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(54) Title: THIADIAZINYL CORTICOTROPIN-RELEASING FACTOR BINDING PROTEIN LIGAND INHIBITORS

(57) Abstract

This invention provides novel derivatives of 2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide which are useful as ligand inhibitors for increasing levels of free corticotropin-releasing factor in the brain. Such ligand inhibitors cause release of corticotropin-releasing factor from the corticotropin-releasing factor/corticotropin-releasing factor binding protein complex. Administration of the ligand inhibitors provide improvement in learning and memory, and are useful in decreasing food intake.
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THIADIAZINYL CORTICOTROPIN-RELEASING FACTOR BINDING PROTEIN LIGAND INHIBITORS

This application claims the benefit of U.S. Provisional Patent Application Serial No. 60/046,741 filed May 16, 1997.

Recent clinical data have implicated corticotropin-releasing factor in neuropsychiatric disorders and in neurodegenerative diseases, such as Alzheimer's disease. Alzheimer's disease is a degenerative disorder of the human brain. Clinically, it appears as a progressive dementia. Its histopathology is characterized by degeneration of neurons, gliosis, and the abnormal deposition of proteins in the brain. Proteinaceous deposits (called "amyloid") appear as neurofibrillary tangles, amyloid plaque cores, and amyloid of the congophilic angiopathy. By current estimates, over two million individuals in the United States suffer from this disease.


Chemical affinity cross-linking studies indicate that the increased corticotropin-releasing factor receptor population in cerebral cortex

Alterations in brain corticotropin-releasing factor content have also been found in Parkinson's disease and progressive supranuclear palsy, neurological disorders that share certain clinical and pathological features with Alzheimer's disease. In cases of Parkinson's disease, corticotropin-releasing factor content is decreased and shows a similar staining pattern similar to instances of Alzheimer's disease. In progressive supranuclear palsy, corticotropin-releasing factor is decreased to approximately 50% of control values in frontal, temporal, and occipital lobes.

Some depressive disorders are also associated with decreased levels of corticotropin-releasing factor. Patients in the depressive state of seasonal depression and in the period of fatigue in chronic fatigue syndrome demonstrate lower levels of corticotropin-releasing factor in the cerebrospinal fluid.

Hypoactivation of the stress system as manifested by low levels of corticotropin-releasing factor may play a role in other disorders as well. For example, some forms of obesity are characterized by a hypoactive hypothalmic-pituitary-adrenal axis. Some patients with post-traumatic stress syndrome have low cortisol excretion. Some patients undergoing withdrawal from smoking have decreased excretion of adrenaline and noradrenaline, as well as decreased amounts of cortisol in blood. These manifestations all point to a central role for corticotropin-releasing factor in these disorders as corticotropin-releasing factor is the major regulator of the hypothalmic-pituitary-adrenal axis.
Treatments for these disorders typically have poor efficacy. In view of the deficiencies in treatments for such disorders, more effective treatments are needed. The present invention exploits the correlation of reduced levels of corticotropin-releasing factor with various neurophysiologically based disorders to effectively treat such conditions by increasing levels of free corticotropin-releasing factor through administration of inhibitors of the corticotropin-releasing factor/corticotropin-releasing factor binding protein complex.

The present invention provides the novel compounds of Formula I

wherein:

R\text{1}\text{a} and R\text{1}\text{b} are C\text{1}-C\text{10} alkyl, aryl(C\text{1}-C\text{10} alkylenyl)-, furyl(C\text{1}-C\text{10} alkylenyl)-, thieryl(C\text{1}-C\text{10} alkylenyl)-, or pyrrolyl(C\text{1}-C\text{10} alkylenyl)-;

A is -S- or -NH-, or A is a monocyclic or bicyclic heterocyclic group containing one or more nitrogen atoms in which A is bound through a nitrogen;
said heterocyclic group being optionally substituted with one or more moieties selected from the group consisting of heterocyclic, C₁-C₆ alkyl, C₁-C₆ alkoxy, heterocyclic(carbonyl)C₁-C₆ alkylene-, C₃-C₆ cycloalkyl, and phenyl,

which phenyl group may be substituted with one, two, or three moieties selected from the group consisting of halo, trifluoromethyl, hydroxy, C₁-C₆ alkyl, and C₁-C₆ alkoxy;

R² is hydrogen, C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, aryl, heterocyclic, heterocyclic(C₁-C₁₀ alkylene)-, aryl(C₁-C₁₀ alkylene)-, or trityl,

said aryl, heterocyclic, heterocyclic(C₁-C₁₀ alkylene)-, or aryl(C₁-C₁₀ alkylene)- groups being substituted with one or more moieties selected from the group consisting of phenyl, C₁-C₆ alkyl, hydroxy, C₁-C₆ alkoxy, halo, trifluoromethyl,

which phenyl group may be substituted with one, two, or three moieties selected from the group consisting of halo, trifluoromethyl, hydroxy, C₁-C₆ alkyl, and C₁-C₆ alkoxy;

provided that when A is a monocyclic or bicyclic heterocyclic group, R² is hydrogen;

further provided that R² is hydrogen only when A is a monocyclic or bicyclic heterocyclic group;

or a pharmaceutically acceptable salt or solvate thereof.
In another embodiment the present invention provides methods of treating a condition associated with a deficiency of corticotropin-releasing factor comprising administering to a mammal in need thereof an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof.

This invention also provides pharmaceutical formulations comprising a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, in combination with one or more pharmaceutically acceptable carriers, diluents, or excipients therefor.

The current invention concerns the discovery that a select group of substituted thiadiazines, those of Formula I, are useful in the treatment of conditions associated with corticotropin-releasing factor.

The terms and abbreviations used in the instant examples have their normal meanings unless otherwise designated. For example “°C” refers to degrees Celsius; “mmol” refers to millimole or millimoles; “g” refers to gram or grams; “ml” means milliliter or milliliters; “M” refers to molar or molarity; “ESMS” refers to electrospray mass spectrometry; and “FDMS” refers to field desorption mass spectrometry.

“C₁-C₁₀ alkoxy” represents a straight or branched alkyl chain having from one to ten carbon atoms attached to an oxygen atom. Typical C₁-C₁₀ alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentoxy and the like. The term “C₁-C₁₀ alkoxy” includes within its definition the terms “C₁-C₆ alkoxy” and “C₁-C₃ alkoxy”.

