(86) Date de dépôt PCT/PCT Filing Date: 2005/03/31
(87) Date publication PCT/PCT Publication Date: 2005/10/20
(85) Entrée phase nationale/National Entry: 2006/10/02
(86) N° demande PCT/PCT Application No.: US 2005/010937
(87) N° publication PCT/PCT Publication No.: 2005/097125
(30) Priorité/Priority: 2004/04/01 (US60/559,261)

(51) Cl.Int./Int.Cl. A61K 31/454 (2006.01)
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(54) Titre : METHODES ET COMPOSITIONS POUR LE TRAITEMENT, LA PREVENTION OU LA GESTION DES TROUBLES DU SOMMEIL ET DES TROUBLES DU SOMMEIL ASSOCIES A UNE MALADIE
(54) Title: METHODS AND COMPOSITIONS FOR THE TREATMENT, PREVENTION OR MANAGEMENT OF DIYSFUNCTIONAL SLEEP AND DIYSFUNCTIONAL SLEEP ASSOCIATED WITH DISEASE

(57) Abrégé/Abstract:
Methods of treating, preventing and/or managing dysfunctional sleep, including but not limited to, dysfunctional sleep associated with chronic neurological or inflammatory condition such as pain and neurodegenerative disorders, which comprise the administration of one or more immunomodulatory compounds or a pharmaceutically acceptable a salt, solvate, stereoisomer, clathrate or prodrug thereof, alone or in combination with known therapeutics are disclosed. Pharmaceutical compositions, single unit dosage forms, and kits suitable for use in methods of the invention are also disclosed.
Title: METHODS AND COMPOSITIONS FOR THE TREATMENT, PREVENTION OR MANAGEMENT OF DYSFUNCTIONAL SLEEP AND DYSFUNCTIONAL SLEEP ASSOCIATED WITH DISEASE

Abstract: Methods of treating, preventing and/or managing dysfunctional sleep, including but not limited to, dysfunctional sleep associated with chronic neurological or inflammatory condition such as pain and neurodegenerative disorders, which comprise the administration of one or more immunomodulatory compounds or a pharmaceutically acceptable salt, solvate, stereoisomer, clathrate or prodrug thereof, alone or in combination with known therapeutics are disclosed. Pharmaceutical compositions, single unit dosage forms, and kits suitable for use in methods of the invention are also disclosed.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.
METHODS AND COMPOSITIONS FOR THE TREATMENT, PREVENTION OR MANAGEMENT OF DYSFUNCTIONAL SLEEP AND DYSFUNCTIONAL SLEEP ASSOCIATED WITH DISEASE

1. **FIELD OF THE INVENTION**

[0001] This invention relates, in part, to methods of treating, preventing and/or managing dysfunctional sleep, which comprise the administration of an immunomodulatory compound or a pharmaceutically acceptable salt, solvate, stereoisomer, clathrate or prodrug thereof, alone or in combination with known therapeutics.

2. **BACKGROUND OF THE INVENTION**

[0002] It is estimated that 40 million Americans suffer from various sleep disorders, such as snoring, sleep apnea, insomnia, narcolepsy, restless leg syndrome, sleep terrors, sleep walking and sleep eating. It has been established that about ten percent of adults in the United States suffer from insomnia; annual costs for its treatment are estimated at $10.9 billion. *JAMA* 1997; 278: 2170-2177 at 2170. Sleep disorders have various etiologies, including stress induced by environmental and life style factors, physical factors, such as disease or obesity, and psychiatric disorders, such as depression. Sleep disorders are often found in conjunction with other conditions, in particular inflammatory and neurological conditions, e.g., complex regional pain syndrome, chronic low back pain, musculoskeletal pain, arthritis, radiculopathy, pain associated with cancer, fibromyalgia, chronic fatigue syndrome, visceral pain, bladder pain, chronic pancreatitis, neuropathies (diabetic, post-herpetic, traumatic or inflammatory), and neurodegenerative disorders such as Parkinson’s Disease, Alzheimer’s Disease, amyotrophic lateral sclerosis, multiple sclerosis and Huntington’s Disease.

[0003] Insomniacs report elevated levels of stress, anxiety, depression and medical illnesses. Possible treatment can be as simple as behavior modification or as involved as mechanical, surgical, or pharmacologic intervention. For example, sleep apnea can be treated by a mechanical device called a pneumatic splint or by allergen proof pillow casings, nasal steroids or pilocarpine. See, *The Pharmacological Basis Of Therapeutics, 9th Ed.*, *Goodman & Gilman*, Pergamon Press, New York, 1996. Narcolepsy can be treated with tricyclic anti-depressants, monoamine oxidase inhibitors, amphetamines, Focalin, Ritalin, and Provigil. *The Merck Manual 953* (17th ed. 1999). Benzodiazepines or melatonin may be used to treat insomnia. Restless leg syndrome can be treated with benzodiazepines and
drug that regulate dopamine, such as anti-Parkinson's drugs. See, The Pharmacological Basis Of Therapeutics, 9th Ed., Goodman & Gilman, Pergamon Press, New York, 1996.

The most common class of medications for treating insomnia are the benzodiazepines, but the adverse effect profile of benzodiazepines include daytime sedation, diminished motor coordination, and cognitive impairments. Furthermore, the National Institutes of Health Consensus conference on Sleeping Pills and Insomnia in 1984 developed guidelines discouraging the use of such sedative-hypnotics beyond 4-6 weeks because of concerns raised over drug misuse, dependency, withdrawal and rebound insomnia. JAMA 1997; 278: 2170-2177 at 2170.

Thus, a need remains for new therapies which improve the time to onset of sleep, the duration of sleep, the quality of sleep and enhance the ability to wake up feeling refreshed after a night's sleep for patients suffering from dysfunctional sleep and sleep disorders associated with chronic neurological or inflammatory conditions.

2.1 IMMUNOMODULATORY COMPOUNDS

A number of studies have been conducted with the aim of providing compounds that can safely and effectively be used to treat diseases associated with abnormal production of TNF-α. See, e.g., Marriott, J.B., et al., Expert Opin. Biol. Ther. 1(4):1-8 (2001); G.W. Muller, et al., Journal of Medicinal Chemistry 39(17): 3238-3240 (1996); and G.W. Muller, et al., Bioorganic & Medicinal Chemistry Letters 8: 2669-2674 (1998). Some studies have focused on a group of compounds selected for their capacity to potently inhibit TNF-α production by LPS stimulated PBMC. L.G. Corral, et al., Ann. Rheum. Dis. 58;(Suppl I) 1107-1113 (1999). These compounds, which are referred to as IMiDs™ (Celgene Corporation) or Immunomodulatory Compounds, show not only potent inhibition of TNF-α but also marked inhibition of LPS induced monocyte IL1β and IL12 production. LPS induced IL6 is also inhibited by immunomodulatory compounds, albeit partially. These compounds are potent stimulators of LPS induced IL10. Id. Particular examples of IMiDs™ include, but are not limited to, the substituted 2-(2,6-dioxopiperidin-3-yl) phthalimides and substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindoles described in United States Patent Nos. 6,281,230 and 6,316,471, both to G.W. Muller, et al.

3. SUMMARY OF THE INVENTION

This invention encompasses methods of treating, preventing or managing dysfunctional sleep, which comprise administering to a patient in need of such treatment, prevention or management a therapeutically or prophylactically effective amount of an
immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, stereoisomer, clathrate, or prodrug thereof.

[0008] The invention further encompasses pharmaceutical compositions, single unit dosage forms, and kits suitable for use in treating, preventing and/or managing dysfunctional sleep, which comprise an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, stereoisomer, clathrate, or prodrug thereof.

[0009] In particular embodiments of the invention, one or more immunomodulatory compounds are used, administered, or formulated with one or more second active agents that affect dysfunctional sleep or symptoms thereof.

4. **DETAILED DESCRIPTION OF THE INVENTION**

[0010] This invention is based on the unexpected discovery that immunomodulatory compounds can affect sleep. Consequently, a first embodiment of the invention encompasses methods of treating or preventing dysfunctional sleep, which comprise administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, stereoisomer, clathrate, or prodrug thereof. Dysfunctional sleep and sleep disorders include, but are not limited to, snoring, sleep apnea, insomnia, narcolepsy, restless leg syndrome, sleep terrors, sleep walking, sleep eating, and dysfunctional sleep associated with chronic neurological or inflammatory conditions. Additionally, the invention encompasses methods of inducing sedation, anesthesia, analgesia, amnesic sedation, sleep or a sedative effect in a patient, which comprise administering to a patient in need thereof an effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, stereoisomer, clathrate, or prodrug thereof.

[0011] Chronic neurological or inflammatory conditions, include, but are not limited to, complex regional pain syndrome, chronic low back pain, musculoskeletal pain, arthritis, radiculopathy, pain associated with cancer, fibromyalgia, chronic fatigue syndrome, visceral pain, bladder pain, chronic pancreatitis, neuropathies (diabetic, post-herpetic, traumatic or inflammatory), and neurodegenerative disorders such as Parkinson’s Disease, Alzheimer’s Disease, amyotrophic lateral sclerosis (ALS), multiple sclerosis, Huntington’s Disease, bradykinesia; muscle rigidity; parkinsonian tremor; parkinsonian gait; motion freezing; depression; defective long-term memory, Rubinstein-Taybi syndrome (RTS); dementia; postural instability; hypokinetic disorders; synuclein disorders; multiple system atrophies; striatonigral degeneration; olivopontocerebellar atrophy; Shy-Drager syndrome; motor
neuron disease with parkinsonian features; Lewy body dementia; Tau pathology disorders; progressive supranuclear palsy; corticobasal degeneration; frontotemporal dementia; amyloid pathology disorders; mild cognitive impairment; Alzheimer disease with parkinsonism; Wilson disease; Hallervorden-Spatz disease; Chediak-Hagashi disease; SCA-3 spinocerebellar ataxia; X-linked dystonia parkinsonism; prion disease; hyperkinetic disorders; chorea; ballismus; dystonia tremors; CNS trauma and myoclonus. Various pain disorders are disclosed by WO 04/037199, incorporated herein by reference in its entirety.

[0012] Another embodiment of the invention encompasses methods of managing dysfunctional sleep which comprise administering to a patient in need of such management a prophylactically effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, stereoisomer, clathrate, or prodrug thereof.

[0013] Another embodiment of the invention encompasses methods of improving the time to onset of sleep, the duration of sleep, the quality of sleep or enhancing the ability to wake up feeling refreshed after a night’s sleep which comprise administering to a patient in need thereof an effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, stereoisomer, clathrate, or prodrug thereof.

