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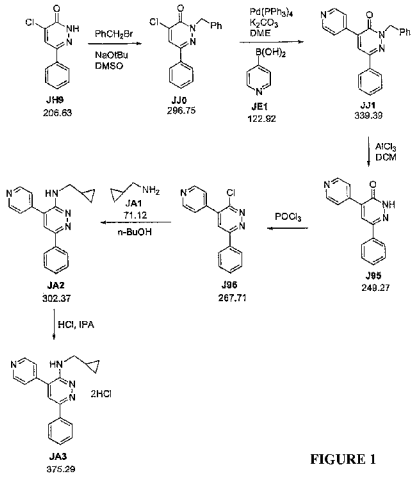

FIGURE 1

(57) Abstract: The invention relates to compounds, compositions, formulations and dosage forms comprising N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine, or a pharmaceutically acceptable salt thereof, and methods for treating multiple sclerosis in a subject using same.

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Compounds, Compositions and Methods for Treatment of Multiple Sclerosis

FIELD OF THE INVENTION

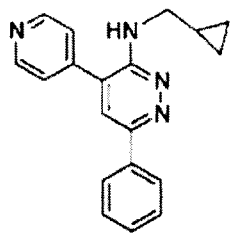
[0001] The invention generally relates to compounds, compositions, formulations and methods for treating multiple sclerosis.

BACKGROUND OF THE INVENTION

[0002] Multiple sclerosis (MS) is a disease of the central nervous system in which the myelin sheaths of the nerve fibers are demyelinated. Current treatments lead only to a decrease of the frequency and intensity of the acute phases of the disease, or they are oriented to the alleviation of the symptoms. Thus, there is a need for satisfactory therapy of multiple sclerosis.

SUMMARY OF THE INVENTION

[0003] Therapeutic agents have been identified which possess profiles of activity that indicate that they may be particularly useful in the treatment of multiple sclerosis. Accordingly, the present invention provides a compound of the formula I



I

for use in treating multiple sclerosis.

[0004] Methods are also provided for treating a subject with multiple sclerosis. In aspects, the methods comprise treating multiple sclerosis by administering to a subject in need thereof a compound of the formula I. In aspects, the methods comprise treating multiple sclerosis by administering to a subject in need thereof a therapeutically effective amount of a compound of the formula I. In aspects, a method of the invention comprises treating a subject exhibiting clinical symptoms of multiple sclerosis comprising administering a compound of the formula I to modulate or ameliorate the disease. In embodiments of the invention, the subject is a female. In other embodiments, the subject is a male.

[0005] In embodiments, the invention relates to a method of treating multiple sclerosis in a subject comprising administering to the subject a therapeutically effective amount of a compound of the formula I. In embodiments, methods are provided for treating multiple sclerosis comprising reducing pathology associated with multiple sclerosis in a subject comprising administering to the subject a therapeutically effective amount of a compound of the formula I. In embodiments, methods are provided for treating multiple sclerosis comprising reducing pathology associated with multiple sclerosis in a subject comprising administering to the subject an amount of a compound of the formula I to reduce the pathology. In embodiments, methods are provided for reducing pathology associated with multiple sclerosis in a subject comprising administering to the subject a therapeutically effective amount of a compound of the formula I. The pathology may include pathology associated with CNS immune and inflammatory events such as excessive activation of glia, especially microglia and their increased production of endogenous proinflammatory mediators including cytokines, chemokines, complement proteins and reactive free radicals, as well as demyelinating lesions (e.g. plaques) in the brain and/or spinal cord, myelin loss, destruction of oligodendrocytes, destruction of axons, macrophage accumulation, reactive T cells and infiltration of leukocytes. In particular, the pathology may be characterized by neuron deterioration, demyelinating lesions or plaques in the spinal cord and brain, myelin loss, destruction or apoptosis of oligodendrocytes, reactive astrogliosis, microglia activation, axonal injury, or activated T cells, B cells and macrophages

[0006] In an embodiment, the present invention relates to a method of reducing demyelination associated with multiple sclerosis in a subject comprising administering to the subject a therapeutically effective amount of a compound of the formula I.

[0007] In an embodiment, the present invention relates to a method of improving remyelination in a subject with multiple sclerosis comprising administering to the subject a therapeutically effective amount of a compound of the formula I.

[0008] The present invention relates to a method of reducing or inhibiting axonal destruction associated with multiple sclerosis in a subject comprising administering to the subject a therapeutically effective amount of a compound of the formula I.

[0009] In an embodiment, the present invention relates to a method of reducing neuron deterioration in the central nervous system associated with multiple sclerosis in a subject comprising administering to the subject a therapeutically effective amount of a compound of the formula I.

[00010] In an embodiment, the present invention relates to a method of reducing axonal injury in the central nervous system associated with multiple sclerosis in a subject comprising administering to the subject a therapeutically effective amount of a compound of the formula I.

[00011] In an embodiment, the present invention relates to a method of reducing demyelinating lesions or plaques in the spinal cord or brain associated with multiple sclerosis in a subject comprising administering to the subject a therapeutically effective amount of a compound of the formula I.

[00012] In an embodiment, the invention relates to a method of reducing or inhibiting astrogliosis associated with multiple sclerosis in a subject comprising administering to the subject a therapeutically effective amount of a compound of the formula I.

[00013] In an embodiment, the invention relates to a method of preserving neurons or improving pathology associated with multiple sclerosis in a subject comprising administering to the subject a therapeutically effective amount of a compound of the formula I.

[00014] In an embodiment, the invention relates to a method of reducing spinal cord inflammatory cell infiltrate or TNF expression in a subject comprising administering to the subject a therapeutically effective amount of a compound of the formula I.

[00015] In an embodiment, the invention relates to a method of reducing relapse in a subject suffering from relapsing multiple sclerosis comprising administering to the subject a therapeutically effective amount of a compound of the formula I.

[00016] In an embodiment, the invention relates to a method of treating multiple sclerosis in a subject comprising administering to the subject a compound of the formula I in an amount to modulate inflammatory responses.

[00017] In an embodiment, the invention relates to a method of treating multiple sclerosis in a subject comprising administering to the subject a compound of the

formula I in an amount to modulate inflammatory responses to improve neurologic outcomes.

[00018] In an embodiment, the invention relates to a method of treating multiple sclerosis in a subject comprising administering to the subject a compound of the formula I in an amount that does not substantially suppress peripheral immune responses (e.g. B-cell and/or T-cell activation).

[00019] In an embodiment, the invention provides a method for inhibiting the accumulation of new active brain lesions in a human subject afflicted with a form of multiple sclerosis detectable by MRI, comprising periodically administering to the human subject a therapeutically effective amount of a compound of the formula I.

[00020] In one embodiment, the invention relates to a method of treating multiple sclerosis in a subject who is fully ambulatory comprising administering to the subject a therapeutically effective amount of a compound of the formula I. In a particular embodiment, the subject has a score of about 1.0 to 4.5 on the Kurtzke Expanded Disability Status Scale.

[00021] In one embodiment, the invention relates to a method of treating multiple sclerosis in a subject with mild to moderate disability comprising administering to the subject a therapeutically effective amount of a compound of the formula I. In a particular embodiment, the subject has a score of about 2 to 4 on the Kurtzke Expanded Disability Status Scale.

[00022] In one embodiment, the invention relates to a method of treating multiple sclerosis in a subject that is ambulatory with severe disability comprising administering to the subject a therapeutically effective amount of a compound of the formula I. In a particular embodiment, the subject has a score of about 4 to 5.5 on the Kurtzke Expanded Disability Status Scale.

[00023] In one embodiment, the invention relates to a method of treating multiple sclerosis in a subject with severe disability requiring intermittent or constant assistance to walk comprising administering to the subject a therapeutically effective amount of a compound of the formula I. In a particular embodiment, the subject has a score of about 6 to 6.5 on the Kurtzke Expanded Disability Status Scale.

[00024] In one embodiment, the invention relates to a method of treating multiple sclerosis in a subject that has impaired ambulation comprising administering to

the subject a therapeutically effective amount of a compound of the formula I. In a particular embodiment, the subject has a score of about 5.0 to 9.5 on the Kurtzke Expanded Disability Status Scale.

[00025] In one embodiment, the invention relates to a method of treating multiple sclerosis in a subject with severe disability and essentially unable to walk comprising administering to the subject a therapeutically effective amount of a compound of the formula I. In a particular embodiment, the subject has a rating of about 7 to 7.5 on the Kurtzke Expanded Disability Status Scale. In another particular embodiment, the subject has a rating of about 7.5 to 9 on the Kurtzke Expanded Disability Status Scale. In another particular embodiment, the subject has a rating of about 9.5 on the Kurtzke Expanded Disability Status Scale.

