assay (AR – FPA):

The androgen receptor fluorescence polarization assay is used to investigate the interaction of the compounds with the androgen receptor.

Compounds are added to the 384 well black plates to a final volume of 0.5 μL. Sufficient Fluormone AL Green and AR-LBD are defrosted on ice to give a final concentration of 1 nM and 25 nM, respectively. AR screening buffer is chilled to 4 °C prior to addition of DTT to give a final concentration of 1 mM. The Fluormone AL Green and AR-LBD in AR Screening Buffer are added to compound plates to give a final volume of 10 μL. The assay is allowed to incubate at 20°C for 5 hours. The plates are counted in a Discovery Analyst with suitable 485 nM excitation and 535 nM emission interference filters. Compounds that interact with the AR result in a lower fluorescence polarization reading. Test compounds are dissolved and diluted in DMSO. Compounds are assayed in singlicate, a four parameter curve fit of the following form being applied

$$y = \frac{a - d}{1 + \left(\frac{x}{c}\right)^b} + d$$

where a is the minimum, b is the Hill slope, c is the IC₅₀ and d is the maximum. Maximum and minimum values are compared to adhesion in the absence of compound and in the presence of 10⁻⁵M dihydrotestosterone. Data is presented as the mean pIC₅₀ with the standard error of the mean of n experiments.

Cellular tyrosine aminotransferase assay:

H4IIE-C3 cells were dispensed into a 96 well plate (40,000 cells/well) and were cultured in low glucose DMEM, 10% FBS, and 1x Pen/Strep. After three days, the cells were fed with an additional 200μl of fresh serum-free media. After 24 hours of serum

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starvation, each well was treated either with vehicle, dexamethasone, or dexamethasone plus the appropriate GR ligand in serum free media. This treatment lasted 24 hours. The media was then removed and the cells were washed once with PBS, followed by the treatment with 50 μ l of solubilization buffer (125mM K₂HPO₄ pH=7.6, 1.0mM EDTA pH=8.0, 0.5% Nonidet P-40, with 1.0mM DTT added immediately before use), which was precooled to 4 °C. This was followed by the 150 μ l treatment of a premixed solution: 130 μ l of an L-tyrosine solution [1.0ml of L-tyrosine stock solution (63.13mg L-tyrosine in 32ml of 125mM K₂HPO₄, 150 μ l 10N KOH) and 0.6ml of 125mM KH₂PO₄], 10 μ l of a 1mM pyridoxyl phosphate solution (4.8mg of pyridoxyl phosphate in 10ml of 125mM K₂HPO₄), and 10 μ l of a 200mM a-ketoglutarate solution (368mg of a-ketoglutarate in 10ml of 125mM K₂HPO₄ and 150 μ l of 10N KOH). The cells were incubated for 30 minutes at 37 °C. At this point 3 μ l of 10N KOH was added and incubated for an additional 30 minutes at 37 °C. Each well was analyzed spectroscopically (Spectramax instrument) at 340nm and IC₅₀s determined using GraphPad Prism 3.0. Compounds with pIC₅₀ greater than 5.0 are preferred.

***In vivo* gluconeogenesis mouse model:**

Nine to ten week old CD-1 male mice were fasted overnight on alpha-dry bedding. The model was separated into three groups: a vehicle group, a control group, and a treatment group. The procedure for each is shown below:

Vehicle Group

After overnight fasting as described above, DMSO (5ml/kg) was administered i.p. thirty minutes prior to saline (10 ml/kg) i.p. Blood glucose was monitored before DMSO administration and 1, 2, and 3 hours after saline administration via tail snips (10 μ l) using a Glucometer Elite XL.

Dexamethasone Group

After overnight fasting as described above, DMSO (5ml/kg) was administered i.p., followed by dexamethasone phosphate in saline thirty minutes later (1mg/kg, 10ml/kg). Blood glucose was monitored before DMSO and 1, 2, and 3 hours after dexamethasone phosphate via tail snips (10 μ l) using a Glucometer Elite XL.

Treatment Group

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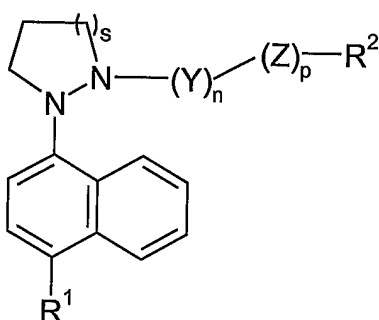
After overnight fasting as described above, GR antagonists (in DMSO, 5ml/kg) were administered i.p. After thirty minutes, Dexamethasone phosphate in saline (1mg/kg, 10ml/kg) was administered i.p. Blood glucose was monitored before GR antagonist dosing and 1, 2, and 3 hours after Dexamethasone administration via tail snips (10ul) using a Glucometer Elite XL.

Compounds that reduce or prevent dexamethasone-induced increases in blood glucose in the treatment group are preferred.

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CLAIMS

What is claimed is:

1. A compound of formula (I):



or a salt or solvate thereof, wherein

s is 1, 2, 3 or 4;

R¹ is cyano or nitro;

Y is -C(O)-;

Z is alkylene or -(R^a)_mO-;

R^a is alkylene;

m is 0 or 1;

n is 0 or 1;

p is 0 or 1;

R² is alkyl, cyano, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, aryl, substituted aryl, heteroaryl, substituted heteroaryl, haloalkyl, diphenylalkyl, alkylsilyl, amino, hydroxyl, -C(O)OCH₃, -CH(CN)CH₂Ph, -CH(OCH₂CH₃)Ph, or -NH(CH₂)₂Ph, wherein

when R² is substituted cycloalkyl, substituted aryl, substituted heteroaryl, or substituted heterocycle, each substituent is independently selected from the group consisting of alkyl, alkenyl, aryl, alkylaryl, alkylthio, alkoxy, alkenoxy, aryloxy, aralkoxy, halo, haloalkyl, haloaryl, haloalkoxy, haloalkylthio, haloalkylaryl, alkylsulfonyl, cyano, nitro, heterocycle, heteroaryl, cycloalkyl-alkylene, CH₃C(O)-, CH₃C(O)OCH₂-, and CH₃C(O)NH-.