[0014] Another embodiment of the invention encompasses methods of treating, preventing and/or managing dysfunctional sleep, which comprise administering to a patient in need of such treatment, prevention and/or management a therapeutically or prophylactically effective amount of an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, stereoisomer, clathrate, or prodrug thereof and a therapeutically or prophylactically effective amount of a second active agent. In a related embodiment, the invention encompasses methods of treating, preventing and/or managing dysfunctional sleep associated with one or more chronic neurological or inflammatory condition such as pain and neurodegenerative disorders, which comprise administering to a patient in need of such treatment, prevention and/or management a therapeutically or prophylactically effective amount of an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, stereoisomer, clathrate, or prodrug thereof and a therapeutically or prophylactically effective amount of a second active agent. In one embodiment, the invention encompasses methods of treating, preventing, or managing dysfunctional sleep associated with the disorders outlined in WO 04/037199, entitled “Methods of Using and Compositions Comprising Immunomodulatory Compounds for Treatment, Modification and Management of Pain” and incorporated herein by reference in its entirety.
In one embodiment of the invention, the methods of treatment, prevention, or management are not necessarily tied to an underlying condition (an underlying condition such as complex regional pain syndrome), but tied necessarily to dysfunctional sleep associated with an underlying condition (again, an underlying condition such as complex regional pain syndrome). For example, in one embodiment of the invention, an immunomodulatory compound may be administered to a patient suffering from dysfunctional sleep associated with complex regional pain syndrome, wherein the administration of the immunomodulatory compound is specifically directed to dysfunctional sleep, rather than to complex regional pain syndrome.

In one embodiment of the invention, the methods of treatment, prevention, or management are coincidentally tied both to an underlying condition (an underlying condition such as complex regional pain syndrome) and to dysfunctional sleep associated with an underlying condition (again, an underlying condition such as complex regional pain syndrome). For example, in one embodiment of the invention, an immunomodulatory compound may be administered to a patient suffering from dysfunctional sleep associated with complex regional pain syndrome, wherein the administration of the immunomodulatory compound is directed both to dysfunctional sleep and to complex regional pain syndrome.

Second active agents can be large molecules (e.g., proteins) or small molecules (e.g., synthetic inorganic, organometallic, or organic molecules). Examples of second active agents include, but are not limited to, cytokines, hematopoietic growth factors, anti-cancer agents such as topoisomerase inhibitors, anti-angiogenic agents, microtubule stabilizing agents, apoptosis inducing agents, alkylating agents and other conventional chemotherapy described in the Physician’s Desk Reference 2004; cholinesterase inhibitors; antivirals; antifungals; antibiotics; anti-inflammatory agents; immunomodulatory agents; immunosuppressive agents such as cyclosporins; and other known or conventional agents used in sleep therapy.

Other agents potentially administered with immunomodulatory compounds include, but are not limited to: tricyclic antidepressant agents, selective serotonin reuptake inhibitors, antiepileptic agents (gabapentin, pregabalin, carbamazepine, oxcarbazepine, levitiracetam, topiramate), antiarrhythmic agents, sodium channel blocking agents, selective inflammatory mediator inhibitors, opioid agents or combination agents.

Without being limited by theory, it is believed that the combined use of such agents may reduce or eliminate adverse effects related to some immunomodulatory compounds, thereby allowing the administration of larger amounts of immunomodulatory
compounds to patients and/or increasing patient compliance. It is further believed that immunomodulatory compounds may reduce or eliminate adverse effects related to some conventional sleep aids, inflammatory agents or neurological agents, thereby allowing the administration of larger amounts of the agents to patients and/or increasing patient compliance. Such adverse effects include, but are not limited to, bitter taste, dry mouth, morning tiredness, morning hangover, headache, dizziness, impairment of psychomotor skills and drowsiness.

[0020] Yet another embodiment of the invention encompasses pharmaceutical compositions comprising an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, stereoisomer, clathrate, or prodrug thereof, and a pharmaceutically acceptable carrier, diluent or excipient. Specific compositions are adapted for parenteral, oral or transdermal administration.

[0021] Also encompassed by the invention are single unit dosage forms comprising an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, stereoisomer, clathrate, or prodrug thereof.

[0022] The invention also encompasses kits which comprise an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, stereoisomer, clathrate, or prodrug thereof, and a second active ingredient or agent.

4.1 IMMUNOMODULATORY COMPOUNDS

[0023] Compounds of the invention can either be commercially purchased or prepared according to the methods described in the patents or patent publications disclosed herein. Further, optically pure compositions can be asymmetrically synthesized or resolved using known resolving agents or chiral columns as well as other standard synthetic organic chemistry techniques. Compounds used in the invention may include immunomodulatory compounds that are racemic, stereomerically enriched or stereomerically pure, and pharmaceutically acceptable salts, solvates, stereoisomers, and prodrugs thereof.

[0024] Preferred compounds used in the invention are small organic molecules having a molecular weight less than about 1,000 g/mol, and are not proteins, peptides, oligonucleotides, oligosaccharides or other macromolecules.

[0025] As used herein and unless otherwise indicated, the terms "immunomodulatory compounds" and "IMiDs" (Celgene Corporation) encompasses small organic molecules that markedly inhibit TNF-α, LPS induced monocyte IL1β and IL12, and partially inhibit IL6 production. Specific immunomodulatory compounds are discussed below.

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TNF-α is an inflammatory cytokine produced by macrophages and monocytes during acute inflammation. TNF-α is responsible for a diverse range of signaling events within cells. Without being limited by theory, one of the biological effects exerted by the immunomodulatory compounds of the invention is the reduction of synthesis of TNF-α. Immunomodulatory compounds of the invention enhance the degradation of TNF-α mRNA.

Further, without being limited by theory, immunomodulatory compounds used in the invention may also be potent co-stimulators of T cells and increase cell proliferation dramatically in a dose dependent manner. Immunomodulatory compounds of the invention may also have a greater co-stimulatory effect on the CD8+ T cell subset than on the CD4+ T cell subset. In addition, the compounds preferably have anti-inflammatory properties, and efficiently co-stimulate T cells. Further, without being limited by a particular theory, immunomodulatory compounds used in the invention may be capable of acting both indirectly through cytokine activation and directly on Natural Killer ("NK") cells, and increase the NK cells’ ability to produce beneficial cytokines such as, but not limited to, IFN-γ.

Specific examples of immunomodulatory compounds, include, but are not limited to, cyano and carboxy derivatives of substituted styrenes such as those disclosed in U.S. patent no. 5,929,117; 1-oxo-2-(2,6-dioxo-3-fluoropiperidin-3yl) isoindolines and 1,3-dioxo-2-(2,6-dioxo-3-fluoropiperidine-3-yl) isoindolines such as those described in U.S. patent nos. 5,874,448 and 5,955,476; the tetra substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolines described in U.S. patent no. 5,798,368; 1-oxo and 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl) isoindolines (e.g., 4-methyl derivatives of thalidomide), including, but not limited to, those disclosed in U.S. patent nos. 5,635,517, 6,476,052, 6,555,554, and 6,403,613; 1-oxo and 1,3-dioxoisoindolines substituted in the 4- or 5-position of the indoline ring (e.g., 4-(4-amino-1,3-dioxoisoindoline-2-yl)-4-carbamoylbutanoic acid) described in U.S. patent no. 6,380,239; isoindoline-1-one and isoindoline-1,3-dione substituted in the 2-position with 2,6-dioxo-3-hydroxytripiperidin-5-yl (e.g., 2-(2,6-dioxo-3-hydroxy-5-fluoropiperidin-5-yl)-4-aminoisoindolin-1-one) described in U.S. patent no. 6,458,810; a class of non-polypeptide cyclic amides disclosed in U.S. patent nos. 5,698,579 and 5,877,200; aminothalidomide, as well as analogs, hydrolysis products, metabolites, derivatives and precursors of aminothalidomide, and substituted 2-(2,6-dioxopiperidin-3-yl) phthalimidates and substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindoles such as those described in U.S. patent nos. 6,281,230 and 6,316,471; and isoindole-imide compounds such as those described in U.S. patent application no. 09/972,487 filed on October 5, 2001,
Other specific immunomodulatory compounds of the invention include, but are not limited to, 1-oxo- and 1,3 dioxo-2-(2,6-dioxopiperidin-3-yl) isoindolines substituted with amino in the benzo ring as described in U.S. Patent no. 5,635,517 which is incorporated herein by reference. These compounds have the structure I:

![Chemical Structure](image)

in which one of X and Y is C=O, the other of X and Y is C=O or CH₂, and R² is hydrogen or lower alkyl, in particular methyl. Specific immunomodulatory compounds include, but are not limited to:

- 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-aminooxindoline;
- 1-oxo-2-(2,6-dioxopiperidin-3-yl)-5-aminooxindoline;
- 1-oxo-2-(2,6-dioxopiperidin-3-yl)-6-aminooxindoline;
- 1-oxo-2-(2,6-dioxopiperidin-3-yl)-7-aminooxindoline;
- 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-4-aminooxindoline; and
- 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-5-aminooxindoline.

Other specific immunomodulatory compounds of the invention belong to a class of substituted 2-(2,6-dioxopiperidin-3-yl) phthalimides and substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindoles, such as those described in U.S. patent nos. 6,281,230; 6,316,471; 6,335,349; and 6,476,052, and International Patent Application No. PCT/US97/13375 (International Publication No. WO 98/03502), each of which is incorporated herein by reference. Representative compounds are of formula:

![Chemical Structure](image)

in which:

one of X and Y is C=O and the other of X and Y is C=O or CH₂;
(i) each of $R^1$, $R^2$, $R^3$, and $R^4$, independently of the others, is halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms or (ii) one of $R^1$, $R^2$, $R^3$, and $R^4$ is -NHR$^5$ and the remaining of $R^1$, $R^2$, $R^3$, and $R^4$ are hydrogen;

$R^5$ is hydrogen or alkyl of 1 to 8 carbon atoms;

$R^6$ is hydrogen, alkyl of 1 to 8 carbon atoms, benzyl, or halo;

provided that $R^6$ is other than hydrogen if X and Y are C=O and (i) each of $R^1$, $R^2$, $R^3$, and $R^4$ is fluoro or (ii) one of $R^1$, $R^2$, $R^3$, or $R^4$ is amino.

Compounds representative of this class are of the formulas:

![Chemical structures](image)

wherein $R^1$ is hydrogen or methyl. In a separate embodiment, the invention encompasses the use of enantiomerically pure forms (e.g. optically pure (R) or (S) enantiomers) of these compounds.