[00026] In embodiments of the invention the multiple sclerosis is a relapsing remitting form.

[00027] In other embodiments of the invention the multiple sclerosis is a primary progressive form of multiple sclerosis.

[00028] In other embodiments of the invention the multiple sclerosis is a secondary progressive form of multiple sclerosis.

[00029] In an aspect of the invention, a method of treating multiple sclerosis in a subject is provided comprising administering to the subject a therapeutically effective amount of a compound of the formula I. In another aspect of the invention, the amount of a compound of the formula I administered to the subject ranges from about 0.25 mg to about 500 mg/day, 0.5 mg to about 500 mg/day, 0.5 mg to about 200 mg/day, 0.5 mg/day to about 100 mg/day, 0.5 mg/day to about 85 mg/day, 0.5 mg/day to about 75 mg/day, 1 mg/day to about 100 mg/day, 1 mg/day to about 85 mg/day, 1 mg/day to about 75 mg/day, 1.5 mg/day to about 100 mg/day, 1.5 mg/day to about 90 mg/day, 1.5 mg/day to about 85 mg/day, 1.5 mg/day to about 75 mg/day, 1.5 mg/day to about 70 mg/day, 5 mg/day to about 100 mg/day, 5 mg/day to about 85 mg/day, 5 mg/day to about 75 mg/day, 10 mg/day to about 100 mg/day, 10 mg/day to about 90 mg/day, 10 mg/day to about 85 mg/day, 10 mg/day to about 75 mg/day, 10 mg/day to about 70 mg/day, 25 mg/day to about 100 mg/day, 25 mg/day to about 85 mg/day, 25 mg/day to about 75 mg/day, 50 mg/day to about 100 mg/day, 50 mg/day to about 90 mg/day, 50 mg/day to about 85 mg/day, 50 mg/day to about 75 mg/day, 50 mg/day to about 70

mg/day, 70 mg/day to about 100 mg/day, 70 mg/day to 90 mg/day, 70 mg/day to 85 mg/day, or 65 mg/day to 90 mg/day.

[00030] In another aspect, the invention provides a method of treating or preventing multiple sclerosis wherein the amount of compound of formula I administered to the subject ranges from about 0.01 to 5 mg/kg body weight, in particular, about 0.1 to 2.0 mg/kg body weight, more particularly about 0.1 to 1.5 mg/kg body weight, and most particularly about 0.5 to 2 mg/kg body weight, about 0.5 to 1.5 mg/kg body weight or about 1 to 1.5 mg/kg body weight.

[00031] It may be appropriate to administer a required dose as two, three, four or more sub-doses at appropriate intervals throughout the day.

[00032] In embodiments of the invention, a compound of the formula I is administered once or twice daily. In additional embodiments, a compound of the formula I is administered in a single dose, once daily. In additional embodiments, a compound of the formula I is administered twice daily. In further or additional embodiments, a compound of the formula I is administered three times per day. In additional embodiments, a compound of the formula I is administered four times per day.

[00033] In another aspect, a compound of the formula I is administered to the patient in the treatment or prevention of multiple sclerosis in a unit dosage form. In another aspect, the unit dosage form is an immediate release dosage form. In another aspect, the unit dosage form is an extended release dosage form. In an aspect of the invention, the prevention or treatment of multiple sclerosis is performed with a unit dosage form comprising 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 10 mg, 15 mg, 25 mg, 50 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 100 mg, 120 mg, 140 mg, 150 mg, or 200 mg, in particular 50 mg, 60 mg, 70 mg, 75 mg, 85 mg, 100 mg or 150 mg, of a compound of the formula I.

[00034] A method of the invention may also comprise administering a compound of the formula I in combination with a second treatment (e.g., a second therapeutic agent) effective for treating or preventing multiple sclerosis. Therefore, the invention relates to a combination treatment for multiple sclerosis comprising administering therapeutically effective amounts of a compound of the formula I, and a second therapeutic agent, in particular a conventional therapeutic agent for multiple sclerosis.

In embodiments, a method of the invention can further comprise administering at least one second therapeutic agent at a therapeutically effective dosage in an effective dosage form at a selected interval.

[00035] In embodiments of the invention, the second therapeutic agent is an immunotherapeutic agent. In embodiments, the second therapeutic agent is a progesterone, precursor, analog or progesterone receptor agonist or antagonist. In embodiments, the second therapeutic agent is a glucocorticoid. In aspects of the invention, the second therapeutic agent is an immunotherapeutic agent or glucocorticoid which acts synergistically with the primary agent to diminish the symptoms of multiple sclerosis.

[00036] In embodiments of the invention, the compound of the formula I and optionally second therapeutic agent are administered for periods up to about 4, 5, 6, 7, 8, 9, 10, 14 or 15 days or 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 20, 24 or 48 weeks. In embodiments, it may be desirable to administer a compound of the formula I and second therapeutic agent either continuously, as an infusion, or in discrete doses separated by a desired time interval.

[00037] The invention also relates to a compound of the formula I for treating multiple sclerosis. In an embodiment, the invention relates to a pharmaceutically acceptable salt of a compound of the formula I for treating multiple sclerosis.

[00038] The invention relates to a pharmaceutical composition for treating multiple sclerosis comprising therapeutically effective amounts of a compound of the formula I, and a pharmaceutically acceptable carrier, excipient, or vehicle. In embodiments, a pharmaceutical composition is provided comprising therapeutically effective amounts of a compound of the formula I, and a pharmaceutically acceptable carrier, excipient, or vehicle that is useful for treating or preventing multiple sclerosis. In embodiments, the invention relates to a pharmaceutical composition comprising an amount of a compound of the formula I for treating multiple sclerosis, and at least one pharmaceutically acceptable component chosen from a carrier, an excipient and a vehicle.

[00039] In additional embodiments, the pharmaceutical compositions of the invention contain adjuvants, excipients, vehicles, preservatives, agents for delaying absorption, fillers, binders, adsorbents, buffers, disintegrating agents, solubilizing

agents, other carriers, other inert ingredients, or combinations thereof. In further or additional embodiments, the pharmaceutical composition is in the form of a tablet, capsule, pill, powder, sustained release formulation, solution, suspension, for parenteral injections as a sterile solution, suspension or emulsion, or for topical administration as an ointment or cream or for rectal administration as a suppository.

[00040] A pharmaceutical composition of the invention can be in a unit dosage form suitable for single administration of precise dosages. In aspects of the invention, a unit dosage form comprises a suboptimal dose of a compound of the formula I and optionally a suboptimal dose of the second therapeutic agent.

[00041] In a further aspect, the invention provides a unit dosage form comprising a compound of the formula I in an amount effective to maintain the compound within an effective drug concentration in the brain that results in therapeutic effects in a subject with multiple sclerosis.

[00042] In another aspect, the invention relates to a sustained-release dosage form of a compound of the formula I which provides beneficial release profiles in the treatment of multiple sclerosis. The release profiles may exhibit different rates and durations of release and may be continuous or pulsatile. Continuous release profiles include release profiles in which a quantity of one or more pharmaceutical compounds is released continuously throughout the dosing interval at either a constant or variable rate. Pulsatile release profiles include release profiles in which at least two discrete quantities of one or more pharmaceutical compounds are released at different rates and/or over different time frames.

[00043] In embodiments, the amount of a compound of the formula I present in a pharmaceutical composition, in particular a unit dosage form, ranges from about 0.25 mg to 500 mg, 0.5 mg to 500 mg, 0.5 mg to 300 mg, 0.5 mg to 200 mg, 0.5 mg to 100 mg, 0.5 mg to 90 mg, 0.5 mg to 85 mg, 0.5 mg to 80 mg. 0.5 mg to 75 mg, 0.5 mg to 70 mg, 1 mg to 100 mg, 1 mg to 85 mg, 1 mg to 75 mg, 1.5 mg to 100 mg, 1.5 mg to 90 mg, 1.5 mg to 85 mg, 1.5 mg to 75 mg, 1.5 mg to 70 mg, 5 mg to 100 mg, 5 mg to 85 mg, 5 mg to 75 mg, 10 mg to 150 mg, 10 mg to 100 mg, 10 mg to 90 mg, 10 mg to 85 mg, 10 mg to 75 mg, 10 mg to 70 mg, 25 mg to 150 mg, 25 mg to 100 mg, 25 mg to 85 mg, 25 mg to 75 mg, 50 mg to 100 mg, 50 mg to 90 mg, 50 mg to 85 mg, 50 mg to 75

mg, 50 mg to 70 mg, 70 mg to 100 mg, 70 mg to 90 mg, 70 mg to 85 mg, or 65 mg to 90 mg.