As used herein, the term “C₁-C₁₀ alkyl” refers to straight or branched, monovalent, saturated aliphatic chains of 1 to 10 carbon atoms and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, penty, isopentyl, and hexyl. The term “C₁-C₁₀ alkyl” includes within its definition the terms “C₁-C₆ alkyl” and “C₁-C₄ alkyl”.
"C₃-C₈ cycloalkyl" represents a saturated hydrocarbon ring structure containing from three to eight carbon atoms. Typical C₃-C₈ cycloalkyl groups include cyclopentyl, cyclohexyl, cycloheptyl, and the like.

"Halo" represents chloro, fluoro, bromo or iodo.

"C₁-C₁₀ alkylthio" represents a straight or branched alkyl chain having from one to ten carbon atoms attached to a sulfur atom. Typical C₁-C₁₀ alkylthio groups include methylthio, ethylthio, propylthio, isopropylthio, butylthio and the like. The term "C₁-C₁₀ alkylthio" includes within its definition the term "C₁-C₆ alkylthio" and "C₁-C₃ alkylthio".

"C₁-C₁₀ alkenyl" refers to a straight or branched, divalent, saturated aliphatic chains of 1 to 10 carbon atoms and includes, but is not limited to, methylenyl, ethylenyl, propylenyl, isopropylenyl, butylenyl, isobutylenyl, t-butylenyl, pentylenyl, isopentylenyl, hexylenyl, octylenyl, 3-methyloctylenyl, decylenyl. The term "C₁-C₆ alkenyl" is encompassed within the term "C₁-C₁₀ alkenyl".

"C₁-C₁₀ alkylamino" represents a group of the formula -NH(C₁-C₁₀ alkyl) wherein a chain having from one to ten carbon atoms is attached to an amino group. Typical C₁-C₄ alkylamino groups include methylamino, ethylamino, propylamino, isopropylamino, butylamino, sec-butylamino and the like.

The term "C₂-C₁₀ alkenyl" as used herein represents a straight or branched, monovalent, unsaturated aliphatic chain having from two to ten carbon atoms. Typical C₂-C₁₀ alkenyl groups include ethenyl (also known as vinyl), 1-methylethenyl, 1-methyl-1-propenyl, 1-buteny1, 1-hexenyl, 2-methyl-2-propenyl, 1-propenyl, 2-propenyl, 2-butenyl, 2-pentenyl, and the like.

The term "C₂-C₁₀ alkynyl" as used herein represents a straight or branched, monovalent, unsaturated aliphatic chain having from two to ten
carbon atoms with at least one triple bond. Typical C\textsubscript{2}-C\textsubscript{10} alkynyl groups include ethynyl, 1-methylethynyl, 1-propynyl, 1-butynyl, 1-hexynyl, 2-propynyl, 2-butynyl, 2-pentynyl, 2,4-dihexynyl, and the like.

"C\textsubscript{3}-C\textsubscript{8} cycloalkenyl" represents a hydrocarbon ring structure containing from three to eight carbon atoms and having at least one double bond within that ring, which is unsubstituted or substituted with 1, 2 or 3 substituents independently selected from halo, halo(C\textsubscript{1}-C\textsubscript{4} alkyl), C\textsubscript{1}-C\textsubscript{4} alkyl, C\textsubscript{1}-C\textsubscript{4} alkoxy, carboxy, C\textsubscript{1}-C\textsubscript{4} alkoxy carbonyl, carbamoyl, N-(C\textsubscript{1}-C\textsubscript{4} alkyl) carbamoyl, amino, C\textsubscript{1}-C\textsubscript{4} alkyl amine, di(C\textsubscript{1}-C\textsubscript{4} alkyl) amino or

\((\text{CH}_2)_a\text{-R}^y\) where \(a\) is 1, 2, 3 or 4 and \(R^y\) is hydroxy, C\textsubscript{1}-C\textsubscript{4} alkoxy, carboxy, C\textsubscript{1}-C\textsubscript{4} alkoxy carbonyl, amino, carbamoyl, C\textsubscript{1}-C\textsubscript{4} alkyl amine or di(C\textsubscript{1}-C\textsubscript{4} alkyl) amino.

The term "amino-protecting group" as used in the specification refers to substituents of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups on the compound. Examples of such amino-protecting groups include formyl, trityl (herein abbreviated as "Tr"), phthalimido, trichloroacetyl, chloroacetyl, bromoacetetyl, iodoacetetyl, and urethane-type blocking groups such as benzyloxy carbonyl, 4-phenylbenzoyl oxycarbonyl, 2-methylbenzoyl oxycarbonyl, 4-methoxybenzoyl oxycarbonyl, 4-fluorobenzoyl oxycarbonyl, 4-chlorobenzoyl oxycarbonyl, 3-chlorobenzoyl oxycarbonyl, 2-chlorobenzoyl oxycarbonyl, 2,4-dichlorobenzoyl oxycarbonyl, 4-bromobenzoyl oxycarbonyl, 3-bromobenzoyl oxycarbonyl, 4-nitrobenzoyl oxycarbonyl, 4-cyanobenzoyl oxycarbonyl, t-butoxy carbonyl (herein abbreviated as "BoC"), 1,1-diphenylethyl-1-yloxy carbonyl, 1,1-diphenylprop-1-yloxy carbonyl, 2-phenylprop-2-yloxy carbonyl, 2-(\(p\)-toluyl)-prop-2-yloxy carbonyl, cyclopentanyloxy carbonyl, 1-methylcyclopentanyloxy carbonyl, cyclohexanyloxy carbonyl, 1-methylcyclohexanyloxy carbonyl, 2-methylcyclohexanyloxy carbonyl, 2-((4-toluylsulfonyl)-ethoxy carbonyl, 2-((methylsulfonyl)ethoxy carbonyl,
2-(triphenylphosphino)-ethoxycarbonyl, fluorenlymethoxy-carbonyl ("FMOC"),
2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl,
1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl,
5-benzisoxazolmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl,
2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl,
cyclopropylmethoxycarbonyl, 4-(decyloxy)benzyloxycarbonyl,
isobornyloxycarbonyl, 1-piperidylloxycarbonyl and the like;
benzoylmethylsulfonyl group, 2-nitrophenylsulfenyl, diphenylphosphine oxide
and like amino-protecting groups. The species of amino-protecting group
employed is usually not critical so long as the derivatized amino group is
stable to the condition of subsequent reactions on other positions of the
intermediate molecule and can be selectively removed at the appropriate point
without disrupting the remainder of the molecule including any other
amino-protecting groups. Preferred amino-protecting groups are trityl,
t-butoxycarbonyl (t-BOC), allyloxycarbonyl and benzylloxycarbonyl. Further
examples of groups referred to by the above terms are described by E. Haslam,
Chapter 2; and T.W. Greene and P.G.M. Wuts, PROTECTIVE GROUPS IN