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2. A compound as claimed in claim 1, wherein s is 1, 2, or 3.
3. A compound as claimed in claim 1, wherein
s is 1;
5 R^1 is cyano or nitro;
Y is $-C(O)-$;
Z is alkylene;
n is 0 or 1;
p is 0 or 1;
- 10 R^2 is alkyl, cycloalkyl, heteroaryl, aryl, substituted aryl, haloalkyl, or amino, wherein
when R^2 is substituted aryl, each substituent is independently selected from the
group consisting of alkyl, alkoxy, halo, haloalkyl, haloalkoxy, cyano, and $CH_3C(O)-$.
4. A compound as claimed in claim 1, wherein
15 s is 3;
 R^1 is cyano or nitro;
Y is $-C(O)-$;
Z is alkylene;
n is 0 or 1;
20 p is 0 or 1;
- R^2 is alkyl, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, aryl,
substituted aryl, heteroaryl, substituted heteroaryl, or haloalkyl, wherein
when R^2 is substituted cycloalkyl, substituted aryl, substituted heteroaryl, or
substituted heterocycle, each substituent is independently selected from the group
25 consisting of alkyl, alkenyl, aryl, alkylaryl, alkoxy, halo, haloalkyl, haloalkoxy, and
cyano.
5. A compound as claimed in claim 1, wherein
s is 2;
30 R^1 is cyano or nitro;
Y is $-C(O)-$;
Z is alkylene or $-(R^a)_mO-$;

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R^a is alkylene;

m is 0 or 1;

n is 0 or 1;

p is 0 or 1;

5 R^2 is alkyl, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, aryl, substituted aryl, heteroaryl, substituted heteroaryl haloalkyl, diphenylalkyl, amino, hydroxyl, $-C(O)OCH_3$, $-CH(CN)CH_2Ph$, $-CH(OCH_2CH_3)Ph$, or $-NH(CH_2)_2Ph$, wherein

10 when R^2 is substituted cycloalkyl, substituted aryl, substituted heteroaryl, or substituted heterocycle, each substituent is independently selected from the group consisting of alkyl, alkenyl, aryl, alkylaryl, alkylthio, alkoxy, alkenoxy, aryloxy, aralkoxy, halo, haloalkyl, haloaryl, haloalkoxy, haloalkylthio, haloalkylaryl, alkylsulfonyl, cyano, nitro, heterocyclyl, cycloalkyl-alkylene, $CH_3C(O)-$, $CH_3C(O)OCH_2-$, and $CH_3C(O)NH-$.

15 6. A compound as claimed in claim 1, wherein

s is 2;

R^1 is cyano or nitro;

Y is $-C(O)-$;

Z is alkylene

20 n is 0 or 1;

p is 1;

R^2 is heterocycle, substituted aryl, or substituted heteroaryl, wherein

25 when R^2 is substituted aryl or substituted heteroaryl, each substituent is independently selected from the group consisting of alkyl, aryl, haloalkyl, haloalkoxy, cyano, and heteroaryl.

7. A compound as claimed in claim 1, wherein s is 2.

8. A compound as claimed in claim 1, wherein n is 0.

30

9. A compound as claimed in claim 1, wherein Y is $-C(O)-$ and n is 1.

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10. A compound as claimed in claim 1, wherein Z is alkylene and p is 1.

11. A compound as claimed in claim 10, wherein Z is methylene and p is 1.

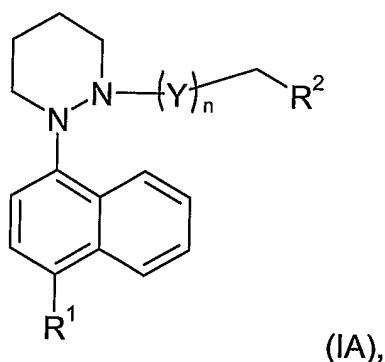
5 12. A compound as claimed in claim 1, wherein R^2 is heterocycle, substituted aryl, or substituted heteroaryl, wherein

when R^2 is substituted aryl or substituted heteroaryl, each substituent is independently selected from the group consisting of alkyl, aryl, haloalkyl, haloalkoxy, cyano, and heteroaryl.

10

13. A compound as claimed in claim 1, wherein R^1 is cyano.

14. A compound of formula (IA):



15 or a salt or solvate thereof, wherein

R^1 is cyano or nitro;

Y is $-C(O)-$;

n is 0 or 1;

R^2 is substituted aryl, heterocycle, or substituted heteroaryl, wherein

20 when R^2 is substituted aryl or substituted heteroaryl, each substituent is independently selected from the group consisting of alkyl, haloalkyl, haloalkoxy, heteroaryl, cyano and aryl.