[0031] Still other specific immunomodulatory compounds of the invention belong to a class of isoindole-imides disclosed in U.S. Patent Application Publication Nos. US 2003/0096841 and US 2003/0045552, and International Application No. PCT/US01/50401 (International Publication No. WO 02/059106), each of which are incorporated herein by reference. Representative compounds are of formula II:
and pharmaceutically acceptable salts, hydrates, solvates, clathrates, enantiomers, diastereomers, racemates, and mixtures of stereoisomers thereof, wherein:

one of X and Y is C=O and the other is CH$_2$ or C=O;

R$^1$ is H, (C$_1$–C$_8$)alkyl, (C$_3$–C$_7$)cycloalkyl, (C$_2$–C$_8$)alkenyl, (C$_2$–C$_8$)alkynyl, benzyl, aryl, (C$_0$–C$_4$)alkyl–(C$_1$–C$_6$)heterocycloalkyl, (C$_0$–C$_4$)alkyl–(C$_2$–C$_5$)heteroaryl, C(O)R$^3$, C(S)R$^3$, C(O)OR$^4$, (C$_1$–C$_8$)alkyl–N(R$^5$)$_2$, (C$_1$–C$_8$)alkyl–OR$^5$, (C$_1$–C$_8$)alkyl–C(O)OR$^5$, C(O)NHR$^3$, C(S)NHR$^3$, C(O)NR$^3$R$^{3''}$, or (C$_1$–C$_8$)alkyl–O(CO)R$^5$;

R$^2$ is H, F, benzyl, (C$_1$–C$_8$)alkyl, (C$_2$–C$_8$)alkenyl, or (C$_2$–C$_8$)alkynyl;

R$^3$ and R$^{3''}$ are independently (C$_1$–C$_8$)alkyl, (C$_3$–C$_7$)cycloalkyl, (C$_2$–C$_8$)alkenyl, (C$_2$–C$_8$)alkynyl, benzyl, aryl, (C$_0$–C$_4$)alkyl–(C$_1$–C$_6$)heterocycloalkyl, (C$_0$–C$_4$)alkyl–(C$_2$–C$_5$)heteroaryl, (C$_0$–C$_8$)alkyl–N(R$^5$)$_2$, (C$_1$–C$_8$)alkyl–OR$^5$, (C$_1$–C$_8$)alkyl–C(O)OR$^5$, (C$_1$–C$_8$)alkyl–O(CO)R$^5$, or C(O)OR$^5$;

R$^4$ is (C$_1$–C$_8$)alkyl, (C$_2$–C$_8$)alkenyl, (C$_1$–C$_4$)alkynyl, (C$_1$–C$_4$)alkyl–OR$^5$, benzyl, aryl, (C$_0$–C$_4$)alkyl–(C$_1$–C$_6$)heterocycloalkyl, or (C$_0$–C$_4$)alkyl–(C$_2$–C$_5$)heteroaryl;

R$^5$ is (C$_1$–C$_8$)alkyl, (C$_2$–C$_8$)alkenyl, (C$_2$–C$_8$)alkynyl, benzyl, aryl, or (C$_2$–C$_5$)heteroaryl;

each occurrence of R$^5$ is independently H, (C$_1$–C$_8$)alkyl, (C$_2$–C$_8$)alkenyl, (C$_2$–C$_8$)alkynyl, benzyl, aryl, (C$_0$–C$_8$)heterocycloalkyl, or (C$_0$–C$_8$)heteroaryl–C(O)O–R$^5$ or the R$^5$ groups can join to form a heterocycloalkyl group;

n is 0 or 1; and

* represents a chiral-carbon center.

[0032] In specific compounds of formula II, when n is 0 then R$^1$ is (C$_3$–C$_7$)cycloalkyl, (C$_2$–C$_8$)alkenyl, (C$_2$–C$_8$)alkynyl, benzyl, aryl, (C$_0$–C$_4$)alkyl–(C$_1$–C$_6$)heterocycloalkyl, (C$_0$–C$_4$)alkyl–(C$_2$–C$_5$)heteroaryl, C(O)R$^3$, C(O)OR$^4$, (C$_1$–C$_8$)alkyl–N(R$^5$)$_2$, (C$_1$–C$_8$)alkyl–OR$^5$, (C$_1$–C$_8$)alkyl–C(O)OR$^5$, C(S)NHR$^3$, or (C$_1$–C$_8$)alkyl–O(CO)R$^5$;

R$^2$ is H or (C$_1$–C$_8$)alkyl; and

R$^3$ is (C$_1$–C$_8$)alkyl, (C$_3$–C$_7$)cycloalkyl, (C$_2$–C$_8$)alkenyl, (C$_2$–C$_8$)alkynyl, benzyl, aryl, (C$_0$–C$_4$)alkyl–(C$_1$–C$_6$)heterocycloalkyl, (C$_0$–C$_4$)alkyl–(C$_2$–C$_5$)heteroaryl, (C$_5$–C$_8$)alkyl–N(R$^5$)$_2$; (C$_0$–C$_8$)alkyl–NH–C(O)O–R$^5$; (C$_1$–C$_8$)alkyl–OR$^5$, (C$_1$–C$_8$)alkyl–C(O)OR$^5$, (C$_1$–C$_8$)alkyl–O(CO)R$^5$, or C(O)OR$^5$; and the other variables have the same definitions.
In other specific compounds of formula II, $R^2$ is H or (C<sub>1</sub>-C<sub>4</sub>) alkyl.

In other specific compounds of formula II, $R^1$ is (C<sub>1</sub>-C<sub>8</sub>) alkyl or benzyl.

In other specific compounds of formula II, $R^1$ is H, (C<sub>1</sub>-C<sub>8</sub>) alkyl, benzyl, CH<sub>2</sub>OCH<sub>3</sub>, CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, or

In another embodiment of the compounds of formula II, $R^1$ is

wherein Q is O or S, and each occurrence of $R^7$ is independently H, (C<sub>1</sub>-C<sub>8</sub>) alkyl, (C<sub>3</sub>-C<sub>7</sub>) cycloalkyl, (C<sub>2</sub>-C<sub>8</sub>) alkenyl, (C<sub>2</sub>-C<sub>8</sub>) alkynyl, benzyl, aryl, halogen, (C<sub>0</sub>-C<sub>4</sub>) alkyl-(C<sub>1</sub>-C<sub>6</sub>) heterocycloalkyl, (C<sub>0</sub>-C<sub>4</sub>) alkyl-(C<sub>2</sub>-C<sub>5</sub>) heteroaryl, (C<sub>0</sub>-C<sub>4</sub>) alkyl-N(R<sup>6</sup>)<sub>2</sub>, (C<sub>1</sub>-C<sub>8</sub>) alkyl-OR<sup>5</sup>, (C<sub>1</sub>-C<sub>8</sub>) alkyl-(C(O))OR<sup>5</sup>, (C<sub>1</sub>-C<sub>8</sub>) alkyl-O(CO)R<sup>5</sup>, or C(O)OR<sup>5</sup>, or adjacent occurrences of $R^7$ can be taken together to form a bicyclic alkyl or aryl ring.

In other specific compounds of formula II, $R^1$ is C(O)R<sup>3</sup>.

In other specific compounds of formula II, $R^3$ is (C<sub>0</sub>-C<sub>4</sub>) alkyl-(C<sub>2</sub>-C<sub>5</sub>) heteroaryl, (C<sub>1</sub>-C<sub>8</sub>) alkyl, aryl, or (C<sub>0</sub>-C<sub>4</sub>) alkyl-OR<sup>5</sup>.

In other specific compounds of formula II, heteroaryl is pyridyl, furyl, or thiophenyl.

In other specific compounds of formula II, $R^1$ is C(O)OR<sup>4</sup>.

In other specific compounds of formula II, the H of C(O)NHC(O) can be replaced with (C<sub>1</sub>-C<sub>8</sub>) alkyl, aryl, or benzyl.

Further examples of the compounds in this class include, but are not limited to: 2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-ylmethyl]-amide; (2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-ylmethyl)-carbamic acid tert-butyl ester; 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione; N-(2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-ylmethyl)-acetamide; N-[(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)methyl] cyclopropyl-carboxamide; 2-chloro-N-[(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)methyl] acetamide; N-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)-3-pyridylcarboxamide; 3-{1-oxo-4-(benzylamino)isoindolin-2-yl} piperidine-2,6-dione; 2-(2,6-dioxo(3-piperidyl))-4-(benzylamino)isoindoline-1,3-dione; N-[(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)]-acetamide;
y)methyl} propanamide; N-[(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl)methyl]carboxamide; N-[(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl)methyl]heptanamide; N-[(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl)methyl]-2-furylcarboxamide; {N-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl)carbamoyl}methyl acetate; N-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl)pentanamide; N-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl)-2-thienylcarboxamide; N-[[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl](butylamino)carboxamide; N-[[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl](octylamino)carboxamide; and N-[[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl](benzylamino)carboxamide.


![Chemical Structure](image)

and pharmaceutically acceptable salts, hydrates, solvates, clathrates, enantiomers, diastereomers, racemates, and mixtures of stereoisomers thereof, wherein:

one of X and Y is C=O and the other is CH₂ or C=O;
R is H or CH₂OCOR';
(i) each of R¹, R², R³, or R⁴, independently of the others, is halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms or (ii) one of R¹, R², R³, or R⁴ is nitro or -NHR and the remaining of R¹, R², R³, or R⁴ are hydrogen;
R² is hydrogen or alkyl of 1 to 8 carbons
R⁵ hydrogen, alkyl of 1 to 8 carbon atoms, benzo, chloro, or fluoro;
R¹' is R²-CHR³⁻¹⁰-N(R⁸R⁹);
R²' is m-phenylene or p-phenylene or -(C₆H₄)n- in which n has a value of 0 to 4; each of R⁸ and R⁹ taken independently of the other is hydrogen or alkyl of 1 to 8 carbon atoms, or R³ and R⁹ taken together are tetramethylene, pentamethylene, hexamethylene, or -CH₂CH₂X₁CH₂CH₂- in which X₁ is -O-, -S-, or -NH-;
R¹⁰ is hydrogen, alkyl of to 8 carbon atoms, or phenyl; and
* represents a chiral-carbon center.