[00044] A pharmaceutical composition of the invention may also comprise a second therapeutic agent. Combinations of a compound of the formula I and a second therapeutic agent may be selected to provide additive effects or greater than additive effects, for example, synergistic effects. In an aspect, the invention relates to a pharmaceutical composition comprising a compound of the formula I and a second therapeutic agent in combination with at least one pharmaceutically acceptable component chosen from a carrier, an excipient, and a vehicle, wherein the amount of a compound of the formula I and second therapeutic agent are selected to provide an additive or synergistic effect in treating or preventing a condition disclosed herein. In an aspect, the invention relates to a pharmaceutical composition comprising a compound of the formula I and a second therapeutic agent in combination with at least one pharmaceutically acceptable component chosen from a carrier, an excipient, and a vehicle, wherein the compound of the formula I, or a pharmaceutically acceptable salt thereof, and second therapeutic agent are selected to provide a synergistic effect, as a combined preparation for simultaneous, separate, or sequential use in treatment of multiple sclerosis. In an aspect, the invention relates to a pharmaceutical composition comprising a compound of the formula I and a second therapeutic agent, wherein said composition achieves a synergistic effect for treating multiple sclerosis in a subject in need thereof. The invention also relates to a pharmaceutical composition in separate containers and intended for simultaneous or sequential administration to a subject, comprising a compound of the formula I and a second therapeutic agent both optionally together with pharmaceutically acceptable carriers, excipients, or vehicles. In aspects of the invention, the second therapeutic agent is an immunotherapeutic agent or glucocorticoid which acts synergistically with a compound of the formula I to diminish the symptoms of multiple sclerosis

[00045] In aspects of the invention, a pharmaceutical composition of the invention comprises: (i) a compound of the formula I; (ii) an immunotherapeutic agent or glucocorticoid; and (iii) optionally one or more pharmaceutically acceptable carrier, excipient, or vehicle.

[00046] A composition or dosage form of the invention may be administered to a subject for about or at least about or up to 2 days, 3 days, 4 days, 5 days, 1 week, 2 weeks to 4 weeks, 2 weeks to 6 weeks, 2 weeks to 8 weeks, 2 weeks to 10 weeks, 2 weeks to 12 weeks, 2 weeks to 14 weeks, 2 weeks to 16 weeks, 2 weeks to 6 months, 2 weeks to 12 months, 2 weeks to 18 months, or 2 weeks to 24 months, periodically, consecutively or continuously.

[00047] The invention still further relates to the use of a compound of the formula I in the preparation of a medicament for treating multiple sclerosis.

[00048] The invention still further relates to the use of a compound of the formula I and optionally at least one second therapeutic agent, composition, dosage form or combination treatment of the present disclosure for ameliorating disease severity, disease symptoms, and/or periodicity of recurrence of multiple sclerosis. Further, the invention relates to the use of a compound of the formula I and optionally a second therapeutic agent as a medicament or in the preparation of a medicament for treating multiple sclerosis. The medicament may be suitable for use in treating multiple sclerosis or is suitable for use in patients who are at risk of developing a condition disclosed herein.

[00049] Still further the invention contemplates pharmaceutical packs or kits comprising a compound of the formula I or a pharmaceutical composition disclosed herein, and optionally a second therapeutic agent. In an aspect, the invention is directed to a kit comprising a first container comprising a pharmaceutical composition comprising a therapeutically effective amount of a compound of the formula I and at least one pharmaceutically acceptable component chosen from a carrier, an excipient, and a vehicle. The kit may further comprise a second container comprising a second therapeutic agent.

[00050] In embodiments, a pharmaceutically acceptable salt, in particular an acid addition salt, of a compound of the formula I is provided for use in the compositions, formulations, dosage forms, methods, uses and kits of the invention. Due to its solubility in water and its dissolution rate, a pharmaceutical composition, formulation or unit dosage form comprising a salt may be obtained with an acceptable bioavailability.

[00051] In embodiments of the compositions, formulations, dosage forms, methods, uses and kits of the invention, a compound of the formula I that is particularly useful is N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine.

[00052] In embodiments of the compositions, formulations, dosage forms, methods, uses and kits of the invention, a compound of the formula I that is particularly useful is an acid addition salt of N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine.

[00053] In embodiments of the compositions, formulations, dosage forms, methods, uses and kits of the invention, a compound of the formula I that is particularly useful is N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine hydrochloride.

[00054] These and other aspects, features, and advantages of the present invention should be apparent to those skilled in the art from the following drawings and detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[00055] Figure 1 is a schematic of a reaction scheme for preparing N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine hydrochloride.

[00056] Figure 2 is a graph showing the clinical score for high (Test H) and low (Test L) doses of N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine hydrochloride in an EAE model.

[00057] Figure 3 is a graph showing relapse rate for high (Test H) and low (Test L) doses of N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine hydrochloride.

[00058] Figure 4 is a graph showing the mean number of lesions per lumbar spinal cord section for high (Test H) and low (Test L) doses of N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine hydrochloride.

[00059] Figure 5 is a graph showing TNF concentration for high (Test H) and low (Test L) doses of N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine hydrochloride.

DETAILED DESCRIPTION OF THE INVENTION

[00060] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to

which this invention belongs. Particular aspects of the disclosure are described in greater detail below. Numerical ranges recited herein by endpoints include all numbers and fractions subsumed within that range (for example, from 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.90, 4, and 5). It is also to be understood that all numbers and fractions thereof are presumed to be modified by the term "about." The term "about" means plus or minus 0.1 to 50%, 5-50%, or 10-40%, preferably 10-20%, more preferably 10% or 15%, of the number to which reference is being made. Further, it is to be understood that "a," "an," and "the" include plural referents unless the content clearly dictates otherwise. Aspects of the present disclosure requiring a particular value in a subject are substantially supported herein by population data in which the relevant value is assessed to be a meaningful delimitation of the subject population.

[00061] References to a compound of formula I in aspects of the invention include pharmaceutically acceptable salts, solvates and complexes thereof and to solvates and complexes of salts thereof, polymorphs, prodrugs, dehydrates, crystals, co-crystals, anhydrous and amorphous forms, and isomers thereof (including optical, geometric and tautomeric isomers). In general, all physical forms of a compound of the formula I are intended to be within the scope of the present invention.

[00062] A "pharmaceutically acceptable salt(s)" refers to a salt that is pharmaceutically acceptable and has the desired pharmacokinetic properties. By pharmaceutically acceptable salts is meant those salts which are suitable for use in contact with the tissues of a subject or patient without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are described for example, in S. M. Berge, et al., J. Pharmaceutical Sciences, 1977, 66:1.

[00063] Suitable salts include salts that may be formed where acidic protons in the compounds are capable of reacting with inorganic or organic bases. Suitable inorganic salts include those formed with alkali metals, e.g. sodium and potassium, magnesium, calcium, and aluminum. Suitable organic salts include those formed with organic bases such as the amine bases, e.g. ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

[00064] Particularly suitable salts include acid addition salts formed with inorganic acids (e.g. hydrochloride and hydrobromic acids) and organic acids (e.g.

acetic acid, citric acid, maleic acid, and the alkane- and arene-sulfonic acids such as methanesulfonic acid and benezenesulfonic acid). A pharmaceutically acceptable addition salt may be a mono-acid-mono-salt, or when there are two or three acidic groups present, a di-salt or a tri-salt, or mixtures of these salts; and similarly where there are more than three or more acidic groups present, some or all of such groups can be salified.

[00065] In embodiments of the compositions, formulations, dosage forms, methods, uses and kits of the invention, a compound of the formula I that is particularly useful is an acid addition salt of N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine.

[00066] In embodiments of the compositions, formulations, dosage forms, methods, uses and kits of the invention, a compound of the formula I that is particularly useful is N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine hydrobromide.

[00067] In embodiments of the compositions, formulations, dosage forms methods, uses and kits of the invention, a compound of the formula I that is particularly useful is N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine hydrochloride.