15. A compound as claimed in claim 14, wherein R^1 is cyano.

25

16. A compound as claimed in claim 14, wherein n is 0.

17. A compound as claimed in claim 14, wherein Y is $-C(O)-$ and n is 1.
18. A compound as claimed in claim 14, wherein Z is alkylene and p is 1.
19. A compound as claimed in claim 18, wherein Z is methylene and p is 1.
20. A compound selected from:
- 4-[2-(phenylmethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
- 4-[2-{[4-(methyloxy)phenyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
- 4-[2-{[3-(ethyloxy)phenyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
- 4-[2-{[4-(ethyloxy)phenyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
- 4-[2-{[4-(butyloxy)phenyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
- 4-[2-{[4-(ethylphenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
- 4-[2-{[4-(1-methylethyl)phenyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
- 4-[2-{[2-bromophenyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
- 4-[2-{[3-bromophenyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
- 4-[2-{[4-bromophenyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
- 4-[2-{[2-chlorophenyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
- 4-[2-{[2-methylphenyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

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4-[2-[(3-chlorophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(4-chlorophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

5 4-[2-[(2-fluorophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(3-fluorophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

10 4-[2-[(4-fluorophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(2-cyanophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(3-cyanophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

15 4-[2-[(4-cyanophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[4-(methylthio)phenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

20 4-[2-[(3,4-dichlorophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(3-methylphenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(4-acetylphenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

25 4-[2-[[4-(methylsulfonyl)phenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[4-(phenyloxy)phenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

30 4-[2-[(4-butylphenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[2-[(1,1-dimethylethyl)thio]phenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

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4-[2-({3-[(trifluoromethyl)thio]phenyl}methyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{{2,4-bis(trifluoromethyl)phenyl}methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

5 4-[2-{{3,5-bis(trifluoromethyl)phenyl}methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(4-methylphenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

10 4-[2-(1-naphthalenylmethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(2-naphthalenylmethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(3-thienylmethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

15 4-[2-{{2,4-bis(methyloxy)phenyl}methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{{2-(trifluoromethyl)phenyl}methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{{4-(trifluoromethyl)phenyl}methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

20 4-[2-{{2-(methyloxy)phenyl}methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{{3-(methyloxy)phenyl}methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

25 4-[2-{{3-(phenyloxy)phenyl}methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(cyclohexylmethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{{2-(2-propen-1-yloxy)phenyl}methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

30 4-[2-(2,1,3-benzoxadiazol-4-ylmethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{{1-(1,1-dimethylethyl)-5-methyl-1H-pyrazol-3-yl}methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

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4-[2-{{[5-(2-pyridinyl)-2-thienyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{{[1-phenyl-1H-pyrazol-5-yl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

5 4-[2-{{[2-phenyl-1H-imidazol-4-yl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{{[3-phenyl-1H-pyrazol-4-yl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

10 N-(5-{{[2-(4-cyano-1-naphthalenyl)tetrahydro-1(2H)-pyridazinyl]methyl}-1,3-thiazol-2-yl)acetamide;

4-[2-(2-pyridinylmethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
(5-{{[2-(4-cyano-1-naphthalenyl)tetrahydro-1(2H)-pyridazinyl]methyl}-2-furanyl)methyl acetate;

15 4-[2-{{[1-phenyl-1H-imidazol-2-yl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{{[6-(methyloxy)-2-pyridinyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(1H-pyrazol-3-ylmethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

20 4-[2-{{[2-ethyl-4-methyl-1H-imidazol-5-yl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

5-{{[2-(4-cyano-1-naphthalenyl)tetrahydro-1(2H)-pyridazinyl]methyl}-3-pyridinecarbonitrile;

25 4-[2-{{[1-phenyl-1H-pyrazol-4-yl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{{[3-methyl-2-thienyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{{[5-methyl-2-thienyl]methyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

30 4-[2-(1H-imidazol-4-ylmethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

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4-[2-[(3,5-dichlorophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(5-chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

5 4-[2-[(3,5-dibromophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(5-[3-(trifluoromethyl)phenyl]-2-furanyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

10 4-[2-[[1-(3,5-dichlorophenyl)-1H-pyrrol-2-yl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[3-fluoro-5-(trifluoromethyl)phenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(3,5-difluorophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

15 4-[2-[[3,5-bis(methoxy)phenyl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(5-ethyl-2-furanyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

20 4-[2-[(5-bromo-2-furanyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(4,5-dimethyl-2-furanyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(3-pyridinylmethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile

25 4-[2-[(6-methyl-2-pyridinyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(4-bromo-1H-pyrazol-3-yl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(5-bromo-2-thienyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

30 4-[2-[[5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(1-methyl-1*H*-imidazol-2-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(4-methyl-1*H*-imidazol-5-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

5 4-[2-[[4-chloro-2-(cyclopropylmethyl)-1*H*-imidazol-5-yl]methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(2-butyl-1*H*-imidazol-4-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

10 4-[2-[(3-bromo-4-pyridinyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(6-[(1,1-dimethylethyl)oxy]-2-pyridinyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(2-ethyl-1*H*-imidazol-4-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

15 4-[2-[(4-bromo-2-thienyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(1*H*-pyrazol-4-ylmethyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

20 4-[2-[(5-methyl-2-furanyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(5-bromo-3-thienyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(1,3-dimethyl-1*H*-pyrazol-5-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

25 4-[2-[(6-bromo-3-pyridinyl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(1*H*-1,2,3-triazol-4-ylmethyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

30 4-[2-(1*H*-imidazol-2-ylmethyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-(2-[[1-(1,1-dimethylethyl)-5-methyl-1*H*-pyrazol-3-yl]methyl]hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

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4-[2-({2-[(trifluoromethyl)oxy]phenyl}methyl)hexahydro-1*H*-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile;

4-[2-(1*H*-1,2,3-triazol-4-ylmethyl)hexahydro-1*H*-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile;

5 4-[2-(phenylmethyl)hexahydro-1*H*-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile;

4-{2-[(4-phenyl-1*H*-imidazol-5-yl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-(2-hexylhexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

10 4-{2-[(3-ethenylphenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-{2-[(2-fluorophenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-{2-[(1-phenyl-1*H*-pyrazol-4-yl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

15 4-[2-(2-pyridinylmethyl)hexahydro-1*H*-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile;

4-{2-[(3,5-dimethylphenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

20 4-{2-[(3-methyl-5-phenyl-4-isoxazolyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-{2-[(2-methylphenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-(2-{[2-(trifluoromethyl)phenyl]methyl}hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