The term "carboxy-protecting group" as used in the specification
refers to substituents of the carboxy group commonly employed to block or
protect the carboxy functionality while reacting other functional groups on the
compound. Examples of such carboxy-protecting groups include methyl,
p-nitrobenzyl, p-methylbenzyl, p-methoxy-benzyl, 3,4-dimethoxybenzyl,
2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl,
pentamethylbenzyl, 3,4-methylenedioxybenzyl, benzhydryl,
4,4'-dimethoxybenzhydryl, 2,2',4,4'-tetramethoxybenzhydryl, t-butyl, t-amyl,
trityl, 4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4''-trimethoxytrityl,
2-phenylprop-2-yl, trimethylsilyl, t-butyldimethylsilyl, phenacyl,
2,2,2-trichloroethyl, 2-(di(n-butyl)methyisilyl)ethyl, p-toluenesulfonylethyl,
The term “hydroxy-protecting groups” as used herein refers to substituents of the hydroxy group commonly employed to block or protect the hydroxy functionality while reacting other functional groups on the compound. Examples of such hydroxy-protecting groups include methoxymethyl, benzyloxymethyl, methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, methylthiomethyl, 2,2-dichloro-1,1-difluoroethyl, tetrahydropyran-1-yl, phenacyl, cyclopropylmethyl, allyl, C1-C6 alkyl, 2,6-dimethylbenzyl, o-nitrobenzyl, 4-picoly, dimethylsilyl, t-butylidimethylsilyl, levulinate, pivaloate, benzoate, dimethylsulfonate, dimethylphosphinyl, isobutyrate, adamantoate and tetrahydropyran-1-yl. Further examples of these groups may be found in T.W. Greene and P.G.M. Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, (1991) at Chapter 3.

The term “leaving group” as used herein refers to a group of atoms that is displaced from a carbon atom by the attack of a nucleophile in a nucleophilic substitution reaction. The term “leaving group” as used in this document encompasses, but is not limited to, activating groups.

The term “activating group” as used herein refers a leaving group which, when taken with the carbonyl (-C=O) group to which it is attached, is more likely to take part in an acylation reaction than would be the case if the group were not present, as in the free acid. Such activating groups are well-known to those skilled in the art and may be, for example, succinimidoxy, phthalimidoxy, benzotriazolylloxy, benzenesulfonyloxy, methanesulfonyloxy, toluenesulfonyloxy, azido, or -O-CO-(C4-C7 alkyl).

The compounds of the present invention are derivatives of 2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide which are named and
numbered according to the RING INDEX, The American Chemical Society, as follows.

\[
\begin{array}{c}
\text{O} \\
\text{S} \\
\text{O} \\
\text{N} \quad \text{N} \\
\text{O} \\
\end{array}
\]

For the purposes of the present invention, all the nomenclature employed herein will employ the above numbering scheme, regardless of the priorities of the substituents.

The compounds of the present invention may have one or more asymmetric centers. As a consequence of these chiral centers, those compounds of the present invention occur as racemates, mixtures of enantiomers and as individual enantiomers, as well as diastereomers and mixtures of diastereomers. All asymmetric forms, individual isomers and combinations thereof, are within the scope of the present invention.

The terms “R” and “S” are used herein as commonly used in organic chemistry to denote specific configuration of a chiral center. The term “R” (rectus) refers to that configuration of a chiral center with a clockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The term “S” (sinister) refers to that configuration of a chiral center with a counterclockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The priority of groups is based upon their atomic number (in order of decreasing atomic number). A partial list of priorities and a discussion of stereochemistry is contained in NOMENCLATURE OF ORGANIC COMPOUNDS: PRINCIPLES AND PRACTICE, (J.H. Fletcher, et al., eds., 1974) at pages 103-120.
In addition to the (R)-(S) system, the older D-L system may also be used in this document to denote absolute configuration, especially with reference to amino acids. In this system a Fischer projection formula is oriented so that the number 1 carbon of the main chain is at the top. The prefix “D” is used to represent the absolute configuration of the isomer in which the functional (determining) group is on the right side of the carbon atom at the chiral center and “L”, that of the isomer in which it is on the left.

In order to preferentially prepare one optical isomer over its enantiomer, the skilled practitioner can proceed by one of two routes. The practitioner may first prepare the mixture of enantiomers and then separate the two enantiomers. A commonly employed method for the resolution of the racemic mixture (or mixture of enantiomers) into the individual enantiomers is to first convert the enantiomers to diastereomers by way of forming a salt with an optically active salt or base. These diastereomers can then be separated using differential solubility, fractional crystallization, chromatography, or like methods. Further details regarding resolution of enantiomeric mixtures can be found in J. Jacques, et al., ENANTIOMERS, RACEMATES, AND RESOLUTIONS, (1991).

In addition to the schemes described above, the practitioner of this invention may also choose an enantiospecific protocol for the preparation of the compounds of Formula I. Such a protocol employs a synthetic reaction design which maintains the chiral center present in the starting material in a desired orientation. These reaction schemes usually produce compounds in which greater than 95 percent of the title product is the desired enantiomer.

As noted supra, this invention includes the pharmaceutically acceptable salts of the compounds defined by Formula I. A compound of this invention can possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of organic and inorganic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.
The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of the above formula which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a pharmaceutically acceptable mineral or organic acid or an organic or inorganic base. Such salts are known as acid addition and base addition salts.

Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as $p$-toluenesulfonic acid, methanesulfonic acid, oxalic acid, $p$-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, hydrochloride, dihydrochloride, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, $\gamma$-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid and methanesulfonic acid.

Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen carries a suitable organic group such as an alkyl, alkenyl, alkynyl, or aralkyl moiety.
Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like. The potassium and sodium salt forms are particularly preferred.

It should be recognized that the particular counterion forming a part of any salt of this invention is usually not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole.

This invention further encompasses the pharmaceutically acceptable solvates of the compounds of Formulas I. Many of the Formula I compounds can combine with solvents such as water, methanol, ethanol and acetonitrile to form pharmaceutically acceptable solvates such as the corresponding hydrate, methanolate, ethanolate and acetonitrilate.

This invention also encompasses the pharmaceutically acceptable prodrugs of the compounds of Formula I. A prodrug is a drug which has been chemically modified and may be biologically inactive at its site of action, but which may be degraded or modified by one or more enzymatic or other in vivo processes to the parent bioactive form. This prodrug should have a different pharmacokinetic profile than the parent, enabling easier absorption across the mucosal epithelium, better salt formation or solubility, or improved systemic stability (an increase in plasma half-life, for example).