[00068] A compound of the formula I may exist in both unsolvated and solvated forms. A "solvate" refers to a physical association of a compound with one or more solvent molecules or a complex of variable stoichiometry formed by a solute (for example, ethanol or cyclohexanehexol) and a solvent, for example, water, ethanol, or acetic acid. The term "hydrate" means a solvate wherein the solvent molecule(s) is/are H_2O, including, mono-, di-, and various poly-hydrates thereof. This physical association may involve varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances, the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. In general, the solvents selected do not interfere with the biological activity of the solute. Solvates encompass both solution-phase and isolatable solvates. Representative solvates include hydrates, ethanolates, methanolates and the like. Solvates can be formed using various methods known in the art. The amount of solvent used to make solvates can be determined by routine testing. For example, a

monohydrate of a compound of the formula I may have about 1 equivalent of solvent (H_2O) for each equivalent of a compound of the formula I. However, more or less solvent may be used depending on the choice of solvate desired.

[00069] A compound of the formula I includes crystalline forms. Crystalline compounds of a compound of the formula I can be in the form of a free base, a salt, or a co-crystal. Free base compounds can be crystallized in the presence of an appropriate solvent in order to form a solvate. Acid salt compounds of a compound of the formula I (e.g. HCl, HBr, benzoic acid) can also be used in the preparation of solvates. For example, solvates can be formed by the use of acetic acid or ethyl acetate. The solvate molecules can form crystal structures via hydrogen bonding, van der Waals forces, or dispersion forces, or a combination of any two or all three forces.

[00070] A compound of the formula I may be amorphous or may have different crystalline polymorphs, possibly existing in different solvation or hydration states. By varying the form, it is possible to vary the physical properties thereof. For example, crystalline polymorphs typically have different solubilities from one another, such that a more thermodynamically stable polymorph is less soluble than a less thermodynamically stable polymorph. Pharmaceutical polymorphs can also differ in properties such as shelf-life, bioavailability, morphology, vapor pressure, density, color, and compressibility.

[00071] The term "prodrug" means a covalently-bonded derivative or carrier of the parent compound or active drug substance which undergoes at least some biotransformation prior to exhibiting its pharmacological effect(s). In general, such prodrugs have metabolically cleavable groups and are rapidly transformed *in vivo* to yield the parent compound, for example, by hydrolysis in blood, and generally include esters and amide analogs of the parent compounds. The prodrug is formulated with the objectives of improved chemical stability, improved patient acceptance and compliance, improved bioavailability, prolonged duration of action, improved organ selectivity, improved formulation (e.g., increased hydrosolubility), and/or decreased side effects (e.g., toxicity). In general, prodrugs themselves have weak or no biological activity and are stable under ordinary conditions. Prodrugs may be produced by replacing appropriate functionalities in a compound of the formula I with certain moieties known to those skilled in the art as 'pro-moieties' (for example, see the

methods as described, in A Textbook of Drug Design and Development, Krogsgaard-Larsen and H. Bundgaard (eds.), Gordon & Breach, 1991, particularly Chapter 5: "Design and Applications of Prodrugs"; Design of Prodrugs, H. Bundgaard (ed.), Elsevier, 1985; Prodrugs: Topical and Ocular Drug Delivery, K. B. Sloan (ed.), Marcel Dekker, 1998; Methods in Enzymology, K. Widder et al. (eds.), Vol. 42, Academic Press, 1985, particularly pp. 309-396; Burger's Medicinal Chemistry and Drug Discovery, 5th Ed., M. Wolff (ed.), John Wiley & Sons, 1995, particularly Vol. 1 and pp. 172-178 and pp. 949-982; Pro-Drugs as Novel Delivery Systems, T. Higuchi and V. Stella (eds.), Am. Chem. Soc., 1975; and Bioreversible Carriers in Drug Design, E. B. Roche (ed.), Elsevier, 1987).

[00072] A compound of the formula I includes all stereoisomers, geometric isomers and tautomeric forms, including compounds of the formula I exhibiting more than one type of isomerism, and mixtures of one or more thereof. A pharmaceutically acceptable salt of a tautomeric, geometric or stereoisomeric form is also contemplated herein. In particular, a compound of the formula I includes without limitation, cis- and trans-geometric isomers, E- and Z-geometric isomers, R- and S-enantiomers, diastereomers, d-isomers, l-isomers, the racemic mixtures thereof and other mixtures thereof. Individual enantiomers may be isolated using conventional methods such as chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). A racemate (or a racemic precursor) may also be reacted with a suitable optically active compound, for example, an alcohol, or, an acidic or basic moiety of a compound of the formula I. Stereoisomeric mixtures may be separated by conventional techniques known to those skilled in the art - see, for example, "Stereochemistry of Organic Compounds" by E.L. Eliel and Samuel H. Wilen (Wiley India Pvt. Ltd, 2009). For example, a mixture of diastereoisomers may be separated by chromatography and/or fractional crystallization, and one or both of the diastereoisomers may be converted to corresponding pure enantiomer(s).

[00073] Isomeric mixtures containing any of a variety of isomer ratios may be utilized in the present invention. For example, where only two isomers are combined, mixtures containing 50:50, 60:40, 70:30, 80:20, 90:10, 95:5, 96:4, 97:3, 98:2, 99:1, or 100:0 isomer ratios are all contemplated by the present invention.

[00074] A compound of the formula I in some aspects also includes a compound of the formula I which is substituted. The term "substituted" refers to the replacement of one or more moiety of a compound of the formula I with a selected group provided that the designated atom's normal valency is not exceeded, and the substitution results in a stable compound having a profile of activity that suggests it is useful in the treatment of multiple sclerosis. Combinations of substituents and/or radicals are permissible only if such combinations result in stable compounds with the desired activity. "Stable compound" refers to a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. Selected substituents include acyl, nitro, cyano, hydroxyl, carboxyl, O, S, C_1-C_6 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, C_1-C_4 alkoxy and haloalkyl.

[00075] The term "C_1-C_6 alkyl" includes a branched or straight chained monovalent saturated aliphatic hydrocarbon radical containing from 1 to 6 carbon atoms. Examples of C_1-C_6 alkyl groups include but are not limited to methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, isopropyl, isobutyl, isopentyl, sec-butyl, tert-butyl, tert-pentyl, n-hexyl, and the like.

[00076] The term "C_2-C_4 alkenyl" includes a branched or straight hydrocarbon chain of 2 to 4 carbon atoms with at least one double bond. Examples of suitable C_2-C_4 alkenyl groups include but are not limited to, ethenyl, propen-1-yl, propen-2-yl (isoprenyl), propen-3-yl (allyl), 2-methyl-propen-3-yl, 2-buten-4-yl, 2-methyl-propen-1-yl, 2-buten-1-yl, 1-buten-1-yl, and the like.

[00077] The term "C_2-C_4 alkynyl" includes a branched or straight hydrocarbon chain of 2 to 4 carbon atoms with at least one carbon-carbon triple bond. Examples of suitable C_2-C_4 alkynyl groups include, but are not limited to, ethynyl, propyn-1-yl, propyn-2-yl, propyn-3-yl, 2-methyl-propyn-3-yl, 2-butyn-4-yl, 2-methyl-propyn-1-yl, butyn-1-yl, butyn-3-yl, pentyn-1-yl, pentyn-2-yl, 4-methoxypentyn-2-yl, 3-methylbutyn-1-yl, hexyn-1-yl, hexyn-2-yl, hexyn-3-yl, and the like.

[00078] The term "halo" includes halogen groups such as fluoro, chloro, bromo or iodo atoms.

[00079] The term "C_1-C_4 alkoxy" includes a straight or branched oxy-containing radical having an alkyl portion of one to four carbon atoms. Examples of suitable C_2-C_4

alkoxy groups include, but are not limited to methoxy, ethoxy, propoxy, butoxy, isopropoxy and tert-butoxy alkyls.

[00080] The term "haloalkyl" includes a C_1-C_6 alkyl group, which is substituted with one or more halo atoms selected from fluoro, chloro, bromo, and iodo. Examples of haloalkyl groups include but are not limited to trifluoromethyl, CH_2CF_3 and the like.

[00081] The term "acyl" includes a "-COR" group where R is hydrogen, C_1-C_6 alkyl, halo, haloalkyl, and/or C_1-C_4 alkoxy. Examples of acyl groups include but are not limited to those in which the alkyl group is C_1-C_6 alkyl, in particular formyl, acetyl and propionyl.

[00082] The term "multiple sclerosis" refers to all types of multiple sclerosis and its variants including without limitation clinically isolated syndrome (CIS), relapsing-remitting multiple sclerosis (RRMS), Primary Progressive MS or PPMS, Secondary Progressive MS (SPMS) primary progressive-relapsing multiple sclerosis, Devic Syndrome (Neuromyelitis Optica), Marburg Disease (Acute Multiple Sclerosis), Balo Concentric Sclerosis and Acute Disseminated Encephalomyelitis. (See, Herndon, RM, Chapter 14, The Pathology of Multiple Sclerosis and Its Variants. In: Multiple Sclerosis: Immunology, Pathology and Pathophysiology, Herndon RM (ed), New York: Demos Medical Publishing, 2003.)