25 4-[2-(3-pyridinylmethyl)hexahydro-1*H*-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile;

4-{2-[(3-phenyl-1*H*-pyrazol-5-yl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

30 5-{[2-(4-cyano-1-naphthalenyl)hexahydro-1*H*-1,2-diazepin-1-yl]methyl}-3-pyridinecarbonitrile;

4-{2-[(2,2,3,3-tetramethylcyclopropyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

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4-{2-[(1,3-dimethyl-1*H*-pyrazol-5-yl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-{2-[(1-phenyl-1*H*-pyrazol-5-yl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

5 4-{2-[(4-bromo-1*H*-pyrazol-3-yl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-{2-[(3-methylphenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

10 4-{2-[(2-cyanophenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-{2-[(3-(4-methylphenyl)-1*H*-pyrazol-4-yl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

4-{2-[(6-methyl-2-pyridinyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

15 4-{2-[(4-cyanophenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-{2-(1*H*-pyrazol-3-ylmethyl)hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

20 4-{2-(4-pyridinylmethyl)hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-{2-(2-cyclopentylethyl)hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-{2-[(3-cyanophenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

25 4-{2-[(4-(trifluoromethyl)phenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

4-{2-[(2-fluoro-3-(trifluoromethyl)phenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

30 4-{2-[(3-(ethyloxy)phenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

4-{2-[(3-fluorophenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-{2-[(3-methyl-2-thienyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-(2-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

5 4-[2-({3-[(trifluoromethyl)oxy]phenyl}methyl)hexahydro-1*H*-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile;

4-[2-({3-[(trifluoromethyl)oxy]phenyl}methyl)hexahydro-1*H*-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile;

10 4-{2-[(5-methyl-2-thienyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-[2-(2-naphthalenylmethyl)hexahydro-1*H*-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile;

4-{2-[(3-phenyl-1*H*-pyrazol-4-yl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

15 4-(2-{[3-(trifluoromethyl)phenyl]methyl}hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

4-(2-{[6-(methyloxy)-2-pyridinyl]methyl}hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

20 4-{2-[(3,5-difluorophenyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-{2-[(4,5-dimethyl-2-furanyl)methyl]hexahydro-1*H*-1,2-diazepin-1-yl}-1-naphthalenecarbonitrile;

4-(2-{[3,5-bis(trifluoromethyl)phenyl]methyl}hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

25 4-[2-(1-naphthalenylmethyl)hexahydro-1*H*-1,2-diazepin-1-yl]-1-naphthalenecarbonitrile;

4-(2-{[4-(methyloxy)phenyl]methyl}hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

30 4-(2-{[3-(methyloxy)phenyl]methyl}hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

4-(2-{[2-(methyloxy)phenyl]methyl}hexahydro-1*H*-1,2-diazepin-1-yl)-1-naphthalenecarbonitrile;

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- 4-[[2-(4-nitro-1-naphthalenyl)tetrahydro-1(2H)-pyridazinyl]methyl]benzonitrile;
1-[[4-(1-methylethyl)phenyl]methyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
1-(4-nitro-1-naphthalenyl)-2-(phenylmethyl)hexahydropyridazine;
5 1-(cyclohexylmethyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
4-[2-(3-phenylbutyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
4-[2-(3-phenylpropyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;
1-(4-nitro-1-naphthalenyl)-2-(3-phenylbutyl)hexahydropyridazine;
1-(4-nitro-1-naphthalenyl)-2-(3-phenylpropyl)hexahydropyridazine;
10 1-methyl-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
Methyl 6-[2-(4-nitro-1-naphthalenyl)tetrahydro-1(2H)-pyridazinyl]hexanoate;
4-{2-[(3-bromophenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;
4-[2-(3-thienylmethyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;
4-(2-{[2,4-bis(trifluoromethyl)phenyl]methyl}-1-pyrazolidinyl)-1-naphthalenecarbonitrile;
15 naphthalenecarbonitrile;
4-{2-[(3-fluorophenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;
4-{2-[(2-bromophenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;
4-{2-[(4-acetylphenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;
4-(2-{[2-(trifluoromethyl)phenyl]methyl}-1-pyrazolidinyl)-1-naphthalenecarbonitrile;
20 naphthalenecarbonitrile;
4-(2-{[4-(1-methylethyl)phenyl]methyl}-1-pyrazolidinyl)-1-naphthalenecarbonitrile;
4-{2-[(4-fluorophenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;
4-(2-{[4-(trifluoromethyl)phenyl]methyl}-1-pyrazolidinyl)-1-naphthalenecarbonitrile;
25 4-[2-({3-[(trifluoromethyl)oxy]phenyl}methyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;
4-{2-[(2-fluorophenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;
4-(2-{[3-(methyloxy)phenyl]methyl}-1-pyrazolidinyl)-1-naphthalenecarbonitrile;
4-(2-{[3,5-bis(trifluoromethyl)phenyl]methyl}-1-pyrazolidinyl)-1-naphthalenecarbonitrile;
30 naphthalenecarbonitrile;
4-(2-{[3-fluoro-5-(trifluoromethyl)phenyl]methyl}-1-pyrazolidinyl)-1-naphthalenecarbonitrile;

4-(2-[[3-(trifluoromethyl)phenyl]methyl]-1-pyrazolidinyl)-1-naphthalenecarbonitrile;

4-{2-[(4-methylphenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

4-[2-(1-naphthalenylmethyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;

5 4-[2-(phenylmethyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;

4-{2-[(3,4-dichlorophenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

4-(2-[[4-(methyloxy)phenyl]methyl]-1-pyrazolidinyl)-1-naphthalenecarbonitrile;