Typically, such chemical modifications include:
1) ester or amide derivatives which may be cleaved by esterases or lipases;

2) peptides which may be recognized by specific or nonspecific proteases; or
3) derivatives that accumulate at a site of action through membrane selection of a prodrug form or a modified prodrug form; or any combination of 1 to 3, supra. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in H. Bundgaard, DESIGN OF PRODRUGS, (1985).

The compounds of the present invention are prepared by reacting a compound of Formula II

\[
\begin{align*}
&\text{II} \\
&\text{O} \quad \text{N} \quad \text{S} \quad \text{O} \\
&R^1 \text{N} \quad \text{S} \quad \text{O} \\
&\text{O} \quad \text{N} \quad \text{S} \quad \text{O} \\
&\text{R}^1
\end{align*}
\]

with a trialkylorthoformate, preferably triethylorthoformate, and a reactivly available amine or thiol. This reaction is generally performed in a lower alkylalcohol. Especially preferred is isopropanol.

This reaction is generally performed at a temperature greater than 30°C, although other temperatures may be employed. This reaction is generally performed at the reflux temperature of the solvent employed.

The compounds of Formula II are prepared essentially as described in A. Herrero, et al., Archives in Pharmacology (Weinheim), 325:509-514 (1992) in which an N,N-bis(substituted)sulfamide is reacted with malonyl chloride.

The following Preparations describe typical reaction conditions.
Preparation 1

Synthesis of N,N'-Diethylsulfamide

\[
\text{H}_3\text{C} \quad \text{N} \quad \text{SO}_2 \quad \text{NH} \quad \text{CH}_3
\]

Sulfuryl chloride (120 g, 0.89 mol) in petroleum ether (200 ml) was added to solution of ethyl amine (140g, 1.77 mol) and pyridine (140 g, 1.77 mol) in petroleum ether (500 ml) at -15°C. The temperature was not allowed to rise above -5°C during the addition. After complete addition of the sulfuryl chloride solution, the reaction was stirred at room temperature for one hour. Evaporated the petroleum ether on a rotary evaporator. The residue was made acidic with 5N aqueous hydrochloric acid, then heated under reflux for two hours. The resulting solution was extracted with diethyl ether in a continuous extractor. Evaporated the diethyl ether to yield N,N'-diethylsulfamide (57.4 g, 0.38 mol, mp 62-65°C).

Preparation 2

Alternative Synthesis of N,N'-Disubstitutedesulfamide

Sulfamide (1.3 g, 13.1 mmol) and 2-thienylethylamine (3.5 g, 27.6 mmol) were heated at 105°C for sixteen hours. Cooled to room temperature then added 2.5N aqueous hydrochloric acid (20 ml) to the
reaction and stirred for 15 minutes. Collected the crude product. Recrystallized the crude product from ethanol to yield N,N'-di-(2-thienylethylamine)sulfamide (2.7g).

**Preparation 3**

Synthesis of 2,6-Diethyl-2,3,5,6-tetrahydro-2,3,5,6-tetrahydro-1,2,6-thiadiazine 1,1-dioxide

![Chemical Structure](image)

This reaction was performed essentially as described in A. Herrero, *et al.*, *Archives in Pharmacology (Weinheim)*, 325:509-514 (1992).

Malonyl chloride (25 g, 177.3 mmol) in dry toluene (100 ml) was added to a solution of N,N'-diethylsulfamide (26.9 g, 0.177.3 mmol) in dry toluene (700 ml). The reaction was heated to 70°C for four hours. Evaporated the solvent on a rotary evaporator to yield the crude product. The crude material was purified by preparative high performance liquid chromatography over silica gel, eluting with 5 to 60% ethyl acetate in hexanes over a 25 minute gradient to yield of 2,6-diethyl-2,3,5,6-tetrahydro-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide (35 g, 159.1 mmol).

**Example 1**

Preparation of 4-[(1,2,3,4-tetrahydroisoquinolin-1-yl)methylene]-2,6-diethyl-2,3,5,6-tetrahydro-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
2,6-Diethyl-2,3,5,6-tetrahydro-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide (0.4 g, 1.8 mmol), 1,2,3,4-tetrahydroisoquinoline (0.36 g, 2.7 mmol), triethylorthoformate (0.8 g, 5.4 mmol), and isopropanol (40 ml) was refluxed for two hours. Evaporated the solvent on a rotary evaporator then recrystallized the residue from ethyl acetate/hexanes to yield 285 mg of the above product.

FDMS 363

mp 130-132°C

The following compounds were prepared essentially as described in the above Preparations and Examples, employing the appropriate amine or thiol.

Example 2

Preparation of 4-[(1,2,3,4-tetrahydroisoquinolin-1-yl)methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 3

Preparation of 4-[(1,2,3,4-tetrahydroisoquinolin-1-yl)methylene]-2,6-bis(3-chlorobenzyl)-2,3,5,6-tetrahydro-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 4

Preparation of 4-[(n-butylthio)methylene]-2,6-diethyl-2,3,5,6-tetrahydro-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

FDMS 320

Example 5

Preparation of 4-[(n-butylthio)methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

FDMS 484
Example 6

Preparation of 4-[(n-butylamino)methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

NMR was consistent with the proposed title structure.

Example 7

Preparation of 4-[(cyclohexylthio)methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 8

Preparation of 4-[(3-methylbutylthio)methylene]-2,6-bis(2-phenylethyl)-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 487 oil
Example 9

Preparation of 4-[[4-(piperidin-1-yl)piperidin-1-yl]methylene]-2,6-bis[2-phenylethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

FDMS 550

mp 54-60°C

Example 10

Preparation of 4-[[benzimidzaol-2-yl)amino]methylene]-2,6-bis(2-phenylethyl)-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
FDMS 515
mp 192-194°C

Example 11

Preparation of 4-[(2-phenylethylthio)methylene]-2,6-bis(2-phenylethyl)-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

FDMS 520
oil
Example 12

Preparation of 4-[(n-butythio)methylene]-2,6-bis(2-phenylethyl)-2,3,5,6-
tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

FDMS 472

Example 13

Preparation of 4-[(benzimidazol-2-yl)amino]methylene]-2,6-bis(3-
chlorobenzyl)-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
FDMS 556
mp >225°C

Example 14

Preparation of 4-[[4-(3-trifluoromethylphenyl)piperazin-1-yl)methylene]-2,6-bis(2-phenylethyl)-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 15