[0044] Other representative compounds are of formula:

wherein:

one of X and Y is C=O and the other of X and Y is C=O or CH₂;

(i) each of R¹, R², R³, or R⁴, independently of the others, is halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms or (ii) one of R¹, R², R³, and R⁴ is -NHR⁵ and the remaining of R¹, R², R³, and R⁴ are hydrogen;

R⁵ is hydrogen or alkyl of 1 to 8 carbon atoms;

R⁶ is hydrogen, alkyl of 1 to 8 carbon atoms, benzo, chloro, or fluoro;

R⁷ is m-phenylene or p-phenylene or -(C₆H₂n)- in which n has a value of 0 to 4;

each of R⁸ and R⁹ taken independently of the other is hydrogen or alkyl of 1 to 8 carbon atoms, or R⁸ and R⁹ taken together are tetramethylene, pentamethylene, hexamethylene, or -CH₂CH₂ X⁻¹CH₂CH₂⁻ in which X⁻¹ is -O⁻, -S⁻, or -NH⁻;

R¹⁰ is hydrogen, alkyl of 1 to 8 carbon atoms, or phenyl.

[0045] Other representative compounds are of formula:

in which:

one of X and Y is C=O and the other of X and Y is C=O or CH₂;

each of R¹, R², R³, and R⁴, independently of the others, is halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms or (ii) one of R¹, R², R³, and R⁴ is nitro or protected amino and the remaining of R¹, R², R³, and R⁴ are hydrogen; and

R⁶ is hydrogen, alkyl of 1 to 8 carbon atoms, benzo, chloro, or fluoro.

[0046] Other representative compounds are of formula:
in which:

one of X and Y is C=O and the other of X and Y is C=O or CH₂;

(i) each of R¹, R², R³, and R⁴, independently of the others, is halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms or (ii) one of R¹, R², R³, and R⁴ is -NHR⁵ and the remaining of R¹, R², R³, and R⁴ are hydrogen;

R⁵ is hydrogen, alkyl of 1 to 8 carbon atoms, or CO-R⁷-CH(R¹⁰)NR⁸R⁹ in which each of R⁷, R⁸, R⁹, and R¹⁰ is as herein defined; and

R⁶ is alkyl of 1 to 8 carbon atoms, benzo, chloro, or fluoro.

Specific examples of the compounds are of formula:

\[
\text{NHCO-R⁷-CH(R¹⁰)NR⁸R⁹}
\]

in which:

one of X and Y is C=O and the other of X and Y is C=O or CH₂;

R⁵ is hydrogen, alkyl of 1 to 8 carbon atoms, benzyl, chloro, or fluoro;

R⁷ is m-phenylene, p-phenylene or -(C₆H₂n)- in which n has a value of 0 to 4;

each of R⁸ and R⁹ taken independently of the other is hydrogen or alkyl of 1 to 8 carbon atoms, or R⁸ and R⁹ taken together are tetramethylene, pentamethylene, hexamethylene, or -CH₂CH₂X¹CH₂CH₂- in which X¹ is -O-, -S- or -NH-; and

R¹⁰ is hydrogen, alkyl of 1 to 8 carbon atoms, or phenyl.

[0047] Preferred immunomodulatory compounds of the invention are 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione and 3-(4-amino-1-oxo-1,3-dihydroisoindol-2-yl)-piperidine-2,6-dione. The compounds can be obtained via standard, synthetic methods (see e.g., United States Patent No. 5,635,517, incorporated herein by reference). The compounds are available from Celgene Corporation, Warren, NJ. 4-(Amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione has the following chemical structure:
The compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione has the following chemical structure:

[0048] In another embodiment, specific immunomodulatory compounds of the invention encompass polymorphic forms of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidene-2,6-dione such as Form A, B, C, D, E, F, G and H, disclosed in U.S. provisional application no. 60/499,723 filed on September 4, 2003, and U.S. non-provisional application no. 10/934,863, filed September 3, 2004, both of which are incorporated herein by reference. For example, Form A of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidene-2,6-dione is an unsolvated, crystalline material that can be obtained from non-aqueous solvent systems. Form A has an X-ray powder diffraction pattern comprising significant peaks at approximately 8, 14.5, 16, 17.5, 20.5, 24 and 26 degrees 2θ, and has a differential scanning calorimetry melting temperature maximum of about 270°C. Form A is weakly or not hygroscopic and appears to be the most thermodynamically stable anhydrous polymorph of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione discovered thus far.

[0049] Form B of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidene-2,6-dione is a hemihydrated, crystalline material that can be obtained from various solvent systems, including, but not limited to, hexane, toluene, and water. Form B has an X-ray powder diffraction pattern comprising significant peaks at approximately 16, 18, 22 and 27 degrees 2θ, and has endotherms from DSC curve of about 146 and 268°C, which are identified dehydration and melting by hot stage microscopy experiments. Interconversion studies show that Form B converts to Form E in aqueous solvent systems, and converts to other forms in acetone and other anhydrous systems.

[0050] Form C of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidene-2,6-dione is a hemisolvated crystalline material that can be obtained from solvents such as, but not limited to, acetone. Form C has an X-ray powder diffraction pattern comprising
significant peaks at approximately 15.5 and 25 degrees 20, and has a differential scanning calorimetry melting temperature maximum of about 269°C. Form C is not hygroscopic below about 85% RH, but can convert to Form B at higher relative humidities.

Form D of 3-(4-amino-1-oxo-1,3 dihydro-isomido-2-yl)-piperidene-2,6-dione is a crystalline, solvated polymorph prepared from a mixture of acetonitrile and water. Form D has an X-ray powder diffraction pattern comprising significant peaks at approximately 27 and 28 degrees 20, and has a differential scanning calorimetry melting temperature maximum of about 270°C. Form D is either weakly or not hygroscopic, but will typically convert to Form B when stressed at higher relative humidities.

Form E of 3-(4-amino-1-oxo-1,3 dihydro-isomido-2-yl)-piperidene-2,6-dione is a dihydrated, crystalline material that can be obtained by slurrying 3-(4-amino-1-oxo-1,3 dihydro-isomido-2-yl)-piperidene-2,6-dione in water and by a slow evaporation of 3-(4-amino-1-oxo-1,3 dihydro-isomido-2-yl)-piperidene-2,6-dione in a solvent system with a ratio of about 9:1 acetone:water. Form E has an X-ray powder diffraction pattern comprising significant peaks at approximately 20, 24.5 and 29 degrees 20, and has a differential scanning calorimetry melting temperature maximum of about 269°C. Form E can convert to Form C in an acetone solvent system and to Form G in a THF solvent system. In aqueous solvent systems, Form E appears to be the most stable form. Desolation experiments performed on Form E show that upon heating at about 125°C for about five minutes, Form E can convert to Form B. Upon heating at 175°C for about five minutes, Form B can convert to Form F.

Form F of 3-(4-amino-1-oxo-1,3 dihydro-isomido-2-yl)-piperidene-2,6-dione is an unsolvated, crystalline material that can be obtained from the dehydration of Form E. Form F has an X-ray powder diffraction pattern comprising significant peaks at approximately 19, 19.5 and 25 degrees 20, and has a differential scanning calorimetry melting temperature maximum of about 269°C.

Form G of 3-(4-amino-1-oxo-1,3 dihydro-isomido-2-yl)-piperidene-2,6-dione is an unsolvated, crystalline material that can be obtained from slurrying forms B and E in a solvent such as, but not limited to, tetrahydrofuran (THF). Form G has an X-ray powder diffraction pattern comprising significant peaks at approximately 21, 23 and 24.5 degrees 20, and has a differential scanning calorimetry melting temperature maximum of about 267°C.

Form H of 3-(4-amino-1-oxo-1,3 dihydro-isomido-2-yl)-piperidene-2,6-dione is a partially hydrated (about 0.25 moles) crystalline material that can be obtained by exposing Form E to 0% relative humidity. Form H has an X-ray powder diffraction pattern
comprising significant peaks at approximately 15, 26 and 31 clegrees 20, and has a
differential scanning calorimetry melting temperature maximum of about 269°C.

[0056] Other specific immunomodulatory compounds of the invention include, but
are not limited to, 1-oxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl) isoindolines and 1,3-dioxo-2-
(2,6-dioxo-3-fluoropiperidine-3-yl) isoindolines such as those described in U.S. patent nos.
5,874,448 and 5,955,476, each of which is incorporated herein by reference. Representative
compounds are of formula:

\[
\begin{align*}
\text{wherein } Y & \text{ is oxygen or } H^2 \text{ and} \\
\text{each of } R^1, R^2, R^3, \text{ and } R^4, \text{ independently of the others, is hydrogen, halo, alkyl of 1} \\
to 4 \text{ carbon atoms, alkoxy of 1 to 4 carbon atoms, or amino.}
\end{align*}
\]

[0057] Other specific immunomodulatory compounds of the invention include, but
are not limited to, the tetra substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisoiindolines
described in U.S. patent no. 5,798,368, which is incorporated herein by reference.
Representative compounds are of formula:

\[
\begin{align*}
\text{wherein each of } R^1, R^2, R^3, \text{ and } R^4, \text{ independently of the others, is halo, alkyl of 1} \\
to 4 \text{ carbon atoms, or alkoxy of 1 to 4 carbon atoms.}
\end{align*}
\]

[0058] Other specific immunomodulatory compounds of the invention include, but
are not limited to, 1-oxo and 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl) isoindolines disclosed in
U.S. patent no. 6,403,613, which is incorporated herein by reference. Representative
compounds are of formula:
in which

Y is oxygen or H₂,

a first of R¹ and R² is halo, alkyl, alkoxy, alkylamino, dialkylamino, cyano, or carbamoyl, the second of R¹ and R², independently of the first, is hydrogen, halo, alkyl, alkoxy, alkylamino, dialkylamino, cyano, or carbamoyl, and

R³ is hydrogen, alkyl, or benzyl.

[0059] Specific examples of the compounds are of formula:

![Chemical Structure](image)

wherein a first of R¹ and R² is halo, alkyl of from 1 to 4 carbon atoms, alkoxy of from 1 to 4 carbon atoms, dialkylamino in which each alkyl is of from 1 to 4 carbon atoms, cyano, or carbamoyl,

the second of R¹ and R², independently of the first, is hydrogen, halo, alkyl of from 1 to 4 carbon atoms, alkoxy of from 1 to 4 carbon atoms, alkylamino in which alkyl is of from 1 to 4 carbon atoms, dialkylamino in which each alkyl is of from 1 to 4 carbon atoms, cyano, or carbamoyl, and

R³ is hydrogen, alkyl of from 1 to 4 carbon atoms, or benzyl. Specific examples include, but are not limited to, 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-methylsoindoline.