4-(2-[[3-(ethyloxy)phenyl]methyl]-1-pyrazolidinyl)-1-naphthalenecarbonitrile;

4-{2-[(4-cyanophenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

10 4-{2-[(3-cyanophenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

4-{2-[(2-methylphenyl)methyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

4-[2-[(4-phenyl-1*H*-imidazol-5-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-

naphthalenecarbonitrile;

4-[2-[[3-(1-methylethyl)-1*H*-pyrazol-4-yl]methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-

15 naphthalenecarbonitrile;

4-[2-[[3-(1-methylethyl)-1*H*-pyrazol-4-yl]methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-

naphthalenecarbonitrile;

4-[2-[(3-ethyl-1*H*-pyrazol-4-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-

naphthalenecarbonitrile;

20 4-[2-[(3-propyl-1*H*-pyrazol-4-yl)methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-

naphthalenecarbonitrile;

4-[2-[[3-(2-pyridinyl)-1*H*-pyrazol-4-yl]methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[3-(3-methylphenyl)-1*H*-pyrazol-4-yl]methyl]tetrahydro-1(2*H*)-pyridazinyl]-1-

25 naphthalenecarbonitrile;

1-(2-[[1,1-dimethylethyl)(dimethyl)silyl]oxy]ethyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

4-[2-(2-[[1,1-dimethylethyl)(dimethyl)silyl]oxy]ethyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

30 4-[2-{2-[2-(trifluoromethyl)phenyl]ethyl}tetrahydro-1(2*H*)-pyridazinyl]-1-

naphthalenecarbonitrile;

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4-[2-[2-(3,4-dichlorophenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-(3-fluorophenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

5 4-[2-[2-(2-methylphenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-[3-(methyloxy)phenyl]ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

10 4-[2-[2-(4-fluorophenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-(4-methylphenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-(2-bromophenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

15 4-[2-[2-(3-methylphenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-(2,4-dichlorophenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(2-phenylethyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

20 4-[2-[2-(1-naphthalenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-[3-(trifluoromethyl)phenyl]ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

25 4-[2-[2-(3-bromophenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-(2,6-dichlorophenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-(2-chloro-4-fluorophenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

30 4-[2-[2-(2-chlorophenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-(2,4,6-trimethylphenyl)ethyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

1-[2-(2,6-dichlorophenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-[2-(2-chloro-4-fluorophenyl)ethyl]-2-(4-nitro-1-

5 naphthalenyl)hexahydropyridazine;

1-[2-(2-chlorophenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-(4-nitro-1-naphthalenyl)-2-[2-(2,4,6-trimethylphenyl)ethyl]hexahydropyridazine;

1-[2-(2-methylphenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-[2-[3-(methoxy)phenyl]ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

10 1-(4-nitro-1-naphthalenyl)-2-[2-[2-

(trifluoromethyl)phenyl]ethyl]hexahydropyridazine;

1-[2-(2-bromophenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-(4-nitro-1-naphthalenyl)-2-[2-(3-nitrophenyl)ethyl]hexahydropyridazine;

1-[2-(3-methylphenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

15 1-[2-(2,4-dichlorophenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-[2-(1-naphthalenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-(4-nitro-1-naphthalenyl)-2-[2-[3-

(trifluoromethyl)phenyl]ethyl]hexahydropyridazine;

1-[2-(3-bromophenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

20 1-[2-(4-fluorophenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

4-[2-[2-(4-nitro-1-naphthalenyl)tetrahydro-1(2H)-pyridazinyl]ethyl]benzonitrile;

1-[2-(4-chlorophenyl)ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-[2-[4-(ethoxy)phenyl]ethyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-(4-nitro-1-naphthalenyl)-2-(2-phenylethyl)hexahydropyridazine;

25 4-[2-(cyclohexylcarbonyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-(2-pentanoyl)tetrahydro-1(2H)-pyridazinyl)-1-naphthalenecarbonitrile;

4-[2-({3-[(phenylmethyl)oxy]phenyl}acetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(cyclopentylacetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

30 4-[2-(phenylacetyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(2-phenylbutanoyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

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4-[2-[[[(1S,2S)-2-phenylcyclopropyl]carbonyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(3-phenylpropanoyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(3,3-dimethylbutanoyl)tetrahydro-1(2H)-pyridazinyl]-1-

5 naphthalenecarbonitrile;

4-[2-[[4-(methyloxy)phenyl]carbonyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-([3-[(trifluoromethyl)oxy]phenyl]carbonyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

10 4-[2-[[3-(methyloxy)phenyl]carbonyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[2-(methyloxy)phenyl]carbonyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

15 4-[2-[[2-(trifluoromethyl)phenyl]carbonyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[3-(trifluoromethyl)phenyl]carbonyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-([4-[(trifluoromethyl)oxy]phenyl]carbonyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

20 4-[2-[(3-cyanophenyl)carbonyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[[4-(trifluoromethyl)phenyl]carbonyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

25 4-[2-([2-[(trifluoromethyl)oxy]phenyl]carbonyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

1-(4-nitro-1-naphthalenyl)-2-pentanoylhexahydropyridazine;

1-(4-nitro-1-naphthalenyl)-2-[[3-(trifluoromethyl)phenyl]carbonyl]hexahydropyridazine;

30 1-(4-nitro-1-naphthalenyl)-2-[[4-(trifluoromethyl)phenyl]carbonyl]hexahydropyridazine;

4-[[2-(4-nitro-1-naphthalenyl)tetrahydro-1(2H)-pyridazinyl]carbonyl]benzonitrile;

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1-[[3-(methyloxy)phenyl]carbonyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-[[4-(methyloxy)phenyl]carbonyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

5 1-(1-naphthalenylcarbonyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-(2-naphthalenylcarbonyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-(4-nitro-1-naphthalenyl)-2-(2-thienylcarbonyl)hexahydropyridazine;