[00083] CIS applies to patients who have suffered a first clinical attack but do not meet the classical diagnostic criteria for MS.

[00084] RRMS is the classic MS clinical pattern. RRMS is characterized by unpredictable acute episodes of neurological dysfunction (relapses), followed by variable recovery and periods of clinical stability. The majority of MS patients are diagnosed with RRMS. The pathology of RRMS consists of lesions (plaques) which can be found anywhere there is central myelin, but in particular they can be found in the periventricular white matter, optic nerves, spinal cord and juxtacortical areas. The lesions include acute plaques with active inflammatory infiltrates and macrophages loaded with lipid and myelin degeneration products, plaques with various degrees of lesser activity, plaques that are active only in their margin, and chronic, inactive demyelinated shrunken glial scars. Areas of white matter outside the plaques show biochemical abnormalities. Three different patterns of demyelination have been observed in active MS lesions: 1) active demyelination associated with T-lymphocyte

and macrophage-dominated inflammation without significant amounts of antibody or complement deposition; 2) active perivenular demyelination associated with T-lymphocyte and macrophage-dominated inflammation with extensive antibody deposition in the tissue and in astrocyte cytoplasm; and 3) active demyelination with an infiltrate of T lymphocytes and activated macrophages and microglia (Lucchineti et al, Ann Neurol 2000; 47:707-717and Lassman et al, J. Neuroimmunol, 1998, 86:213-217). RRMS is also characterized by a second demyelinating process consisting of the demyelination of individual fibers or small groups of fibers in the spinal cord.

[00085] Greater than 50% of RRMS patients go on to develop SPMS which is characterized by sustained deterioration with or without relapses superimposed. Primary progressive-relapsing multiple sclerosis is characterized by development of progressive deterioration from the beginning with relapses later on (Committee for Proprietary Medicinal Products. "Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis." London, 16 November 2006, Doc. Ref. CPMP/EWP/561/98 Rev. 1). SPMS is usually marked by a slowly ascending paralysis or, more rarely progressive ataxia, and it commonly occurs in patients in their 40s or 50s who have had MS for a number of years. The pathology of SPMS consists of a progressive loss of axons in the spinal cord with cord atrophy. The spinal cord shows chronic inactive or occasionally active plaques, demyelination and/or degeneration of multiple individual fibers. The individual fiber demyelination is widely scattered with a few scattered macrophages along the sheaths.

[00086] About 10-15% of MS patients develop PPMS characterized by a sustained deterioration of their neurological function from the beginning. The disease begins with a progression of disability primarily affecting the spinal cord without exacerbations or remissions. PPMS is equally common in men and women and has a later onset, usually after age 40. The pathology of PPMS consists of inflammation dominated by T lymphocytes and the death of oligodendrocytes in per-plaque white matter adjacent to areas of demyelination. DNA fragmentation without features of apoptosis can be observed in the dying oligodendrocytes.

[00087] Acute MS or Marburg Disease is marked by rapid onset and continual progression of demyelination. Many patients die within a few months to a year and those that survive may go on to have a relapsing remitting disease. The pathology is

characterized by intense and wide-spread inflammation with T lymphocytes, large numbers of lipid-laden macrophages, and a dispersion of B lymphocytes (Prineas JW and McDonald WI, Demyelinating Diseases. In: Graham DI, Lantos PL (eds), Greenfields Neuropathology, 6th ed, 813-896 and Marburg, O, Psychiat Neurol (Leizig) 1906, 27:213-311). The disease essentially involves total demyelination. Lesions comprise extensive IgG and complement product and there is no evidence of oligodendroglia death surrounding the plaques. Demyelinated axons are irregularly constricted, and perivascular cuffs may be present.

[00088] Balo Concentric Sclerosis is an aggressive variant of MS which can lead to death in weeks to months. The disease is characterized by large demyelination plaques with concentric bands of preserved or regenerated myelin.

[00089] Acute Disseminated Encephalomyelitis (ADEM) most closely corresponds to experimental autoimmune encephalomyelitis (EAE). ADEM is an acute diffuse inflammatory demyelinating disorder that may occur 1-3 weeks following a viral infection or immunization. The severity and intensity of the disorder vary but typically only a small percentage of patients develop a relapsing remitting disease. Fatal cases generally follow smallpox vaccination, measles infection or rabies vaccine. Improvement occurs over many months for survivors of an acute episode. The gross pathology of ADEM is characterized by swelling and congestion, and the brain may show numerous petechia or appear swollen. ADEM is also characterized by perivenous inflammation and demyelination. Prominent cuffs of lymphocytes and macrophages surround venules and the tissue has a reticulate appearance due to long strips of perivenous demyelination. In more severe ADEM cases, edema and necrosis of blood vessels with fibrin deposition, numerous ring or ball hemorrhages, numerous neutrophils in the infiltrate and areas of tissue necrosis are observed.

[00090] Neuromyelitis Optica (Devic Disease) is an acute disorder involving optic neuritis and transverse myelitis which occur within a short time of each other with little or no involvement of other parts of the CNS. The disease is most common in Asians and Africans. It has a different clinical pattern and a relatively poorer recovery after attacks compared with typical MS. For example, in Devic Disease, axonal destruction in lesions is much greater and complete blindness, paraplegia or quadriplegia is common in Devic Disease but extremely rare in MS. The acute stage is

characterized by necrosis of the cord, extending over 3 or more segments, which is usually swollen and soft in the affected areas. Additional lesions may be present in cord segments but the brain is not involved. The CSF often consists of 50 to 100 or more cells, predominantly lymphocytes with monocytes and neutrophil leucocytes. Devic Disease is also characterized by extensive perivascular cuffs comprising macrophages and granulocytes, including eosinophils and CD3+ lymphocytes (Lucchinette CF et al, Brain 2002, 125:1450-1461). Further the disease is characterized by extensive macrophage infiltration with lymphocytes and often polymorphonuclear leucocytes, deposition of IgG and complement products mainly on and around blood vessels and extensive oligodendrocyte destruction. Late stage disease is characterized by cavitation and necrosis of gray and white matter most of the length of the spinal cord, extensive scarring with marked hyalinization, thickening of the blood vessels, perivascular fibrosis and numerous macrophages in necrotic areas (Mandler RN et al, Ann Neurol 1993, 34:162-168). Demyelination is seen in the optic nerve but necrosis and thickening and hyalinization of blood vessels is not observed.

[00091] The McDonald's criteria (McDonald WI, et al, "Recommended Diagnostic Criteria for Multiple Sclerosis: Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis", Ann Neurol 2001; 50:121-127) may be used to diagnose a patient as having "Multiple Sclerosis", "possible MS" (for those at risk for MS, but for whom diagnostic evaluation is equivocal), or "not MS" (McDonald et al, 2001). New lesions identified in a second MRI conducted at least three months apart is an accepted criterion for a diagnosis of MS.

[00092] The Kurtzke Expanded Disability Scale may also be used to evaluate disability in multiple sclerosis (Koziol JA et al, J Neurol. 1996 Mar; 243(3):209-13). Using this scale neurologists assign a Functional System Score (FSS) from eight Functional Systems including pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral and others. A FSS of 1.0 to 4.5 refers to patients with multiple sclerosis who are fully ambulatory while a FSS of 5.0 to 9.5 refers to patients defined by the impairment to ambulation. Other methods can be used to quantify various aspects of disability in multiple sclerosis including MRI scans, The Scripps Neurologic Rating Scale (Sharrack B and Hughes RA. J Neurol Sci. 1996 Jan;135(1):1-9) and the Krupp Fatigue Severity Scale (Krupp LB et al, 1989 Oct;46(10):1121-3).

[00093] The term "treating" refers to reversing, alleviating, prohibiting, preventing, restraining, slowing, stopping, reversing or inhibiting the progression or severity of a symptom or disorder. Depending on the state of the subject, the term in some aspects of the invention may refer to preventing a condition, and includes preventing the onset, or preventing the symptoms associated with a condition. The term also includes maintaining the condition and/or symptom such that the condition and/or symptom do not progress in severity. A treatment may be either performed in an acute or chronic way. The term also refers to reducing the severity of a condition or symptoms associated with such condition prior to affliction with the disease. Such prevention or reduction of the severity of a condition prior to affliction refers to administration of a compound of the formula I, or composition, or combination of the present invention to a subject that is not at the time of administration afflicted with the condition. Preventing also includes preventing the recurrence of a condition, or of one or more symptoms associated with such condition. The terms "treatment" and "therapeutically," refer to the act of treating, as "treating" is defined above. The purpose of intervention is to combat the condition and includes the administration of an active compound to prevent or delay the onset of the symptoms or complications, or alleviate the symptoms or complications, or eliminate the condition. For example, a compound, composition, or combination disclosed herein may be used to ameliorate symptoms associated with multiple sclerosis.