[0060] Other representative compounds are of formula:

![Chemical Structure](image)

wherein a first of R¹ and R² is halo, alkyl of from 1 to 4 carbon atoms, alkoxy of from 1 to 4 carbon atoms, dialkylamino in which each alkyl is of from 1 to 4 carbon atoms, cyano, or carbamoyl,

the second of R¹ and R², independently of the first, is hydrogen, halo, alkyl of from 1 to 4 carbon atoms, alkoxy of from 1 to 4 carbon atoms, alkylamino in which alkyl is of from 1 to 4 carbon atoms, dialkylamino in which each alkyl is of from 1 to 4 carbon atoms, cyano, or carbamoyl, and

R³ is hydrogen, alkyl of from 1 to 4 carbon atoms, or benzyl.
Specific examples include, but are not limited to, 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-methylisooindolone.

Other specific immunomodulatory compounds of the invention include, but are not limited to, 1-oxo and 1,3-dioxoisooindolines substituted in the 4- or 5-position of the indoline ring described in U.S. patent no. 6,380,239 and co-pending U.S. application no. 10/900,270, filed July 28, 2004, which are incorporated herein by reference. Representative compounds are of formula:

\[
\begin{align*}
\text{in which the carbon atom designated } C^* \text{ constitutes a center of chirality (when } n \text{ is not zero and } R^1 \text{ is not the same as } R^2; \text{ one of } X^1 \text{ and } X^2 \text{ is amino, nitro, alkyl of one to six carbons, or NH-Z, and the other of } X^1 \text{ or } X^2 \text{ is hydrogen; each of } R^1 \text{ and } R^2 \text{ independent of the other, is hydroxy or NH-Z; } R^3 \text{ is hydrogen, alkyl of one to six carbons, halo, or haloalkyl; } Z \text{ is hydrogen, aryl, alkyl of one to six carbons, formyl, or acyl of one to six carbons; and } n \text{ has a value of } 0, 1, \text{ or } 2; \text{ provided that if } X^1 \text{ is amino, and } n \geq 1 \text{ or } 2, \text{ then } R^1 \text{ and } R^2 \text{ are not both hydroxy; and the salts thereof.}
\end{align*}
\]

Further representative compounds are of formula:

\[
\begin{align*}
\text{in which the carbon atom designated } C^* \text{ constitutes a center of chirality when } n \text{ is not zero and } R^1 \text{ is not } R^2; \text{ one of } X^1 \text{ and } X^2 \text{ is amino, nitro, alkyl of one to six carbons, or NH-Z, and the other of } X^1 \text{ or } X^2 \text{ is hydrogen; each of } R^1 \text{ and } R^2 \text{ independent of the other, is hydroxy or NH-Z; } R^3 \text{ is alkyl of one to six carbons, halo, or hydrogen; } Z \text{ is hydrogen, aryl or an alkyl or acyl of one to six carbons; and } n \text{ has a value of } 0, 1, \text{ or } 2.
\end{align*}
\]

Specific examples include, but are not limited to, 2-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-4-carbamoyl-butyric acid and 4-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-4-carbamoyl-butyric acid, which have the following structures, respectively, and pharmaceutically acceptable salts, solvates, prodrugs, and stereoisomers thereof:
Other representative compounds are of formula:

\[
\text{in which the carbon atom designated } C^* \text{ constitutes a center of chirality when } n \text{ is not zero and } R^1 \text{ is not } R^2; \text{ one of } X^1 \text{ and } X^2 \text{ is amino, nitro, alkyl of one to six carbons, or NH-Z, and the other of } X^1 \text{ or } X^2 \text{ is hydrogen; each of } R^1 \text{ and } R^2 \text{ independent of the other, is hydroxy or NH-Z; } R^3 \text{ is alkyl of one to six carbons, halo, or hydrogen; } Z \text{ is hydrogen, aryl, or an alkyl or acyl of one to six carbons; and } n \text{ has a value of 0, 1, or 2; and the salts thereof.}
\]

Specific examples include, but are not limited to, 4-carbamoyl-4-\{4-[(furan-2-yl-methyl)-amino]-1,3-dioxo-1,3-dihydro-isooindol-2-yl\}-butyric acid, 4-carbamoyl-2-\{4-[(furan-2-yl-methyl)-amino]-1,3-dioxo-1,3-dihydro-isooindol-2-yl\}-butyric acid, 2-\{4-[(furan-2-yl-methyl)-amino]-1,3-dioxo-1,3-dihydro-isooindol-2-yl\}-4-phenylcarboxamoyl-butyric acid, and 2-\{4-[(furan-2-yl-methyl)-amino]-1,3-dioxo-1,3-dihydro-isooindol-2-yl\}-pentanedioic acid, which have the following structures, respectively, and pharmaceutically acceptable salts, solvate, prodrugs, and stereoisomers thereof:

Other specific examples of the compounds are of formula:
wherein one of $X^1$ and $X^2$ is nitro, or NH-Z, and the other of $X^1$ or $X^2$ is hydrogen; each of $R^1$ and $R^2$, independent of the other, is hydroxy or NH-Z; $R^3$ is alkyl of one to six carbons, halo, or hydrogen; $Z$ is hydrogen, phenyl, an acyl of one to six carbons, or an alkyl of one to six carbons; and $n$ has a value of 0, 1, or 2; provided that if one of $X^1$ and $X^2$ is nitro, and $n$ is 1 or 2, then $R^1$ and $R^2$ are other than hydroxy; and if -$COR^2$ and -(CH$_2$)$_n$COR$^1$ are different, the carbon atom designated C$^*$ constitutes a center of chirality. Other representative compounds are of formula:

wherein one of $X^1$ and $X^2$ is alkyl of one to six carbons; each of $R^1$ and $R^2$, independent of the other, is hydroxy or NH-Z; $R^3$ is alkyl of one to six carbons, halo, or hydrogen; $Z$ is hydrogen, phenyl, an acyl of one to six carbons, or an alkyl of one to six carbons; and $n$ has a value of 0, 1, or 2; and if -$COR^2$ and -(CH$_2$)$_n$COR$^1$ are different, the carbon atom designated C$^*$ constitutes a center of chirality.

Still other specific immunomodulatory compounds of the invention include, but are not limited to, isoindoline-1-one and isoindoline-1,3-dione substituted in the 2-position with 2,6-dioxo-3-hydroxypiperidin-5-yl described in U.S. patent no. 6,458,810, which is incorporated herein by reference. Representative compounds are of formula:
wherein:

the carbon atoms designated * constitute centers of chirality;
X is -C(O)- or -CH₂-;
R¹ is alkyl of 1 to 8 carbon atoms or -NHR²;
R² is hydrogen, alkyl of 1 to 8 carbon atoms, or halogen;
and
R³ is hydrogen,
alkyl of 1 to 8 carbon atoms, unsubstituted or substituted with alkoxy of 1 to 8 carbon atoms, halo, amino, or alkylamino of 1 to 4 carbon atoms,
cycloalkyl of 3 to 18 carbon atoms,
phenyl, unsubstituted or substituted with alkyl of 1 to 8 carbon atoms, alkoxy 0·f 1 to 8 carbon atoms, halo, amino, or alkylamino of 1 to 4 carbon atoms,
benzyl, unsubstituted or substituted with alkyl of 1 to 8 carbon atoms, alkoxy 0·f 1 to 8 carbon atoms, halo, amino, or alkylamino of 1 to 4 carbon atoms, or -COR⁴ in which
R⁴ is hydrogen,
alkyl of 1 to 8 carbon atoms, unsubstituted or substituted with alkoxy of 1 to 8 carbon atoms, halo, amino, or alkylamino of 1 to 4 carbon atoms,
cycloalkyl of 3 to 18 carbon atoms,
phenyl, unsubstituted or substituted with alkyl of 1 to 8 carbon atoms, alkoxy 0·f 1 to 8 carbon atoms, halo, amino, or alkylamino of 1 to 4 carbon atoms, or
benzyl, unsubstituted or substituted with alkyl of 1 to 8 carbon atoms, alkoxy 0·f 1 to 8 carbon atoms, halo, amino, or alkylamino of 1 to 4 carbon atoms.

[0069] Compounds of the invention can either be commercially purchased or prepared according to the methods described in the patents or patent publications disclosed herein. Further, optically pure compounds can be asymmetrically synthesized or resolved using known resolving agents or chiral columns as well as other standard synthetic organic chemistry techniques.

[0070] As used herein and unless otherwise indicated, the term "pharmaceutically acceptable salt" encompasses non-toxic acid and base addition salts of the compound to which the term refers. Acceptable non-toxic acid addition salts include those derived from organic and inorganic acids or bases known in the art, which include, for example,
Compounds that are acidic in nature are capable of forming salts with various pharmaceutically acceptable bases. The bases that can be used to prepare pharmaceutically acceptable base addition salts of such acidic compounds are those that form non-toxic base addition salts, i.e., salts containing pharmacologically acceptable cations such as, but not limited to, alkali metal or alkaline earth metal salts and the calcium, magnesium, sodium or potassium salts in particular. Suitable organic bases include, but are not limited to, N,N-dibenzylethlenediamine, chlorprocaaine, choline, diethanolamine, ethylenediamine, meglumaine (N-methylglucamine), lysine, and procaine.

As used herein, and unless otherwise specified, the term “solvate” means a compound of the present invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. Where the solvent is water, the solvate is a hydrate.

As used herein and unless otherwise indicated, the term “prodrug” means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to provide the compound. Examples of prodrugs include, but are not limited to, derivatives of immunomodulatory compounds of the invention that comprise biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Other examples of prodrugs include derivatives of immunomodulatory compounds of the invention that comprise -NO, -NO₂, -ONO, or -ONO₂ moieties. Prodrugs can typically be prepared using well-known methods, such as those described in 1 Burger’s Medicinal Chemistry and Drug Discovery, 172-178, 949-982 (Manfred E. Wolff ed., 5th ed. 1995), and Design of Prodrugs (H. Bundgaard ed., Elselvier, New York 1985).