Preparation of 4-[[4-[(pyrroldin-1-yl)carbonyl]methyl]piperazin-1-yl]methylene]-2,6-bis(2-phenylethyl)-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

Example 16

Preparation of 4-[(isopropylthio)methylene]-2,6-bis(2-phenylethyl)-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 17

Preparation of 4-[[benzimidazol-2-yl]amino]methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 18

Preparation of 4-[(isopropylmethylamino)methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

FDMS 303

Example 19

Preparation of 4-[(2-phenylethylamino)methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

FDMS 351
Example 20

Preparation of 4-[[benzothiazol-2-yl]amino]methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

Example 21

Preparation of 4-[[2-(pyridin-3-yl)pyrrolidin-1-yl]methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 22

Preparation of 4-[[thiazol-2-yl]amino]methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 331
Example 23

Preparation of 4-[[4-(4-fluorophenyl)piperazin-1-yl)methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 411

Example 24

Preparation of 4-[[4-(pyridin-2-yl)piperazin-1-yl)methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 20

Preparation of 4-[[4-(piperidin-1-yl)piperidin-1-yl]methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 26

Preparation of 4-[[2-(piperidin-1-yl)ethylamino]methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 241, 349

Example 27

Preparation of 4-[(prop-2-enylamino)methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 171, 216, 278
Example 28

Preparation of 4-[(4-phenylpiperazin-1-yl)methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 393

Example 29

Preparation of 4-[4-[(3-trifluoromethylphenyl)piperazin-1-yl)methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 30

Preparation of 4-[[4-(isopropyl)piperazin-1-yl]methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 31

Preparation of 4-[[4-(phenyl)-1,2,5,6-tetrahydropyridin-1-yl]methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

Example 32

Preparation of 4-[[4-(piperidin-1-yl)piperidin-1-yl]methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 33

Preparation of 4-[(cyclopropylamino)methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 281, 298, 338
Example 34

Preparation of 4-[(fur-2-yl)methylamino]methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

![Chemical Structure]

ESMS 280, 303

Example 35

Preparation of 4-[(indolin-1-yl)methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

![Chemical Structure]

ESMS 281, 298
Example 36

Preparation of 4-[[2-(cyclohexen-1-yl)ethylamino]methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 346, 364, 471

Example 37

Preparation of 4-[[4-(2-methoxyphenyl)piperazin-1-yl]methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 423
Example 38

Preparation of 4-[[4-(2-fluorophenyl)piperazin-1-yl]methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 411

Example 39

Preparation of 4-[[4-benzylpiperazin-1-yl]methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 40

Preparation of 4-[[4-[[pyrrolidin-1-yl]carbonyl]methyl]piperazin-1-yl)methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 428
Example 41

Preparation of 4-[(morpholin-4-yl)methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 318

Example 42

Preparation of 4-[(piperidin-1-yl)methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 221, 289
Example 43

Preparation of 4-[[2-(morpholin-4-yl)ethylamino]methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiaziazin-3,5-dione 1,1-dioxide

ESMS 361

Example 44

Preparation of 4-[[2-(pyridin-2-yl)ethylamino]methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiaziazin-3,5-dione 1,1-dioxide

ESMS 353
Example 45

Preparation of 4-[[2-(phenyl)ethylamino)methylene]-2,6-diethyl-2,3,5,6-
tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 352

Example 46

Preparation of 4-[[2-(propyn-2-yl)amino)methylene]-2,6-diethyl-2,3,5,6-
tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 286
Example 47

Preparation of 4-[[3-methylbutylamino]methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 353

Example 48

Preparation of 4-[[triazol-2-yl]amino]methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 49

Preparation of 4-[[tetrazol-2-yl]amino)methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

Example 50

Preparation of 4-[[benzothiazin-2-yl]amino)methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 51

Preparation of 4-[[3-phenyl-1,2,4-thiadiazol-5-yl]amino)methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 52

Preparation of 4-[[3-phenyl-1,3-thiazol-2-yl]amino]methylene]-2,6-diethyl-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

Example 53

Preparation of 4-[[4-phenylpiperazin-1-yl]methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 54

Preparation of 4-[(4-(3-trifluoromethylphenyl)piperazin-1-yl)methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 55

Preparation of 4-[(4-isopropylpiperazin-1-yl)methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 523

Example 56

Preparation of 4-[(4-(phenyl)1,2,5,6-tetrahydropyridin-1-yl)methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 57

Preparation of 4-[(4-(piperidin-1-yl)piperidin-1-yl)methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 58

Preparation of 4-[(isopropylamino)methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 452

Example 59

Preparation of 4-[(fur-2-ylmethylamino)methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 60

Preparation of 4-[(indolin-1-yl)methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 61

Preparation of 4-[(2-phenylethlamino)methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

Example 62

Preparation of 4-[[4-(2-hydroxyphenyl)piperazin-1-yl)methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 63

Preparation of 4-[[4-(2-fluorophenyl)piperazin-1-yl]methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 64

Preparation of 4-[[4-(benzyl)piperazin-1-yl]methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

Example 65

Preparation of 4-[[4-[[pyrrolidin-1-yl]carbonyl]methyl]piperazin-1-yl]methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 66

Preparation of 4-[(morpholin-4-yl)methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 67

Preparation of 4-[(piperidin-1-yl)methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

Example 68

Preparation of 4-[[2-(morpholin-4-yl)ethylamino]methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 69

Preparation of 4-[[2-(pyridin-2-yl)ethylamino]methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 70

Preparation of 4-[[2-(phenyl)ethylamino]methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

Example 71

Preparation of 4-[(prop-2-ynylamino)methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 72

Preparation of 4-[(3-methylbutylamino)methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 73

Preparation of 4-[(triazol-2-yl)amino]methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 163

Example 74

Preparation of 4-[(tetrazol-2-yl)amino]methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 75

Preparation of 4-[(benzothiazol-2-yl)amino)methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 76

Preparation of 4-[[3-phenyl-1,2,4-thiadiazol-4-yl]amino)methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 178

Example 77

Preparation of 4-[[4-phenyl-1,3-thiazol-2-yl]amino)methylene]-2,6-bis[2-(thien-2-yl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 78

Preparation of 4-[(4-phenylpiperazin-1-yl)methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 79

Preparation of 4-[(4-(3-trifluoromethylphenyl)piperazin-1-yl)methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

Example 80

Preparation of 4-[(4-(isopropyl)piperazin-1-yl)methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 81