1-(2-methylpropanoyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-[(2-bromophenyl)carbonyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

10 1-[(3-bromophenyl)carbonyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-[(4-bromophenyl)carbonyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-[(2,4-dichlorophenyl)carbonyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-[[4-(1,1-dimethylethyl)phenyl]carbonyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

15 1-(4-nitro-1-naphthalenyl)-2-[(phenyloxy)acetyl]hexahydropyridazine;

1-(4-nitro-1-naphthalenyl)-2-(2-phenylbutanoyl)hexahydropyridazine;

1-(4-nitro-1-naphthalenyl)-2-(phenylacetyl)hexahydropyridazine;

1-(cyclopropylcarbonyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-(3-methylbutanoyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

20 1-(cyclohexylcarbonyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-[(3-methylphenyl)carbonyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-[(4-methylphenyl)carbonyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-(4-nitro-1-naphthalenyl)-2-[[2-(trifluoromethyl)phenyl]carbonyl]hexahydropyridazine;

25 1-[[3-(methyloxy)phenyl]acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-[[4-(butyloxy)phenyl]carbonyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-(cyclobutylcarbonyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-(cyclopentylcarbonyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-(cyclopentylacetyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

30 1-(2-methylpentanoyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-(3-cyclopentylpropanoyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-[(2-bromophenyl)acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

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- 1-(3,3-dimethylbutanoyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
1-(4-nitro-1-naphthalenyl)-2-[(1*S*,2*S*)-2-phenylcyclopropyl]carbonyl}hexahydropyridazine;
1-(4-nitro-1-naphthalenyl)-2-(3-phenylpropanoyl)hexahydropyridazine;
5 1-[(4-chlorophenyl)acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
1-(diphenylacetyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
1-{[4-(methyloxy)phenyl]acetyl}-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
1-(4-nitro-1-naphthalenyl)-2-({3-[(trifluoromethyl)oxy]phenyl}carbonyl)hexahydropyridazine;
10 4-(2-acetyl-1-pyrazolidinyl)-1-naphthalenecarbonitrile;
4-[2-(2-methylpropanoyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;
4-[2-(3-phenylpropanoyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;
4-(2-butanoyl-1-pyrazolidinyl)-1-naphthalenecarbonitrile;
4-[2-(cyclopropylcarbonyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;
15 4-[2-(3-methylbutanoyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;
4-[2-(phenylcarbonyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;
4-(2-{[3-(trifluoromethyl)phenyl]carbonyl}-1-pyrazolidinyl)-1-naphthalenecarbonitrile;
4-{2-[(2-fluorophenyl)carbonyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;
20 4-{2-[(3-methylphenyl)carbonyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;
4-[2-(2-furanylcarbonyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;
4-{2-[(3-fluorophenyl)carbonyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;
4-{2-[(2-methylphenyl)carbonyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;
4-[2-(cyclopentylcarbonyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;
25 4-[2-(2-phenylbutanoyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;
4-[2-({2-[(trifluoromethyl)oxy]phenyl}acetyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;
4-[2-({[2-(methyloxy)phenyl]acetyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;
30 4-[2-({[4-(ethyloxy)phenyl]acetyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{[2-(ethyloxy)phenyl]acetyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{[3-(methyloxy)phenyl]acetyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

5 4-[2-{[3-(ethyloxy)phenyl]acetyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{[4-[(trifluoromethyl)oxy]phenyl]acetyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

10 4-[2-{[2-fluoro-6-(trifluoromethyl)phenyl]acetyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{[2-fluorophenyl]acetyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{[2,3-difluorophenyl]acetyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

15 4-[2-{[2-(phenyloxy)phenyl]acetyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{[2-iodophenyl]acetyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

20 4-[2-{[pentafluorophenyl]acetyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{[2-naphthalenylacetyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{[2-bromophenyl]acetyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

25 4-[2-{[3-(trifluoromethyl)phenyl]acetyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{[2,4-difluorophenyl]acetyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

30 4-[2-{[2-[(phenylmethyl)oxy]phenyl]acetyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{[2-(trifluoromethyl)phenyl]acetyl}tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(2,6-difluorophenyl)acetyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(2-chloro-4-fluorophenyl)acetyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

5 4-[2-[(4-fluorophenyl)acetyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(3-nitrophenyl)acetyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

10 4-[2-[(3,4-dichlorophenyl)acetyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(2-chloro-6-fluorophenyl)acetyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(2-methylphenyl)acetyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

15 4-[2-[(3-methylphenyl)acetyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-({3-[(trifluoromethyl)oxy]phenyl}acetyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

20 4-[2-({3-[(trifluoromethyl)oxy]phenyl}acetyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;

4-[2-({3-[(trifluoromethyl)oxy]phenyl}acetyl)-1-pyrazolidinyl]-1-naphthalenecarbonitrile;

4-{2-[(2-fluorophenyl)acetyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

4-(2-{[3-(trifluoromethyl)phenyl]acetyl}-1-pyrazolidinyl)-1-naphthalenecarbonitrile;

25 4-{2-[(2-bromophenyl)acetyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

4-{2-[(3-methylphenyl)acetyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

4-{2-[(2-methylphenyl)acetyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

4-{2-[(3,4-dichlorophenyl)acetyl]-1-pyrazolidinyl}-1-naphthalenecarbonitrile;

4-[2-({2-[(trifluoromethyl)oxy]phenyl}acetyl)-1-pyrazolidinyl]-1-

30 naphthalenecarbonitrile;

4-[2-(3-isoxazolylacetyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

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4-[2-[(1-methyl-1*H*-indol-3-yl)acetyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[(ethyloxy)(phenyl)acetyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

5 4-[2-(2-thienylacetyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(3-thienylacetyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(2-furanylacetyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[3-(4-fluorophenyl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-

naphthalenecarbonitrile;

10 4-[2-[3-(3-bromophenyl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-

naphthalenecarbonitrile;

4-[2-[3-(3,4-dichlorophenyl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-

naphthalenecarbonitrile;