As used herein and unless otherwise indicated, the terms “biohydrolyzable amide,” “biohydrolyzable ester,” “biohydrolyzable carbamate,” “biohydrolyzable carbonate,” “biohydrolyzable ureide,” “biohydrolyzable phosphate” mean an amide, ester, carbamate, carbonate, ureide, or phosphate, respectively, of a compound that either: 1) does not interfere with the biological activity of the compound but can confer upon that compound advantageous properties in vivo, such as uptake, duration of action, or onset of action; or 2) is biologically inactive but is converted in vivo to the biologically active compound. Examples of biohydrolyzable esters include, but are not limited to, lower alkyl
esters, lower acyloxyalkyl esters (such as acetoxyethylmethyl, acetoxyethyl, aminocarboxyloxymethyl, pivaloyloxymethyl, and pivaloxygenyethyl esters), lactonyl esters (such as phthalidyl and thiopthalidyl esters), lower alkoxyacyloxyalkyl esters (such as methoxy carbonyl-oxyethyl, ethoxycarbonyloxymethyl and isopropoxycarbonyloxyethyl esters), alkoxyalkyl esters, choline esters, and acylamino alkyl esters (such as acetamidomethyl esters). Examples of biohydrolyzable amides include, but are not limited to, lower alkyl amides, α-amino acid amides, alkoxyacetyl amides, and alkylaminoxalkylcarbonyl amides. Examples of biohydrolyzable carbamates include, but are not limited to, lower alkylamines, substituted ethylenediamines, amino acids, hydroxyalkylamines, heterocyclic and heteroaromatic amines, and polyether amines.

[0075] As used herein, and unless otherwise specified, the term “stereoisomer” encompasses all enantiomerically/stereomerically pure and enantiomerically/stereomerically enriched compounds of this invention.

[0076] As used herein, and unless otherwise indicated, the term “stereomerically pure” or “enantiomerically pure” means that a compound comprises one stereoisomer and is substantially free of its counter stereoisomer or enantiomer. For example, a compound is stereomerically or enantiomerically pure when the compound contains 80%, 90%, or 95% or more of one stereoisomer and 20%, 10%, or 5% or less of the counter stereoisomer. In certain cases, a compound of the invention is considered optically active or stereomerically/enantiomerically pure (i.e., substantially the R-form or substantially the S-form) with respect to a chiral center when the compound is about 80% ee (enantiomeric excess) or greater, preferably, equal to or greater than 90% ee with respect to a particular chiral center, and more preferably 95% ee with respect to a particular chiral center.

[0077] As used herein, and unless otherwise indicated, the term “stereomerically enriched” or “enantiomerically enriched” encompasses racemic mixtures as well as other mixtures of stereoisomers of compounds of this invention (e.g., R/S = 30/70, 35/65, 40/60, 45/55, 55/45, 60/40, 65/35 and 70/30). Various immunomodulatory compounds of the invention contain one or more chiral centers, and can exist as racemic mixtures of enantiomers or mixtures of diastereomers. This invention encompasses the use of stereomerically pure forms of such compounds, as well as the use of mixtures of those forms. For example, mixtures comprising equal or unequal amounts of the enantiomers of a particular immunomodulatory compounds of the invention may be used in methods and compositions of the invention. These isomers may be asymmetrically synthesized or resolved using standard techniques such as chiral columns or chiral resolving agents. See, e.g., Jacques, J., et al., *Enantiomers, Racemates and Resolutions* (Wiley-Interscience, New
It should be noted that if there is a discrepancy between a depicted structure and a name given that structure, the depicted structure is to be accorded more weight. In addition, if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it.

4.2 SECOND ACTIVE INGREDIENTS OR AGENTS

As discussed above, a second active ingredient or agent can be used in the methods and compositions of the invention together with an immunomodulatory compound. Examples include conventional agents used to treat or manage dysfunctional sleep. Specific second active agents also stimulate the division and differentiation of committed erythroid progenitors in cells in vitro or in vivo.

In one embodiment, the second active ingredient or agent is a tricyclic antidepressant agent, a selective serotonin reuptake inhibitor, an antiepileptic agent (gabapentin, pregabalin, carbamazepine, oxcarbazepine, levitiracetam, topiramate), an antiarrhythmic agent, a sodium channel blocking agent, a selective inflammatory mediator inhibitor, an opioid agent, a second immunomodulatory compound or a combination agent.

In a preferred embodiment, the second active ingredient or agent is Neurontin, oxycontin, morphine, or topiramate.

In another preferred embodiment, the second active ingredient or agent is a tricyclic antidepressant such as amitriptyline, or nortryptiline, or carbamazepine.

In another embodiment, the second active ingredient or agent is a dopamine agonist or antagonist, such as, but not limited to, Levodopa, L-DOPA, cocaine, α-methyl-tyrosine, reserpine, tetrabenazine, benztropine, pargyline, fenodolpam mesylate, cabergoline, pramipexole dihydrochloride, ropinorole, amantadine hydrochloride, selegiline hydrochloride, carbidopa, pergolide mesylate, Sinemet CR, or Symmetrel.

In another embodiment, the second active ingredient or agent is an MAO inhibitor, for example, but not limited to, iproniazid, clorgyline, phenelzine and isocarboxazid.

In another embodiment, the second active ingredient or agent is a COMT inhibitor, for example, but not limited to, tolcapone and entacapone.
In another embodiment, the second active ingredient or agent is a cholinesterase inhibitor, for example, but not limited to, physostigmine salicylate, physostigmine sulfate, physostigmine bromide, neostigmine bromide, neostigmine methylsulfate, ambenonim chloride, edrophonium chloride, tacrine, pralidoxime chloride, obidoxime chloride, trimedoxime bromide, diacetyl monoxim, endrophonium, pyridostigmine, and demecarium.

In yet another embodiment, the second active ingredient or agent is an anti-inflammatory agent, including, but not limited to, naproxen sodium, diclofenac sodium, diclofenac potassium, celecoxib, sulindac, oxaprozin, diflunisal, etodolac, meloxicam, ibuprofen, ketoprofen, nabumetone, refecoxib, methotrexate, leflunomide, sulfasalazine, gold salts, RH\(_{0}\)-D Immune Globulin, mycophenylate mofetil, cyclosporine, azathioprine, tacrolimus, basiliximab, daclizumab, salicylic acid, acetyl salicylic acid, methyl salicylate, diflunisal, salsalate, olsalazine, sulfasalazine, acetaminophen, indomethacin, sulindac, mefenamic acid, meclofenamate sodium, tolmetin, ketorolac, dichlofenac, flurbinprofen, oxaprozin, piroxicam, meloxicam, ampiroxicam, drxicam, pivoxican, tenoxicam, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, apazone, zileuton, aurothioglaucose, gold sodium thiomalate, auranofin, methotrexate, colchicine, allopurinol, probenecid, sulfinpyrazone and benzbromarone or betamethasone and other glucocorticoids.

In even another embodiment, the second active ingredient or agent is an antiemetic agent, for example, but not limited to, metoclopramide, domperidone, prochlorperazine, promethazine, chlorpromazine, trimethobenzamide, ondansetron, granisetron, hydroxyzine, acetylleucine monoethanolamine, alizapride, azasetron, benzquinamide, bietanautine, bromopride, buclizine, clebopride, cyclizine, dimenhydrinate, diphenidol, dolasetron, meclizine, mehtallat, metopimazne, nabilone, oxyperndyl, pipamazine, scopolamine, sulpiride, tetrahydrocannabinol, thiethylperazine, thioproperazine, tropisetron, and mixtures thereof.

4.3 METHODS OF TREATMENT AND MANAGEMENT

Methods of this invention encompass methods of treating, preventing or managing dysfunctional sleep. Methods of this invention also encompass methods of treating, preventing or managing dysfunctional sleep associated with chronic neurological or inflammatory condition. Dysfunctional sleep and sleep disorders include, but are not limited to, snoring, sleep apnea, insomnia, narcolepsy, restless legs syndrome, sleep terrors, sleep walking and sleep eating. Chronic neurological or inflammatory conditions, include, but are not limited to, complex regional pain syndrome, chronic low back pain, musculoskeletal pain, arthritis, radiculopathy, pain associated with cancer, fibromyalgia,
Chronic fatigue syndrome, visceral pain, bladder pain, chronic pancreatitis, neuropathies (diabetic, post-herpetic, traumatic or inflammatory), and neurodegenerative disorders such as Parkinson’s Disease, Alzheimer’s Disease, multiple sclerosis, Huntington’s Disease, bradykinesia; muscle rigidity; parkinsonian tremor; parkinsonian gait; motion freezing; depression; defective long-term memory, Rubinstein-Taybi syndrome (RTS); dementia; postural instability; hypokinetic disorders; synuclein disorders; multiple system atrophies; striatonigral degeneration; olivopontocerebellar atrophy; Shy-Drager syndrome; motor neuron disease with parkinsonian features; Lewy body dementia; Tau pathology disorders; progressive supranuclear palsy; corticobasal degeneration; frontotemporal dementia; amyloid pathology disorders; mild cognitive impairment; Alzheimer disease with parkinsonism; Wilson disease; Hallervorden-Spatz disease; Chediak-Hagashi disease; SCA-3 spinocerebellar ataxia; X-linked dystonia parkinsonism; prion disease; hyperkinetic disorders; chorea; ballismus; dystonia tremors; Amyotrophic Lateral Sclerosis (ALS); CNS trauma and myoclonus.

[0090] As used herein, unless otherwise indicated, the term “associated with” means that certain diseases, conditions, disorders, dysfunctions or biological phenomena are (a) caused by, (b) incident to, (c) causes of, (d) symptoms of, (e) indicated by, or (f) in any other way related to certain other diseases, conditions, disorders, dysfunctions, or biological phenomena.

[0091] As used herein, unless otherwise indicated, the term “dysfunctional sleep” refers to any sleep disorder such as, snoring, sleep apnea, insomnia, narcolepsy, restless leg syndrome, sleep terrors, sleep walking or sleep eating.

[0092] As used herein, unless otherwise specified, the term “treating” refers to the administration of a composition after the onset of symptoms of dysfunctional sleep, preferably dysfunctional sleep associated with one or more chronic neurological or inflammatory conditions or disorders.

[0093] As used herein, unless otherwise specified, the term “preventing” refers to the administration prior to the onset of symptoms, particularly to patients at risk of dysfunctional sleep, preferably dysfunctional sleep associated with one or more chronic neurological or inflammatory condition.

[0094] As used herein and unless otherwise indicated, the term “managing” encompasses preventing the recurrence of symptoms of dysfunctional sleep in a patient as well as improving the time to onset of sleep, the duration of sleep, the quality of sleep or enhancing the ability to wake up feeling refreshed after a night’s sleep.
Methods encompassed by this invention comprise administering an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, stereoisomer, clathrate, or prodrug thereof to a patient (e.g., a human) suffering, or likely to suffer, from dysfunctional sleep.

Another method comprises administering 1) an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, stereoisomer, clathrate, or prodrug thereof, and 2) a second active agent or active ingredient. Examples of the second active agents are also disclosed herein (see, e.g., section 4.2).