Preparation of 4-[(4-(phenyl)1,2,5,6-tetrahydropyridin-1-yl)methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 82

Preparation of 4-[[4-(piperidin-1-yl)piperidin-1-yl]methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

Example 83

Preparation of 4-[(isopropylamino)methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 84

Preparation of 4-[[[(fur-2-yl)methyl]amino]methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

Example 85
Preparation of 4-[(indolin-1-yl)methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

Example 86

Preparation of 4-[[2-(phenyl)ethylamino]methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 87

Preparation of 4-[[4-(2-hydroxyphenyl)piperazin-1-yl]methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 88

Preparation of 4-[[4-(2-fluorophenyl)piperazin-1-yl]methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

Example 89

Preparation of 4-[[4-(benzyl)piperazin-1-yl]methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 90

Preparation of 4-[[4-[[pyrrolidin-1-yl]carbonyl]methyl]piperazin-1-yl]methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 91

Preparation of 4-[(morpholin-4-yl)methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-
tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 277, 364, 547

Example 92

Preparation of 4-[(piperidin-1-yl)methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-
tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 93

Preparation of 4-[[2-(morpholin-4-yl)ethylamino)methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thia-azin-3,5-dione 1,1-dioxide
Example 94

Preparation of 4-[[2-(pyridin-2-yl)ethylamino)methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 268, 360, 505

Example 95

Preparation of 4-[[2-(phenyl)ethylamino)methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 96

Preparation of 4-[[prop-2-ynylamino]methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thia diazin-3,5-dione 1,1-dioxide
Example 97

Preparation of 4-[3-(methyl)butyl]methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 185

Example 98

Preparation of 4-[[triazol-2-yl]amino]methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 99

Preparation of 4-[[tetrazol-2-yl]amino]methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 100

Preparation of 4-[[benzothiazol-2-yl]amino]methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

Example 101

Preparation of 4-[[3-phenyl-1,2,4-thiadiazol-5-yl]amino]methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Example 102

Preparation of 4-[[4-phenyl-1,3-thiazol-2-yl]amino)methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
**Example 103**

Preparation of 4-[(cyclohexylthio)methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Thin layer chromatography was consistent with the proposed title structure.

**Example 104**

Preparation of 4-[(2-chlorophenylthio)methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

Thin layer chromatography was consistent with the proposed title structure.

**Example 105**

Preparation of 4-[(2,6-dichlorophenylthio)methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Thin layer chromatography was consistent with the proposed title structure.

Example 106

Preparation of 4-[(tritylthio)methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

Thin layer chromatography was consistent with the proposed title structure.
Example 107

Preparation of 4-[(t-butylthio)methylene]-2,6-bis[2-(phenyl)ethy]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

Thin layer chromatography was consistent with the proposed title structure.

Example 108

Preparation of 4-[(isopropylthio)methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
ESMS 459

Example 109

Preparation of 4-[(n-butylthio)methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 473.
Example 110

Preparation of 4-[(n-hexylthio)methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide

ESMS 501.

Example 111

Preparation of 4-[(2-methylfurfurylthio)methylene]-2,6-bis[2-(phenyl)ethyl]-2,3,5,6-tetrahydro-1,2,6-thiadiazin-3,5-dione 1,1-dioxide
Thin layer chromatography was consistent with the proposed title structure.

The present invention provides methods for increasing the level of free corticotropin-releasing factor in the brain through the administration of a ligand inhibitor of a corticotropin-releasing factor/corticotropin-releasing factor-binding protein complex. The increase in the level of free corticotropin-releasing factor may be measured by in vitro assays, such as ELISA, stimulation of ACTH release, or stimulation of cAMP production. In any of those assays, an increase in free corticotropin-releasing factor due to administration of the ligand inhibit is measured relative to a reference ligand inhibitor, usually recombinantly produced hamster corticotropin-releasing factor-binding protein (6-33).

**Ligand Immunoradiometric Assay (LIRMA)**

A preferred mode of screening candidate ligand inhibitors is by an in vitro ligand immunoradiometric assay (LIRMA). For LIRMA, corticotropin-releasing factor-binding protein may be isolated from brain tissue, serum, or cells expressing a recombinant form. This procedure is described in S. Sutton, et al., *Endocrinology*, 136:1097-1102 (1995). The isolated corticotropin-releasing factor is added to wells of a 96-well plate, to small polypropylene microfuge tubes, or to glass borosilicate tubes in a binding buffer (0.02% NP-40 in 50 mM phosphate-buffered saline).

Radiolabeled (¹²⁵I) corticotropin-releasing factor and the candidate ligand inhibitor (10 µM) are added, and the reaction is incubated for one hour at room temperature. An appropriately diluted anti-corticotropin-releasing factor-binding protein antibody, such as rabbit, is added to each tube and, after further incubation, bound complexes are precipitated by the further addition of a goat anti-rabbit antibody. The precipitate containing ¹²⁵I-CRF is
collected by centrifugation and the amount of radioactivity in the pellet id
determined. Maximum inhibition (i.e., 100%) of the binding of the
radiolabeled corticotropin-releasing factor to the binding protein is defined by
the amount of radioactivity left in the pellets after incubation with 10 \mu M of
the peptide ligand recombinantly produced hamster corticotropin-releasing
factor-binding protein (6-33).

The compounds of Formula I demonstrated efficacy as inhibitors
of the corticotropin-releasing factor/corticotropin-releasing factor-binding
protein compound. As such, the compounds of Formula I are useful in
treating conditions associated with decreased levels of corticotropin-releasing
factor. Such diseases of syndromes include symptoms of dementia or learning
and memory loss, obesity, chronic fatigue syndrome, atypical depression, post-
partum depression, premenstrual syndrome (or late luteal phase disorder)
seasonal depression, hypothyroidism, post-traumatic stress syndrome,
icotine withdrawal, vulnerability to inflammatory diseases. Definitions of
these syndromes (except for obesity, chronic fatigue syndrome, and
vulnerability to inflammatory diseases) are provided in DIAGNOSIS AND
abbreviated as DSM-IV).

The compounds of Formula I are usually administered in the
form of pharmaceutical compositions. These compounds can be administered
by a variety of routes including oral, rectal, transdermal, subcutaneous,
intravenous, intramuscular, and intranasal. These compounds are effective
as both injectable and oral compositions. Such compositions are prepared in a
manner well known in the pharmaceutical art and comprise at least one
active compound.