4-[2-[3-(1,3-benzodioxol-5-yl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-

15 naphthalenecarbonitrile;

4-[2-[3-[3,5-bis(trifluoromethyl)phenyl]propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-

naphthalenecarbonitrile;

4-[2-[(3*R*)-3-phenylbutanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-

naphthalenecarbonitrile;

20 4-[2-{3-[4-(trifluoromethyl)phenyl]propanoyl}tetrahydro-1(2*H*)-pyridazinyl]-1-

naphthalenecarbonitrile;

4-[2-(3-[4-[(trifluoromethyl)oxy]phenyl]propanoyl)tetrahydro-1(2*H*)-pyridazinyl]-1-

naphthalenecarbonitrile;

4-[2-[3-(3,4-difluorophenyl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-

25 naphthalenecarbonitrile;

4-[2-{3-[2-(methyloxy)phenyl]propanoyl}tetrahydro-1(2*H*)-pyridazinyl]-1-

naphthalenecarbonitrile;

4-[2-[3-(2-bromophenyl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-

naphthalenecarbonitrile;

30 4-[2-[3-(3-chlorophenyl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-

naphthalenecarbonitrile;

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4-[2-(3,3-diphenylpropanoyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile

4-[2-{3-[3-(methyloxy)phenyl]propanoyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

5 4-[2-[3-(2-chlorophenyl)propanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[3-(4-methylphenyl)propanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

10 4-[2-{3-[3-(trifluoromethyl)phenyl]propanoyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{3-[4-(methyloxy)phenyl]propanoyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-(3-phenylbutanoyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

15 4-[2-[3-(2-fluorophenyl)propanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-{[4-fluoro-2-(trifluoromethyl)phenyl]acetyl}tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[3-(2-methylphenyl)propanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

20 4-[2-[3-(3-fluorophenyl)propanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[3-(4-bromophenyl)propanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-(phenyloxy)propanoyl]tetrahydro-1(2H)-pyridazinyl]-1-

25 naphthalenecarbonitrile;

4-[2-(2-cyano-3-phenylpropanoyl)tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[3-methyl-3-(1H-pyrrol-1-yl)butanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

30 4-[2-[3-(2-furanyl)propanoyl]tetrahydro-1(2H)-pyridazinyl]-1-naphthalenecarbonitrile;

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4-[2-[3-(4-methyl-1,3-thiazol-5-yl)propanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-(phenyloxy)butanoyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

5 1-[(4-methylphenyl)acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-(4-nitro-1-naphthalenyl)-2-[[4-(trifluoromethyl)phenyl]acetyl]hexahydropyridazine;

1-(4-nitro-1-naphthalenyl)-2-({2-[(trifluoromethyl)oxy]phenyl}acetyl)hexahydropyridazine;

10 1-(4-nitro-1-naphthalenyl)-2-[[3-(trifluoromethyl)phenyl]acetyl]hexahydropyridazine;

1-[(3-bromophenyl)acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-(4-nitro-1-naphthalenyl)-2-({2-[(phenylmethyl)oxy]phenyl}acetyl)hexahydropyridazine;

15 1-[[2-(ethyloxy)phenyl]acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-(4-nitro-1-naphthalenyl)-2-[[2-(trifluoromethyl)phenyl]acetyl]hexahydropyridazine;

1-[(3-methylphenyl)acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-[[3-(ethyloxy)phenyl]acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

20 1-(2-naphthalenylacetyl)-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-[[2-(methyloxy)phenyl]acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-[[4-(ethyloxy)phenyl]acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-[(4-bromophenyl)acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

1-[(2-methylphenyl)acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

25 1-(4-nitro-1-naphthalenyl)-2-[[3-(phenyloxy)phenyl]acetyl]hexahydropyridazine;

1-[[3,4-bis(methyloxy)phenyl]acetyl]-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;

4-[2-(2-hydroxyethyl)tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

2-[2-(4-nitro-1-naphthalenyl)tetrahydro-1(2*H*)-pyridazinyl]ethanol;

30 4-[2-[2-(phenyloxy)ethyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-[2-[(3-chlorophenyl)oxy]ethyl]tetrahydro-1(2*H*)-pyridazinyl]-1-naphthalenecarbonitrile;

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1-(4-nitro-1-naphthalenyl)-2-[2-(phenyloxy)ethyl]hexahydropyridazine;
1-{2-[(2-methylphenyl)oxy]ethyl}-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
1-{2-[(3-chlorophenyl)oxy]ethyl}-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
1-{2-[(4-methylphenyl)oxy]ethyl}-2-(4-nitro-1-naphthalenyl)hexahydropyridazine;
5 2-(4-cyano-1-naphthalenyl)tetrahydro-1(2H)-pyridazinecarbonitrile;
2-(4-nitro-1-naphthalenyl)tetrahydro-1(2H)-pyridazinecarbonitrile;
4-[2-(2,2,2-trifluoroethyl)hexahydro-1H-1,2-diazepin-1-yl]-1-

naphthalenecarbonitrile;

4-[2-({3-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methyl)tetrahydro-1(2H)-
10 pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-({3-[2-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methyl)tetrahydro-1(2H)-
pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-({3-(4-chlorophenyl)-1H-pyrazol-4-yl}methyl)tetrahydro-1(2H)-pyridazinyl]-1-
naphthalenecarbonitrile;

15 4-[2-({3-(4-fluorophenyl)-1H-pyrazol-4-yl}methyl)tetrahydro-1(2H)-pyridazinyl]-1-
naphthalenecarbonitrile;

4-[2-({3-[3-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methyl)tetrahydro-1(2H)-
pyridazinyl]-1-naphthalenecarbonitrile;

and salts and solvates thereof.