[00094] The term "administering" or "administration" refers to the process by which a compound of the formula I, compositions, dosage forms and/or combinations disclosed herein are delivered to a subject for treatment or prophylactic purposes. Compounds of the formula I, compositions, dosage forms and/or combinations are administered in accordance with good medical practices taking into account the subject's clinical condition, the site and method of administration, dosage, subject age, sex, body weight, and other factors known to the physician. For example, the terms "administering" or "administration" as used herein refer to (1) providing, giving, dosing and/or prescribing by either a health practitioner or his/her authorized agent or under his/her direction a compound of the formula I, compositions, dosage forms and/or combinations disclosed herein, and (2) putting into, taking or consuming by the patient

or person himself or herself, a compound of the formula I, compositions, dosage forms and/or combinations disclosed herein.

[00095] A "combination treatment," "administering....in combination" or "administered in combination" means use of multiple pharmaceutical agents in combination as active ingredients administered concurrently to a patient being treated. The terms include use as a combination drug, use as a kit, and use in a combination characterized by independent administration of each by the same or different administration routes and the like. When administered in combination each component may be administered at the same time, or sequentially in any order at different points in time. Therefore, each component may be administered separately, but sufficiently close in time to provide a desired effect, such as an additive or synergistic effect. The first compound may be administered in a regimen that additionally comprises treatment with a second therapeutic agent. In aspects of the invention, the terms refer to the administration of a compound of the formula I or a composition of the invention, and a second therapeutic agent including separate administration of medicaments each containing one of the compounds, as well as simultaneous administration whether or not the compounds are combined in one formulation or whether they are in separate formulations.

[00096] An "additive effect" of a compound of the formula I and a second therapeutic agent refers to an effect that is equal to the sum of the effects of the two individual agents.

[00097] A "synergistic effect" of a compound of the formula I and a second therapeutic agent refers to an effect that is greater than the additive effect that results from the sum of the effects of the two individual agents.

[00098] The terms "subject," "individual" and "patient" refer to an animal including a warm-blooded animal, such as a mammal. Mammal includes without limitation any member of the kingdom Mammalia. Mammal includes humans, but the term also includes domestic animals bred for food or as pets, such as horses, cows, sheep, poultry, fish, pigs, cats, dogs, and zoo animals, goats, apes (e.g. gorilla or chimpanzee), and rodents such as rats and mice. Subjects for treatment include mammals, such as humans, susceptible to, suffering from, suspected of having, being pre-disposed or that have suffered a condition disclosed herein.

[00099] The phrase "pharmaceutically acceptable component chosen from a carrier, an excipient and a vehicle" or "pharmaceutically acceptable carrier, excipient, or vehicle" refers to a medium which is useful for the preparation of a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable. It is generally selected so that it does not interfere with the effectiveness or activity of an active ingredient and is not toxic to the hosts to which it is administered. The phrase as used in the specification and claims includes one, and more than one such carrier, excipient, or vehicle. Acceptable carriers, excipients, or vehicles may be chosen or selected from any of those commercially used in the art. By way of example, a carrier, excipient, or vehicle includes diluents, binders, adhesives, lubricants, disintegrates, bulking agents, wetting or emulsifying agents, pH buffering agents, adjuvants, preservatives, agents for delaying absorption, fillers, adsorbents, buffers, solubilizing agents, other inert ingredients, or combinations thereof, and miscellaneous materials such as absorbants that may be needed in order to prepare a particular composition. Examples of carriers, excipients, and vehicles include but are not limited to saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. The use of such media and agents for an active substance is well known in the art. For example, suitable pharmaceutical carriers, excipients, and vehicles are described in the standard text, *Remington: The Science and Practice of Pharmacy* (21st Edition, Popovich, N (eds), Advanced Concepts Institute, University of the Sciences in Philadelphia, Philadelphia, PA. 2005).

[000100] "Therapeutically effective amount" refers to the amount or dose of active compound(s) or a composition of the invention that will lead to one or more desired effects, in particular therapeutic effects. A therapeutically effective amount of a substance can vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the substance to elicit a desired response in the individual. A dosage regimen may be adjusted to provide the optimum therapeutic response (such as sustained therapeutic effects). For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

[000101] "Suboptimal dose" refers to a dose of an active compound which is less than the optimal dose for that compound when used in monotherapy.

[000102] A "unit dosage form" refers to a unitary, i.e. a single dose, which is capable of being administered to a patient, and which may be readily handled and packed, remaining as a physically and chemically stable unit dose comprising either the active agents as such or a mixture with one or more solid or liquid pharmaceutical excipients, carriers, or vehicles.

[000103] A compound of the formula I may be administered by any of the accepted modes of systemic administration including oral, subdermal, intramuscular, parenteral, and other systemic routes of administration. Any pharmaceutically acceptable mode of administration can be used, including solid, semi-solid, or liquid dosage forms, such as for example, tablets, pills, capsules, powders, liquids, suspensions, or the like. Those dosage forms may be in a unit dosage form suitable for administration of precise dosages, or in sustained or controlled dosage forms, such as extended, release forms for the prolonged administration of the compound at a predetermined rate.

[000104] Compositions comprising a compound of the formula I may be formulated as sterile, substantially isotonic and in full compliance with all Good Manufacturing Practice (GMP) regulations of appropriate regulatory authorities such as the US Food and Drug Administration. The compositions will typically include at least one pharmaceutically acceptable component chosen from a carrier, an excipient, and a vehicle and the active compound and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, and the like. Carriers, excipients, and vehicles are generally selected based on the intended form of administration, and consistent with conventional pharmaceutical practices.

[000105] Parenteral administration is generally characterized by injection, whether subcutaneously or intramuscularly. Injectables can be prepared in conventional forms, either as liquid solutions or suspension, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients include, for example, water, saline, aqueous dextrose, glycerol, ethanol or the like. In addition, if desired, the pharmaceutical compositions may also contain minor amounts of non-toxic substances such as wetting or emulsifying agents, auxiliary pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, and the like.

[000106] A compound of the formula I may be administered in substantially pure form as a powder or a powder contained in, for example, a gelatin capsule. It may also be administered in solid compositions with conventional non-toxic carriers, for example, mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like may be used.

[000107] A compound of the formula I may be admixed, encapsulated, conjugated or otherwise associated with molecules to facilitate uptake, distribution and/or absorption of the compound. Various known delivery systems can be used to administer a medicament of the invention, e.g. encapsulation in liposomes, microparticles, microcapsules, and the like. Medicaments can also be formulated as pharmaceutically acceptable salts.

[000108] For delayed release, a compound of the formula I may be included in a pharmaceutical composition formulated for slow release, such as in microcapsules formed with biocompatible polymers, polymer coated multiparticulates or in liposomal carrier systems according to methods known in the art. The compositions may also be advantageously administered as bi-layer tablets containing an immediate release component and a delayed release component.

[000109] For extended release of active agent, a compound of the formula I may be covalently conjugated to a water soluble polymer, such as a polylactide or biodegradable hydrogel derived from an amphipathic block copolymer, as described in U.S. Pat. No. 5,320,840. A compound of the formula I may also be incorporated into a polymer or multi-polymer matrix having properties that release the active compound through diffusion from the matrix, erosion of the matrix or a combination of diffusion and erosion.

[000110] The compositions may be advantageously compounded into unit dosage forms containing a predetermined, standard amount of the active compound, to make dosing and patient compliance simpler. For example, capsules, tablets, liquid or controlled release delivery forms may be formulated and manufactured to contain, for example, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 10 mg, 15 mg, 25 mg, 50 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 100 mg, 120 mg, 140 mg, 150 mg, 160 mg, 170 mg, 200 mg, 250 mg, 300 mg, 350 mg, or 500 mg of a compound of the formula I. In embodiments, capsules, tablets, liquid or controlled release delivery forms may contain

about 50, 60, 70, 75, 85, 100 or 150 mg of a compound of the formula I. Capsules, tablets, liquids or controlled release delivery forms may be used for administration of one unit dosage form or any combination of unit dosage forms, that is, more than one unit dosage form, to achieve the total dosage required as determined by the prescribing physician.