The present invention also includes methods employing
pharmaceutical compositions which contain, as the active ingredient, the
compounds of Formula I associated with pharmaceutically acceptable carriers. In making the compositions of the present invention the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing for example up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxybenzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.
The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The active compound is effective over a wide dosage range. For examples, dosages per day normally fall within the range of about 0.5 to about 30 mg/kg of body weight. In the treatment of adult humans, the range of about 1 to about 15 mg/kg/day, in single or divided dose, is especially preferred. However, it will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several smaller doses for administration throughout the day.

For preparing solid compositions such as tablets the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit
dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention.

The tablets or pills of the present invention may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face mask, tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.
The following examples illustrate the pharmaceutical compositions of the present invention.

**Formulation Preparation 1**

Hard gelatin capsules containing the following ingredients are prepared:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (mg/capsule)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>30.0</td>
</tr>
<tr>
<td>Starch</td>
<td>305.0</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>5.0</td>
</tr>
</tbody>
</table>

The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

**Formulation Preparation 2**

A tablet formula is prepared using the ingredients below:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (mg/tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>25.0</td>
</tr>
<tr>
<td>Cellulose, microcrystalline</td>
<td>200.0</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>10.0</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>5.0</td>
</tr>
</tbody>
</table>

The components are blended and compressed to form tablets, each weighing 240 mg.
Formulation Preparation 3

A dry powder inhaler formulation is prepared containing the following components:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>5</td>
</tr>
<tr>
<td>Lactose</td>
<td>95</td>
</tr>
</tbody>
</table>

The active mixture is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

Formulation Preparation 4

Tablets, each containing 30 mg of active ingredient, are prepared as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (mg/tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>30.0 mg</td>
</tr>
<tr>
<td>Starch</td>
<td>45.0 mg</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>35.0 mg</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone (as 10% solution in water)</td>
<td>4.0 mg</td>
</tr>
<tr>
<td>Sodium carboxymethyl starch</td>
<td>4.5 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Talc</td>
<td>1.0 mg</td>
</tr>
<tr>
<td>Total</td>
<td>120 mg</td>
</tr>
</tbody>
</table>
The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50-60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 120 mg.

**Formulation Preparation 5**

Capsules, each containing 40 mg of medicament are made as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (mg/capsule)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>40.0 mg</td>
</tr>
<tr>
<td>Starch</td>
<td>109.0 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.0 mg</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>150.0 mg</td>
</tr>
</tbody>
</table>

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

**Formulation Preparation 6**

Suppositories, each containing 25 mg of active ingredient are made as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
</table>

Active Ingredient

Saturated fatty acid glycerides to

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.
Formulation Preparation 7

Suspensions, each containing 50 mg of medicament per 5.0 ml dose are made as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>50.0 mg</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>4.0 mg</td>
</tr>
<tr>
<td>Sodium carboxymethyl cellulose (11%)</td>
<td></td>
</tr>
<tr>
<td>Microcrystalline cellulose (89%)</td>
<td>50.0 mg</td>
</tr>
<tr>
<td>Sucrose</td>
<td>1.75 g</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td>10.0 mg</td>
</tr>
<tr>
<td>Flavor and Color</td>
<td>q.v.</td>
</tr>
<tr>
<td>Purified water to</td>
<td>5.0 ml</td>
</tr>
</tbody>
</table>

The medicament, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.
Formulation Preparation 8

Capsules, each containing 15 mg of medicament, are made as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (mg/capsule)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>15.0 mg</td>
</tr>
<tr>
<td>Starch</td>
<td>407.0 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>3.0 mg</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>425.0 mg</strong></td>
</tr>
</tbody>
</table>

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 425 mg quantities.

Formulation Preparation 9

An intravenous formulation may be prepared as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>250.0 mg</td>
</tr>
<tr>
<td>Isotonic saline</td>
<td>1000 ml</td>
</tr>
</tbody>
</table>
Formulation Preparation 10

A topical formulation may be prepared as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>1-10 g</td>
</tr>
<tr>
<td>Emulsifying Wax</td>
<td>30 g</td>
</tr>
<tr>
<td>Liquid Paraffin</td>
<td>20 g</td>
</tr>
<tr>
<td>White Soft Paraffin</td>
<td>to 100 g</td>
</tr>
</tbody>
</table>

15 The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.

Formulation Preparation 11

Sublingual or buccal tablets, each containing 10 mg of active ingredient, may be prepared as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity Per Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient(s)</td>
<td>10.0 mg</td>
</tr>
<tr>
<td>Glycerol</td>
<td>210.5 mg</td>
</tr>
<tr>
<td>Water</td>
<td>143.0 mg</td>
</tr>
<tr>
<td>Sodium Citrate</td>
<td>4.5 mg</td>
</tr>
<tr>
<td>Polyvinyl Alcohol</td>
<td>26.5 mg</td>
</tr>
</tbody>
</table>
Polyvinylpyrrolidone
Total

15.5 mg
410.0 mg

The glycerol, water, sodium citrate, polyvinyl alcohol, and polyvinylpyrrolidone are admixed together by continuous stirring and maintaining the temperature at about 90°C. When the polymers have gone into solution, the solution is cooled to about 50-55°C and the medicament is slowly admixed. The homogenous mixture is poured into forms made of an inert material to produce a drug-containing diffusion matrix having a thickness of about 2-4 mm. This diffusion matrix is then cut to form individual tablets having the appropriate size.

Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Patent 5,023,252, issued June 11, 1991, herein incorporated by reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Frequently, it will be desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of biological factors to specific anatomical regions of the body, is described in U.S. Patent 5,011,472, issued April 30, 1991, which is herein incorporated by reference.

Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentinization by the conversion of hydrophilic drugs into lipid-soluble drugs or prodrugs. Latentation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by
intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.
We Claim:

1. A compound of the formula

\[
\begin{align*}
R^1 & \quad \text{N} \quad \text{N} \quad R^1' \\
& \quad \text{O} \quad \text{S} \quad \text{O} \\
& \quad \text{O} \quad \text{C} \quad \text{N} \\
& \quad \text{A} \quad \text{R}^2
\end{align*}
\]

wherein:

- \( R^1 \) and \( R^{1'} \) are \( C_1-\text{C}_{10} \) alkyl, aryl(\( C_1-\text{C}_{10} \) alklylenyl)-, furyl(\( C_1-\text{C}_{10} \) alklylenyl)-, thienyl(\( C_1-\text{C}_{10} \) alklylenyl)-, or pyrrolyl(\( C_1-\text{C}_{10} \) alklylenyl)-;