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21. A compound selected from:

4-[2-({3,5-bis(trifluoromethyl)phenyl}methyl)tetrahydro-1(2H)-pyridazinyl]-1-
naphthalenecarbonitrile;

4-[2-({3-phenyl-1H-pyrazol-4-yl}methyl)tetrahydro-1(2H)-pyridazinyl]-1-
25 naphthalenecarbonitrile;

4-[2-({1-(1,1-dimethylethyl)-5-methyl-1H-pyrazol-3-yl}methyl)tetrahydro-1(2H)-
pyridazinyl]-1-naphthalenecarbonitrile;

4-[2-({6-methyl-2-pyridinyl}methyl)tetrahydro-1(2H)-pyridazinyl]-1-
naphthalenecarbonitrile;

30 4-[2-({4-phenyl-1H-imidazol-5-yl}methyl)tetrahydro-1(2H)-pyridazinyl]-1-
naphthalenecarbonitrile;

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1-(4-nitro-1-naphthalenyl)-2-({2-
[(trifluoromethyl)oxy]phenyl}acetyl)hexahydropyridazine;

4-[2-(1H-pyrazol-3-ylmethyl)tetrahydro-1(2H)-pyridazinyl]-1-
naphthalenecarbonitrile;

5 4-[2-[(3-cyanophenyl)methyl]tetrahydro-1(2H)-pyridazinyl]-1-
naphthalenecarbonitrile;

4-[2-[[3-(3-furanyl)-1H-pyrazol-4-yl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-
naphthalenecarbonitrile;

10 4-[2-[[3-(1-methylethyl)-1H-pyrazol-4-yl]methyl]tetrahydro-1(2H)-pyridazinyl]-1-
naphthalenecarbonitrile;
and salts and solvates thereof.

22. A compound as claimed in claims 1 to 21 substantially as hereinbefore defined
with reference to any one of the Examples.

15

23. A pharmaceutical composition comprising a compound according to any one of
claims 1 to 21.

24. A compound according to any one of claims 1 to 21 for use as an active
20 therapeutic substance.

25. A compound according to any one of claims 1 to 21 for use in the treatment of
conditions or disorders that respond to glucocorticoid receptor modulation.

25 26. A compound according to any one of claims 1 to 21 for use in the treatment of
type 2 diabetes, type 1 diabetes, hyperglycemia, insulin resistance, metabolic
syndrome X, diabetic dyslipidemia, bipolar disorder (manic depression), drug
dependency, sleep disorders, schizophrenia, obsessive-compulsive disorder, post-
traumatic stress disorder, social anxiety disorder, and generalized anxiety disorder.

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27. A method for the treatment of type 2 diabetes, type 1 diabetes, hyperglycemia,
insulin resistance, metabolic syndrome X, diabetic dyslipidemia, bipolar disorder (manic

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depression), drug dependency, sleep disorders, schizophrenia, obsessive-compulsive disorder, post-traumatic stress disorder, social anxiety disorder, and generalized anxiety disorder

comprising the administration of a compound according to any one of claims 1 to 21.

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28. A method for the treatment of conditions or disorders that respond to glucocorticoid receptor modulation comprising the administration of a compound according to any one of claims 1 to 21.

10 29. Use of a compound according to any one of claims 1 to 21 in the manufacture of a medicament for use in the treatment of type 2 diabetes, type 1 diabetes, hyperglycemia, insulin resistance, metabolic syndrome X, diabetic dyslipidemia, bipolar disorder (manic depression), drug dependency, sleep disorders, schizophrenia, obsessive-compulsive disorder, post-traumatic stress disorder, social anxiety disorder,
15 and generalized anxiety disorder.

30. Use of a compound according to any one of claims 1 to 21 in the manufacture of a medicament for use in the treatment of conditions or disorders that respond to glucocorticoid receptor modulation.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/006096

A. CLASSIFICATION OF SUBJECT MATTER C07D237/04 C07D231/04 C07D243/02 A61P3/00 A61P25/00 A61K31/495 A61K31/551 A61K31/415 C07D409/06 C07D413/06 C07D401/06 C07D403/06 C07D405/06 C07D417/06 C07D409/14				
According to International Patent Classification (IPC) or to both national classification and IPC				
B. LIDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D A61P A61K				
Documentation searched other than minimum documentation to the extent that such documents are included in the classification searched				
Electronic data bases consulted during the international search (name of data base and, where practical, search terms used) EP: Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Cat.	ity*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	
A		WO 2004/110978 A (SMITHKLINE BEECHAM CORPORATION; CADILLA, RODOLFO; LARKIN, ANDREW, L; S) 23 December 2004 (2004-12-23) abstract; compound (I)	1-30	
A		FR 2 835 835 A (AVENTIS PHARMA SA) 15 August 2003 (2003-08-15) abstract; compound (I) page 17, line 19 - line 25	1-30	
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.				
* S Categories of cited documents: "A" Document defining the general state of the art which is not considered to be of particular relevance "E" Earlier document but published on or after the international filing date "L" Document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another claim 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 after 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 "Z" Document member of the same patent family				
Date	Date of actual completion of the international search		Date of mailing of the international search report	
	24 May 2006		07/06/2006	
Name	Mailing address of the ISA/ European Patent Office, P.O. 5818 Patentlehn 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3018		Authorized officer Eberhard, M	

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2006/006096

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/006096

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

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

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

Although claims 27 and 28 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds/compositions.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2006/006096

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 2004110978	A	23-12-2004	EP	1636167 A2	22-03-2006
FR 2835835	A	15-08-2003	AU	2003222363 A1	04-09-2003
			BR	0307565 A	21-12-2004
			CA	2475439 A1	21-08-2003
			EP	1476434 A2	17-11-2004
			WO	03068140 A2	21-08-2003
			JP	2005525334 T	25-08-2005
			MX	PA04007186 A	29-10-2004