Administration of immunomodulatory compound and second active agents to a patient can occur simultaneously or sequentially by the same or different routes of administration. The suitability of a particular route of administration employed for a particular active agent will depend on the active agent itself (e.g., whether it can be administered orally without decomposing prior to entering the blood stream) and the disease being treated. A preferred route of administration for the immunomodulatory compound is oral. Preferred routes of administration for the second active agents or ingredients of the invention are known to those of ordinary skill in the art. See, e.g., Physicians’ Desk Reference, 1755-1760 (57th ed., 2003).

In one embodiment of the invention, an immunomodulatory compound is administered orally and in a single or divided daily doses in an amount of from about 0.10 to about 150 mg/day. In one embodiment, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione is administered in an amount of from about 5 to about 25 mg per day, or alternatively from about 10 to about 50 mg every other day. In another embodiment, 4-(amino)-2-(2,6-dioxo-(3-piperidyl))-isoindoline-1,3-dione is administered in an amount of from about 0.10 to about 1 mg per day, or alternatively from about 0.10 to about 5 mg every other day. In one embodiment of the invention, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione is administered orally and in a single or divided daily doses in an amount of from about 0.10 to about 150 mg/day. In a particular embodiment, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione is administered in an amount of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 1-10, 3-7, or 4-6 mg/day.

In another embodiment, an immunomodulatory compound is administered in conjunction with the second active agent. The second active agent is administered orally, intravenously or subcutaneously and once or twice daily in an amount of from about 1 to about 1000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg, or from about 50 to about 200 mg. The specific amount of the second active agent will depend on the specific agent used, the disorder being treated or managed, the severity and stage of the
In certain embodiments, the prophylactic or therapeutic agents of the invention are cyclically administered to a patient. Cycling therapy involves the administration of a first agent for a period of time, followed by the administration of the agent and/or the second agent for a period of time and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

In a preferred embodiment, prophylactic or therapeutic agents are administered in a cycle of about 24 weeks, about once or twice every day. One cycle can comprise the administration of a therapeutic or prophylactic agent and at least one (1) or three (3) weeks of rest. The number of cycles administered is from about 1 to about 12 cycles, more typically from about 2 to about 10 cycles, and more typically from about 2 to about 8 cycles.

4.4 PHARMACEUTICAL COMPOSITIONS AND SINGLE UNIT DOSAGE FORMS

Pharmaceutical compositions can be used in the preparation of individual, single unit dosage forms. Pharmaceutical compositions and dosage forms of the invention comprise a an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, stereoisomer, clathrate, or prodrug thereof. Pharmaceutical compositions and dosage forms of the invention can further comprise one or more excipients.

Pharmaceutical compositions and dosage forms of the invention can also comprise one or more additional active ingredients. Consequently, pharmaceutical compositions and dosage forms of the invention comprise the active ingredients disclosed herein (e.g., an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, stereoisomer, clathrate, or prodrug thereof, and a second active ingredient or agent). Examples of optional additional active ingredients are disclosed herein (see, e.g., section 4.2).

Single unit dosage forms of the invention are suitable for oral, mucosal (e.g., nasal, sublingual, vaginal, buccal, or rectal), or parenteral (e.g., subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), transdermal or transcutaneous administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions;
The composition, shape, and type of dosage forms of the invention will typically vary depending on their use. For example, a dosage form used in the acute treatment of a sleep dysfunction may contain larger amounts of one or more of the active ingredients it comprises than a dosage form used in the chronic treatment of the same disease. Similarly, a parenteral dosage form may contain smaller amounts of one or more of the active ingredients it comprises than an oral dosage form used to treat the same disease. These and other ways in which specific dosage forms encompassed by this invention will vary from one another will be readily apparent to those skilled in the art. See, e.g., Remington’s Pharmaceutical Sciences, 18th ed., Mack Publishing, Easton PA (1990).

Typical pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form. For example, the decomposition of some active ingredients may be accelerated by some excipients such as lactose, or when exposed to water. Active ingredients that comprise primary or secondary amines are particularly susceptible to such accelerated decomposition. Consequently, this invention encompasses pharmaceutical compositions and dosage forms that contain little, if any, lactose other mono- or di-saccharides. As used herein, the term “lactose-free” means that the amount of lactose present, if any, is insufficient to substantially increase the degradation rate of an active ingredient.

Lactose-free compositions of the invention can comprise excipients that are well known in the art and are listed, for example, in the U.S. Pharmacopeia (USP) 25-NF20 (2002). In general, lactose-free compositions comprise active ingredients, a binder/filler, etc.
and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. Preferred lactose-free dosage forms comprise active ingredients, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

[00108] This invention further encompasses anhydrous pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (e.g., 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. See, e.g., Jens T. Carstensen, Drug Stability: Principles & Practice, 2d. Ed., Marcel Dekker, NY, NY, 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

[00109] Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine are preferably anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

[00110] An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are preferably packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (e.g., vials), blister packs, and strip packs.

[00111] The invention further encompasses pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.

[00112] Like the amounts and types of excipients, the amounts and specific types of active ingredients in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients. However, typical dosage forms of the invention comprise 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione or 4-(amino)-2-(2,6-dioxo-(3-piperidyl))-isoindoline-1,3-dione, or a pharmaceutically acceptable salt, solvate, hydrate, clathrate, or prodrug thereof in an amount of about 0.1, 1,
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In a specific embodiment, a preferred dosage form comprises 3-(4-amino-1-oxo-1,3-dihydro-isooindol-2-yl)-piperidine-2,6-dione in an amount of about 5, 10, 25 or 50 mg. In another specific embodiment, a preferred dosage form comprises 4-(amino)-2-(2,6-dioxo-(3-piperidyl))-isoindoline-1,3-dione in an amount of about 1, 2, 5, 10, 25 or 50 mg. Typical dosage forms comprise the second active ingredient in an amount of 1 to about 1000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg, or from about 50 to about 200 mg. Of course, the specific amount of the second active ingredient will depend on the specific agent used, the type of diseases or conditions being treated or managed, and the amounts of 3-(4-amino-1-oxo-1,3-dihydro-isooindol-2-yl)-piperidine-2,6-dione, 4-(amino)-2-(2,6-dioxo-(3-piperidyl))-isoindoline-1,3-dione and any optional additional active agents concurrently administered to the patient.

4.4.1 ORAL DOSAGE FORMS

[00113] Pharmaceutical compositions of the invention that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (e.g., chewable tablets), caplets, capsules, and liquids (e.g., flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. See generally, Remington*’s Pharmaceutical Sciences, 18th ed., Mack Publishing, Easton PA (1990).

[00114] Typical oral dosage forms of the invention are prepared by combining the active ingredients in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (e.g., powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

[00115] Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid excipients are employed. If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.
For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

Examples of excipients that can be used in oral dosage forms of the invention include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA), and mixtures thereof. An specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103™ and Starch 1500 LM.

Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions of the invention is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

Disintegrants are used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms of the invention. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions
comprise from about 0.5 to about 15 weight percent of disintegrant, preferably from about 1 to about 5 weight percent of disintegrant.

Disintegrants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-g elatinized starch, other starches, clays, other algins, other celluloses, gums, and mixtures thereof.

Lubricants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosil of synthetic silica (marketed by Degussa Co. of Plano, TX), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

A preferred solid oral dosage form of the invention comprises an immunomodulatory compound, anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

4.4.2 DELAYED RELEASE DOSAGE FORMS

Active ingredients of the invention can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single
unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

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

Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

4.4.3 PARENTERAL DOSAGE FORMS

Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial. Because their administration typically bypasses patients' natural defenses against contaminants, parenteral dosage forms are preferably sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

Suitable vehicles that can be used to provide parenteral dosage forms of the invention are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as,
but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms of the invention. For example, one might use cyclodextrin and its derivatives to increase the solubility of an immunomodulatory compound.

4.4.4 **TOPICAL AND MUCOSAL DOSAGE FORMS**

Topical and mucosal dosage forms of the invention include, but are not limited to, sprays, aerosols, solutions, emulsions, suspensions, or other forms known to one of skill in the art. *See, e.g., Remington’s Pharmaceutical Sciences, 16th and 18th eds., Mack Publishing, Easton PA (1980 & 1990); and Introduction to Pharmaceutical Dosage Forms, 4th ed., Lea & Febiger, Philadelphia (1985).* Dosage forms suitable for treating mucosal tissues within the oral cavity can be formulated as mouthwashes or as oral gels.

Suitable excipients (*e.g.*, carriers and diluents) and other materials that can be used to provide topical and mucosal dosage forms encompassed by this invention are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, typical excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof to form solutions, emulsions or gels, which are non-toxic and pharmaceutically acceptable. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well known in the art. *See, e.g., Remington’s Pharmaceutical Sciences, 16th and 18th eds., Mack Publishing, Easton PA (1980 & 1990).*

The pH of a pharmaceutical composition or dosage form may also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.
4.4.5 **KITS**

[00132] Typically, active ingredients of the invention are preferably not administered to a patient at the same time or by the same route of administration. This invention therefore encompasses kits which, when used by the medical practitioner, can simplify the administration of appropriate amounts of active ingredients to a patient.

[00133] A typical kit of the invention comprises a dosage form of an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, stereoisomer, clathrate, or prodrug thereof. Kits encompassed by this invention can further comprise additional active ingredients. Examples of the additional active ingredients include, but are not limited to, those disclosed herein (see, e.g., section 4.2).

[00134] Kits of the invention can further comprise devices that are used to administer the active ingredients. Examples of such devices include, but are not limited to, syringes, drip bags, patches, and inhalers.

[00135] Kits of the invention can further comprise pharmaceutically acceptable vehicles that can be used to administer one or more active ingredients. For example, if an active ingredient is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active ingredient can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer’s Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer’s Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

5. **EXAMPLES**

[00136] The following studies are intended to further illustrate the invention without limiting its scope.