- \( A \) is -S- or -NH-, or \( A \) is a monocyclic or bicyclic heterocyclic group containing one or more nitrogen atoms in which \( A \) is bound through a nitrogen;

said heterocyclic group being optionally substituted with one or more moieties selected from the group consisting of heterocyclic, \( C_1-\text{C}_6 \) alkyl, \( C_1-\text{C}_6 \) alkoxy, heterocyclic(carbonyl)\( C_1-\text{C}_6 \) alklylenyl-, \( C_3-\text{C}_8 \) cycloalkyl, and phenyl,

which phenyl group may be substituted with one, two, or three moieties selected from the group consisting of halo, trifluoromethyl, hydroxy, \( C_1-\text{C}_6 \) alkyl, and \( C_1-\text{C}_6 \) alkoxy;
R² is hydrogen, C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, aryl, heterocyclic, heterocyclic(C₁-C₁₀ alkylenyl)-, aryl(C₁-C₁₀ alkylenyl)-, or trityl,

said aryl, heterocyclic, heterocyclic(C₁-C₁₀ alkylenyl)-, or aryl(C₁-C₁₀ alkylenyl)- groups being substituted with one or more moieties selected from the group consisting of phenyl, C₁-C₅ alkyl, hydroxy, C₁-C₆ alkoxy, halo, trifluoromethyl,

which phenyl group may be substituted with one, two, or three moieties selected from the group consisting of halo, trifluoromethyl, hydroxy, C₁-C₅ alkyl, and C₁-C₆ alkoxy;

provided that when A is a monocyclic or bicyclic heterocyclic group, R² is hydrogen;

further provided that R² is hydrogen only when A is a monocyclic or bicyclic heterocyclic group;

or a pharmaceutically acceptable salt or solvate thereof.

2. A method of treating diseases associated with a deficiency of corticotropin-releasing factor comprising administering to a mammal in need thereof an effective amount of a compound of the formula
wherein:

R¹ and R¹⁸ are C₁-C₁₀ alkyl, aryl(C₁-C₁₀ alkyl), aryl(C₁-C₁₀ alkenyl)-, furyl(C₁-C₁₀ alkenyl)-, thieryl(C₁-C₁₀ alkenyl)-, or pyrrolyl(C₁-C₁₀ alkenyl)-;

A is -S- or -NH-, or A is a monocular or bicyclic heterocyclic group containing one or more nitrogen atoms in which A is bound through a nitrogen;

said heterocyclic group being optionally substituted with one or more moieties selected from the group consisting of heterocyclic, C₁-C₆ alkyl, C₁-C₆ alkoxy, heterocyclic(carbonyl)C₁-C₆ alkenyl, C₃-C₈ cycloalkyl, and phenyl,

which phenyl group may be substituted with one, two, or three moieties selected from the group consisting of halo, trifluoromethyl, hydroxy, C₁-C₆ alkyl, and C₁-C₆ alkoxy;

R² is hydrogen, C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, aryl, heterocyclic, heterocyclic(C₁-C₁₀ alkenyl)-, aryl(C₁-C₁₀ alkenyl)-, or trityl,

said aryl, heterocyclic, heterocyclic(C₁-C₁₀ alkenyl)-, or aryl(C₁-C₁₀ alkenyl)- groups being substituted with one or more
moieties selected from the group consisting of phenyl, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, trifluoromethyl,

which phenyl group may be substituted with one, two, or three moieties selected from the group consisting of halo, trifluoromethyl, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy;

provided that when A is a monocyclic or bicyclic heterocyclic group, R² is hydrogen;

further provided that R² is hydrogen only when A is a monocyclic or bicyclic heterocyclic group;

or a pharmaceutically acceptable salt or solvate thereof.

3. A pharmaceutical formulation comprising a compound of the formula

\[
\begin{align*}
R^{1a} & \quad SO \quad SO \\
N & \quad A \quad R^2 \\
O & \quad CO \quad CO
\end{align*}
\]

wherein:

R¹ and R¹a are C₁₋₆ alkyl, aryl(C₁₋₁₀ alkyl)-, furyl(C₁₋₁₀ alkyl)-, thienyl(C₁₋₁₀ alkyl)-, or pyrrolyl(C₁₋₁₀ alkyl)-;
A is -S- or -NH-, or A is a monocyclic or bicyclic heterocyclic group containing one or more nitrogen atoms in which A is bound through a nitrogen;

said heterocyclic group being optionally substituted with one or more moieties selected from the group consisting of heterocyclic, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, heterocyclic(carbonyl)C<sub>1</sub>-C<sub>6</sub> alkylenyl-, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, and phenyl,

which phenyl group may be substituted with one, two, or three moieties selected from the group consisting of halo, trifluoromethyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkyl, and C<sub>1</sub>-C<sub>6</sub> alkoxy;

R<sup>2</sup> is hydrogen, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, aryl, heterocyclic, heterocyclic(C<sub>1</sub>-C<sub>10</sub> alkylenyl)-, aryl(C<sub>1</sub>-C<sub>10</sub> alkylenyl)-, or trityl,

said aryl, heterocyclic, heterocyclic(C<sub>1</sub>-C<sub>10</sub> alkylenyl)-, or aryl(C<sub>1</sub>-C<sub>10</sub> alkylenyl)- groups being substituted with one or more moieties selected from the group consisting of phenyl, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, halo, trifluoromethyl,

which phenyl group may be substituted with one, two, or three moieties selected from the group consisting of halo, trifluoromethyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkyl, and C<sub>1</sub>-C<sub>6</sub> alkoxy;

provided that when A is a monocyclic or bicyclic heterocyclic group, R<sup>2</sup> is hydrogen;
further provided that \( R^2 \) is hydrogen only when \( A \) is a monocyclic or bicyclic heterocyclic group;

or a pharmaceutically acceptable salt or solvate thereof, associated with one or more pharmaceutically acceptable carriers, diluents, or excipients therefor.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) : A61K 31/54; C07D 285/16
US CL : 544/8; 514/222.5
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 544/8; 514/222.5

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE STRUCTURE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>US 4,544,742 A (SCHMITT et al.) 01 October 1985, entire document.</td>
<td>1-3</td>
</tr>
<tr>
<td>A</td>
<td>US 4,443,587 A (SCHMITT et al.) 17 April 1984, entire document.</td>
<td>1-3</td>
</tr>
</tbody>
</table>

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

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "B" earlier document published on or after the international filing date
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  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"a." document member of the same patent family

Date of the actual completion of the international search
21 JULY 1998

Date of mailing of the international search report
10 SEP 1998

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Form PCT/ISA/210 (second sheet) (July 1992)
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