[000111] In an embodiment, a unit dosage form comprises about 0.5 to 500 mg, 0.5 to 300 mg, 0.5 to 200 mg, 0.5 to 100 mg, 0.5 to 90 mg, 0.5 to 85 mg, 0.5 to 80 mg. 0.5 to 75 mg, 0.5 to 70 mg, 5 to 100 mg, 25 to 100 mg or 75 to 100 mg.

[000112] In an embodiment, a unit dosage form comprises about 0.5 mg/day to about 500 mg/day, 0.5 mg/day to about 400 mg/day, 0.5 mg/day to about 300 mg/day, 0.5 mg/day to about 200 mg/day, 0.5 mg/day to about 100 mg/day.

[000113] In an embodiment, a unit dosage form comprises about 0.5 mg/day to about 500 mg/day, 0.5 mg/day to about 200 mg/day, 0.5 mg/day to about 100 mg/day, 1 mg/day to about 100 mg/day, 1 mg/day to about 85 mg/day, 1 mg/day to about 75 mg/day, 1.5 mg/day to about 100 mg/day, 1.5 mg/day to about 90 mg/day, 1.5 mg/day to about 85 mg/day, 1.5 mg/day to about 75 mg/day, 1.5 mg/day to about 70 mg/day, 5 mg/day to about 100 mg/day, 5 mg/day to about 85 mg/day, 5 mg/day to about 75 mg/day, 10 mg/day to about 100 mg/day, 10 mg/day to about 90 mg/day, 10 mg/day to about 85 mg/day, 10 mg/day to about 75 mg/day, 10 mg/day to about 70 mg/day, 25 mg/day to about 100 mg/day, 25 mg/day to about 85 mg/day, 25 mg/day to about 75 mg/day, 50 mg/day to about 100 mg/day, 50 mg/day to about 90 mg/day, 50 mg/day to about 85 mg/day, 50 mg/day to about 75 mg/day, 50 mg/day to about 70 mg/day, 70 mg/day to about 100 mg/day, 70 mg/day to 90 mg/day, 70 mg/day to 85 mg/day or 65 mg/day to 90 mg/day.

[000114] The amount of active compound administered will be dependent on the subject being treated, the amount or severity of the condition, the particular disease state being treated (e.g. a disease state in which proinflammatory responses or over-activated glial cell types is a cause or risk factor), the manner of administration and the judgment of the prescribing physician.

[000115] In aspects of the invention, an effective dosage may be in the range of about 0.01 to 25 mg/kg, in particular, about 0.01 to 10 mg/kg body weight, about 0.01 to 5 mg/kg body weight, about 0.2 to 5 mg/kg body weight, or about 0.1 to 2.0 mg/kg

body weight, more particularly about 0.1 to 1.5 mg/kg body weight, and most particularly about 0.5 to 2 mg/kg body weight, about 0.5 to 1.5 mg/kg body weight, about 1.0 to 2.0 mg/kg body weight or about 1 to 1.5 mg/kg body weight.

[000116] In other aspects of the invention, the amount of a compound of the formula I administered to the subject ranges from about 0.25 mg to about 500 mg/day, 0.5 mg to about 500 mg/day, 0.5 mg to about 300 mg/day, 0.5 mg to about 200 mg/day, 0.5 mg/day to about 100 mg/day, 0.5 mg/day to about 90 mg/day, 0.5 mg/day to about 85 mg/day, 0.5 mg/day to about 80 mg/day, 0.5 mg/day to about 75 mg/day, 0.5 mg/day to about 70 mg/day, 1 mg/day to about 100 mg/day, 1 mg/day to about 85 mg/day, 1 mg/day to about 75 mg/day, 1.5 mg/day to about 100 mg/day, 1.5 mg/day to about 90 mg/day, 1.5 mg/day to about 85 mg/day, 1.5 mg/day to about 75 mg/day, 1.5 mg/day to about 70 mg/day, 5 mg/day to about 100 mg/day, 5 mg/day to about 85 mg/day, 5 mg/day to about 75 mg/day, 10 mg/day to about 150 mg/day, 10 mg/day to about 100 mg/day, 10 mg/day to about 90 mg/day, 10 mg/day to about 85 mg/day, 10 mg/day to about 75 mg/day, 10 mg/day to about 70 mg/day, 25 mg/day to about 150 mg/day, 25 mg/day to about 100 mg/day, 25 mg/day to about 85 mg/day, 25 mg/day to about 75 mg/day, 50 mg/day to about 100 mg/day, 50 mg/day to about 90 mg/day, 50 mg/day to about 85 mg/day, 50 mg/day to about 75 mg/day, 50 mg/day to about 70 mg/day, 70 mg/day to about 100 mg/day, 70 mg/day to about 90 mg/day, 70 mg/day to about 85 mg/day, or 65 mg/day to about 90 mg/day. Daily dosages may be achieved by once a day, twice a day or three times or more daily administration, preferably once a day administration.

[000117] The duration of treatment can be adapted to the conditions of the patient. A subject may be treated with a compound of the formula I, composition, dosage form or formulation thereof on substantially any desired schedule. A compound of the formula I, composition, dosage form or formulation of the invention may be administered one or more times per day, in particular 1 or 2 times per day, once per week, once a month or continuously. However, a subject may be treated less frequently, such as every other day or once a week, or more frequently. A compound of the formula I, composition, dosage form or formulation of the invention may be administered to a subject for about or at least about 2 days, 3 days, 4 days, 5 days, 1 week, 2 weeks to 4 weeks, 1 week to 10 weeks, 1 week to 20 weeks, 1 week to 24

weeks, 1 week to 48 weeks, 2 weeks to 6 weeks, 2 weeks to 8 weeks, 2 weeks to 10 weeks, 2 weeks to 12 weeks, 2 weeks to 14 weeks, 2 weeks to 15 weeks, 2 weeks to 16 weeks, 2 weeks to 20 weeks, 2 weeks to 24 weeks, 2 weeks to 48 weeks, 2 weeks to 18 months, or 2 weeks to 24 months periodically, consecutively or continuously.

[000118] Dosage forms or compositions may be prepared containing a compound of the formula I in the range of 0.25 to 100%, with the balance, when less than 100%, is made up from non-toxic carriers, excipients or vehicles. For oral administration, a pharmaceutically acceptable non-toxic composition is formed, optionally with the incorporation of any of the normally employed pharmaceutical carriers, excipients or vehicles and may contain 1%-100% active ingredient, preferably 25%-75%. Percentages recited in the compositions herein are weight percentages or w/w.

[000119] In an embodiment, a compound of the formula I or composition of the invention is administered as one or more doses daily, in particular a single dose, intravenously. In an embodiment, about 1 to 100 mg/day, in particular about 25 to 100 mg /day, more particularly about 50 to 100 mg/day or 75 to 100 mg/day of a compound of the formula I or composition of the invention is administered once or twice daily.

[000120] A compound of the formula I may be administered in combination with other medications (such as second therapeutic agents) or other medical procedures to treat the same or other aspects of the disease state being treated. A second therapeutic agent may either be within the same pharmaceutical composition (combination compositions), or the two agents may be administered in separate compositions at substantially the same time or at different times as required in the judgment of the prescribing physician. The second therapeutic agent may be a corticosteroid (e.g. glucocorticoid, glucocorticoid precursor or analog, glucocorticoid receptor agonist or antagonist), azathrioprine, glatiramer acetate, methotrexate, antineoplastic, monoclonal antibody, or an immunomodulating treatment or immunotherapeutic agent, e.g. an interferon.

[000121] In embodiments, the second therapeutic agent is an immunotherapeutic agent, for example, β-interferon (e.g., Avonex, Rebiff, Betaseron), glatiramer acetate copolymer-1 (Copaxone), an antineoplastic (e.g. mitoxantrone), a human monoclonal antibody (e.g., natalizumab, Antegren), an immunosuppressant (e.g. mycophenolate mofetil, CellCept), paclitaxel (Taxol), a cyclosporine (e.g. cyclosporine A), a

corticosteroid (glucocorticoid such as prednisone and methyl prednisone), azathioprine, cyclophosphamide, methotrexate, cladribine, 4-aminopyridine and/or tizanidine.

[000122] In embodiments, the second therapeutic agent is an interferon beta-1a (e.g. Avonex, CinnoVex, ReciGen and Rebif), interferon-beta-1b (e.g. Betaseron, Betaferon), glatiramer acetate (Copaxone), mitoxantrone, natalizumab (e.g. Tysabri), alemtuzumab, daclizumab, rituximab, fingolimod, progesterone, progesterone precursor or analog, progesterone receptor agonist or antagonist, prednisone, or methyl prednisone (e.g. Solumedrol).