5.1 **EXAMPLE 1: EFFECTS ON THE SLEEP EEG OF RATS**

[00137] This example is designed to demonstrate the effects of 3-(4-amino-1-oxo-1,3-dihydro-isoeindol-2-yl)-piperidine-2,6-dione on the sleep EEG of the rat. The animals are 250-275 gram male Sprague-Dawley rats, in whom stainless steel screw cortical EEG electrodes and stainless-steel nuchal EMG electrodes are surgically implanted at least
one week before recording. The recordings, of one hour duration, are performed at 8:00 p.m. with the lights on, using a polygraph calibrated to 50 μV/10 mm. and a paper speed of 10 mm/sec. Sleep stages are determined in 30 second epochs according to standard criteria: waking=low amplitude, mixed frequency EEG and high EMG; non REM sleep=high amplitude, low frequency EEG and low amplitude EMG. W. B. Mendelson et al., *Pharmacology Biochemistry and Behavior* 2: 553-56, 1974. The two parameters tabulated are sleep latency (time from the beginning of recording to sleep onset defined as a least one continuous minute of sleep) and total sleep (total time of non REM and REM sleep).

Statistical significance is assessed by a one-way analysis of variance. The four independent treatment groups are given intraperitoneally 1) saline placebo; or 2) 36 mg/kg of 3-(4-amino-1-oxo-1,3-dihydro-isooindol-2-yl)-piperidine-2,6-dione.

5.2 **EXAMPLE 2: EFFECTS ON THE SLEEP EEG OF HUMANS**

[00138] Six individuals with varying degrees of sleep apnea are studied on two different nights at least 5 days apart. These volunteer subjects are given saline (control) on one night and 3-(4-amino-1-oxo-1,3-dihydro-isooindol-2-yl)-piperidine-2,6-dione on the other night. Once the subjects have fallen asleep as demonstrated by their EEG, they are monitored for 60 minutes without any intervention. One ml volumes of either saline or 3-(4-amino-1-oxo-1,3-dihydro-isooindol-2-yl)-piperidine-2,6-dione are then delivered into the posterior pharynx via a small catheter (2.5 mm outer diameter and placed transnasally) after the subjects have fallen asleep as verified by electroencephalographic (EEG) monitoring. For the 60 minutes prior to instillation of saline or 3-(4-amino-1-oxo-1,3-dihydro-isooindol-2-yl)-piperidine-2,6-dione and the subsequent 60 minutes following instillation, sleep stage (I, II, III, IV, or REM) is monitored via EEG, inspiratory and expiratory air flow is monitored via a pneumotachometer attached to a close-fitting nasal mask, inspiratory muscle activity is monitored via electromyography with two surface electrodes placed 2 to 4 cm above the right costal margin in the anterior axillary line, arterial oxyhemoglobin saturation is continuously monitored via ear oximetry, and end-tidal CO₂ is measured breath by breath.

[00139] Hypopnea is defined as a 20% decrease in tidal volume in three or more consecutive breaths compared to the preceding breath, apnea as cessation of flow for ≥ 5 seconds, and desaturation as ≥ 2% decrease in oxygen saturation from baseline. A Respiratory Disturbance Index (RDI) is defined as the number of hypopneas, apneas, and desaturations per hour of sleep. The degree of desaturation for each event (ΔSpO₂ %) is also computed. For a detailed discussion of sleep scoring techniques, see Mitterer, et al., "Sleep Scoring Techniques", *in Sleep Disturbances*, Yancy Press, NY: 1991.
5.3 **EXAMPLE 3: PITTSBURGH SLEEP QUALITY INDEX**

[00140] Twelve subjects were treated with 10 mg/day of 3-(4-amino-1-oxo-1,3-dihydro-isooindol-2-yl)-piperidine-2,6-dione orally for 12 weeks. Subjects were seen every 2 weeks until study completion. Subjects were asked to keep a daily sleep diary asking how much interference with sleep (0-10 scale) was experienced. Patients were also asked to complete the Pittsburgh Sleep Quality Inventory (PSQI) at the start of the treatment and ever 4 weeks thereafter, Buysse, DJ et al., *Journal of Psychiatric Research*, 28 (2), 193-213, 1989.

[00141] The results of the study indicated that the overall sleep quality, the need for sleep medications, and the presence of daytime sleepiness were all significantly improved with 3-(4-amino-1-oxo-1,3-dihydro-isooindol-2-yl)-piperidine-2,6-dione at 10 mg in a 12 week study.

5.4 **EXAMPLE 4: CYCLING THERAPY**

[00142] In a specific embodiment, an immunomodulatory compound is cyclically administered to patients with dysfunctional sleep. Cycling therapy involves the administration of a first agent for a period of time, followed by the administration of the agent and/or the second agent for a period of time and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

[00143] In a specific embodiment, 3-(4-amino-1-oxo-1,3-dihydro-isooindol-2-yl)-piperidine-2,6-dione or 4-(amino)-2-(2,6-dioxo-(3-piperidyl))-isoindoline-1,3-dione in an amount of from about 0.1 to about 25 mg/d is administered in a cycle of about 24 weeks, about once or twice every day. One cycle can comprise the administration of a therapeutic on prophylactic agent and at least one (1), two (2), or three (3) weeks of rest. The number of cycles administered is from about 1 to about 12 cycles, more typically from about 2 to about 10 cycles, and more typically from about 2 to about 8 cycles.

[00144] Embodiments of the invention described herein are only representative of the invention. The full scope of the invention is better understood with reference to the attached claims.
CLAIMS

What is claimed is:

1. A method of treating or preventing dysfunctional sleep, which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

2. A method of managing dysfunctional sleep, which comprises administering to a patient in need of such management a prophylactically effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

3. A method of improving the time to onset of sleep, the duration of sleep or the quality of sleep, or enhancing the ability to wake up feeling refreshed after a night’s sleep, which comprises administering to a patient in need of such improvement or enhancement a therapeutically or prophylactically effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

4. The method of claim 1, 2 or 3 wherein the immunomodulatory compound is

![Chemical Structure]

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

5. The method of claim 1, 2, or 3 wherein the immunomodulatory compound is

![Chemical Structure]

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.
The method of claim 2 wherein the dysfunctional sleep is associated with complex regional pain syndrome, chronic low back pain, musculoskeletal pain, arthritis, radiculopathy, pain associated with cancer, fibromyalgia, chronic fatigue syndrome, visceral pain, bladder pain, chronic pancreatitis, diabetic neuropathy, post-herpetic neuropathy, traumatic neuropathy, inflammatory neuropathy, Parkinson’s Disease, Alzheimer’s Disease, multiple sclerosis, Huntington’s Disease, bradykinesia, muscle rigidity, parkinsonian tremor, parkinsonian gait, motion freezing, depression, defective long-term memory, Rubinstein-Taybi syndrome (RTS), dementia, postural instability, hypokinetic disorders, synuclein disorders, multiple system atrophies, striatonigral degeneration, olivopontocerebellar atrophy, Shy-Drager syndrome, motor neuron disease with parkinsonian features, Lewy body dementia, Tau pathology disorders, progressive supranuclear palsy, corticobasal degeneration, frontotemporal dementia, amyloid pathology disorders, mild cognitive impairment, Alzheimer disease with parkinsonism, Wilson disease, Hallervorden-Spatz disease, Chediak-Hagashi disease, SCA-3 spinocerebellar ataxia, X-linked dystonia parkinsonism, prion disease, hyperkinetic disorders, chorea, ballismus, dystonia tremors, amyotrophic lateral sclerosis (ALS), CNS trauma or myoclonus.
8. The method of claim 6 wherein the dysfunctional sleep is associated with complex regional pain syndrome, Parkinson's Disease, Alzheimer's Disease, amyotrophic lateral sclerosis, multiple sclerosis or Huntington's Disease.

9. The method of claim 7 wherein the dysfunction sleep is associated with complex regional pain syndrome, Parkinson's Disease, Alzheimer's Disease, amyotrophic lateral sclerosis, multiple sclerosis or Huntington's Disease.

10. A method of treating or preventing dysfunctional sleep, which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, and a therapeutically or prophylactically effective amount of at least one second active ingredient or agent.

11. A method of managing dysfunctional sleep, which comprises administering to a patient in need of such management a prophylactically effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, and a therapeutically or prophylactically effective amount of at least one second active ingredient or agent.

12. A method of improving the time to onset of sleep, the duration of sleep or the quality of sleep or enhancing the ability to wake up feeling refreshed after a night's sleep, which comprises administering to a patient in need thereof a therapeutically or prophylactically effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, and a therapeutically or prophylactically effective amount of at least one second active ingredient or agent.

13. The method of claim 10, wherein the second active ingredient or agent is a tricyclic antidepressant agent, a selective serotonin reuptake inhibitor, an antiepileptic agent, an antiarrhythmic agent, a sodium channel blocking agent, a selective inflammatory mediator inhibitor, an opioid agent, gabapentin, pregabalin, carbamazepine, oxcarbazepine, levetiracetam, topiramate Neurontin, oxycontin, morphine, topiramate, amitryptiline, nortryptiline, or carbamazepine.

14. The method of claim 11, wherein the second active ingredient or agent is a tricyclic antidepressant agent, a selective serotonin reuptake inhibitor, an antiepileptic agent, an
antiarhythmic agent, a sodium channel blocking agent, a selective inflammatory mediator inhibitor, an opioid agent, gabapentin, pregabalin, carbamazepine, oxcarbazepine, levitiracetam, topiramate Neurontin, oxycontin, morphine, topiramate, amitriptyline, nortriptyline, or carbamazepine.

15. The method of claim 12, wherein the second active ingredient or agent is a tricyclic antidepressant agent, a selective serotonin reuptake inhibitor, an antiepileptic agent, an antiarhythmic agent, a sodium channel blocking agent, a selective inflammatory mediator inhibitor, an opioid agent, gabapentin, pregabalin, carbamazepine, oxcarbazepine, levitiracetam, topiramate Neurontin, oxycontin, morphine, topiramate, amitriptyline, nortriptyline, or carbamazepine.

16. The method of any one of claim 1, 2, 3, 10, 11 or 12, wherein the stereoisomer of the immunomodulatory compound is R or S enantiomer.

17. A pharmaceutical composition comprising an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate or stereoisomer thereof in an amount effective to treat, prevent or manage dysfunctional sleep, and a carrier.

18. A pharmaceutical composition comprising an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, in an amount effective to treat, prevent or manage dysfunctional sleep, and a second active ingredient or agent.

19. The pharmaceutical composition of claim 18, wherein the second active ingredient or agent is a tricyclic antidepressant agent, a selective serotonin reuptake inhibitor, an antiepileptic agent, an antiarhythmic agent, a sodium channel blocking agent, a selective inflammatory mediator inhibitor, an opioid agent, gabapentin, pregabalin, carbamazepine, oxcarbazepine, levitiracetam, topiramate Neurontin, oxycontin, morphine, topiramate, amitriptyline, nortriptyline, or carbamazepine.

20. A kit suitable for use in treating, preventing or managing dysfunctional sleep which comprises an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.