[000123] The dose of the second therapeutic agent can be determined according to the dose employed clinically, and having regard to the age and body weight of the subject, condition, administration time, dosage form, administration method, combination and the like. The mode of administration of the second therapeutic agent is not particularly limited.

[000124] The invention also relates to articles of manufacture and kits containing materials useful for treating a condition disclosed herein. An article of manufacture may comprise a container. Examples of suitable containers include bottles, vials, and test tubes which may be formed from a variety of materials including glass and plastic. A container holds a medicament or formulation of the invention comprising a compound of the formula I or pharmaceutical composition disclosed herein, and optionally a second therapeutic agent which is effective for treating a condition disclosed herein. The container may have a label which indicates that the medicament or formulation is used for treating the condition, and may also indicate directions for use. In aspects of the invention, a medicament or formulation in a container may comprise any of the medicaments or formulations disclosed herein.

[000125] A kit may additionally include other materials desirable from a commercial end user standpoint, including, without limitation, buffers, diluents, filters, needles, syringes, and package inserts with instructions for performing any methods disclosed herein. A medicament or formulation in a kit of the invention may comprise any of the compounds, dosage forms or compositions disclosed herein.

[000126] According to aspects of the invention, a kit is provided comprising a compound of the formula I or pharmaceutical composition disclosed herein, and optionally one or more second therapeutic agent. The kit can be a package which

houses a container which contains a compound of the formula I or pharmaceutical composition disclosed herein, and also houses instructions for administering the compound of the formula I or pharmaceutical composition disclosed herein. Written materials may also be associated with the container such as instructions for use, or a notice in the form prescribed by a governmental agency regulating the labeling, manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use, or sale for human administration. In aspects, the invention relates to a commercial package comprising a compound of the formula I or pharmaceutical composition disclosed herein together with instructions for simultaneous, separate or sequential use. In particular a label may include amount, frequency, and method of administration.

[000127] The present invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of parameters which can be changed or modified to yield essentially the same results.

EXAMPLES

Example 1

Synthesis of N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine hydro- chloride

[000128] N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine hydrochloride is produced using the following 6-step synthesis which is set out in the reaction scheme in Figure 1.

1. The first step involves deprotonation of 4-chloro-6-phenyl-2H-pyridazin-3-one (JH9) to form an anion, and benzylating the anion using Na-t-Butoxide (NaOtBu) or Na-t-pentoxide (Na-t-Pe) with benzyl bromide in DMSO to form JJ0. (See Coudert et al, Journal of Heterocyclic Chemistry. 1988, 25(3), 799-802 for a procedure for synthesizing 4-chloro-6-phenyl-2H-pyridazin-3-one).
2. The second step is a Suzuki coupling of JJ0 with 4-pyridine boronic acid using a palladium catalyst in dimethoxyethane (DME) to produce JJ1.
3. JJ1 is debenzylated using excess aluminum chloride ($AlCl_3$) in dichloromethane (DCM) as a solvent, resulting in compound J95.

4. The carbonyl on the amide of J95 is converted to a chloro group by reacting in phosphorus oxychloride ($POCl_3$) to yield J96.
5. The free base of the molecule (JA2) is formed by coupling of the chloro compound J96 with cyclopropyl methyl amine (JA1) in n-butanol (n-BuOH) as a solvent.
6. The hydrochloride salt (JA3) is formed by treating the free base with hydrochloric acid in isopropyl alcohol (IPA) to yield N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine hydrochloride. The resulting material is dried in a drying oven under vacuum to reduce moisture, residual hydrochloride and residual IPA.

[000129] The resulting N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine hydrochloride has the molecular formula $C_{19}H_{18}N_4$. The compound is a brown to yellow solid and the powder is slightly hygroscopic. The molecular weight of the free base is 302.38. The pH of an aqueous solution of the compound is acidic and the solubility of the compound increases with decreasing pH.

Example 2

[000130] Experimental autoimmune encephalomyelitis (EAE) is a T-cell mediated autoimmune disease of the CNS, which serves as a model of multiple sclerosis (MS). To induce EAE, female SJL mice are injected subcutaneously with proteolipid protein peptide PLP139-151 and are monitored for disease progression as previously described (Karpus et al., J. Immunol. 155, 5003-5010, 1995), or alternatively, by adoptive transfer of PLP139-151 antigen activated T cells. Animals are graded according to their clinical severity (0, no abnormality; 1, limp tail; 2, limptail/hindlimb weakness; 3, partial hindlimb paralysis; 4, complete hind paralysis; 5, death).

[000131] The ability of the test compound N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine hydrochloride to prevent accumulation of inflammatory cells in the CNS and to inhibit EAE progression in an *in vivo* model of relapsing-remitting MS was studied. The study design involved randomized groups of 6-7 week-old mice, which received low- or high-dose test compound (or vehicle) daily starting at the time of EAE induction and continuing for 21 consecutive days. The exact timing, dose, and route of administration for the study are based on the half-life, potency and bioavailability of the test article and are described below.

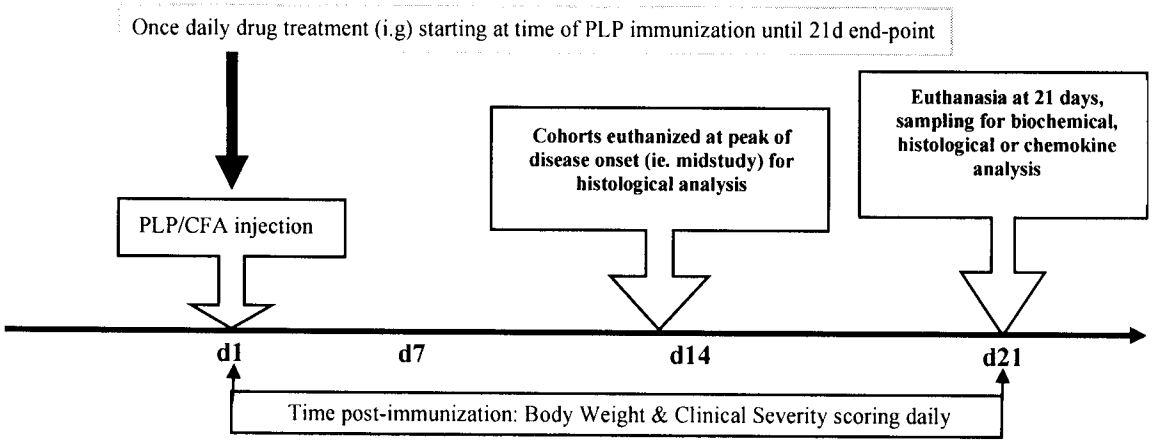
[000132] The study evaluated the effect of the test compound on disease development and progression in an EAE model of MS. Functional endpoints evaluated motor defects and included median clinical EAE severity score, disease incidence (number of animals that develop clinical signs of EAE), and mean time of disease onset. In addition, changes in TNFα and recruitment of inflammatory cells were investigated. The compound was administered by intragavage (i.g.) at two dose levels, and vehicle.

Study Groups: (n = 15 mice/group):

1. **Test compound**: N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine hydrochloride administered orally (i.g.) QD for 21 days starting at time of PLP immunization. High Dose - 15 mg/kg and Low Dose - 5 mg/kg.

2. **Vehicle** - Saline

Below is a schematic of the study protocol.



Route of Drug Administration:

[000133] The compound (high- and low-doses) and vehicle were administered orally (i.g.) once daily for 21 days starting at the time of EAE induction (immunization with PLP139-151).

Study end-points:

[000134] Functional endpoints evaluated the efficacy of the compound on disease incidence (the number of mice that develop clinical signs of EAE), mean time of disease onset, and EAE progression. The latter was facilitated by observations of clinical disease severity scored during a post-immunization time-line (every other day

or TBD). Clinical severity is scored as (0, no abnormality; 1, limp tail; 2, limptail/hindlimb weakness; 3, partial hindlimb paralysis; 4, complete hind paralysis; 5, death).

[000135] In addition, the effects of the test compound on TNFα expression (regulator of CNS inflammatory cell migration/infiltrating mononuclear cells) were examined in CNS homogenates at the peak of clinical disease (ELISA) and at the end of the study.

[000136] Antibody-stained spinal cord histological sections were also evaluated for evidence of decreased macrophage CNS infiltration (CD45hiCD11b+ cells), reduction in perivascular inflammatory cell infiltrates/lesions, and decreased demyelination - both at peak of clinical disease and end of experiment.

[000137] Changes in CNS accumulation of leukocyte populations (activated T cells: CD4+/CD8+; regulatory T cells: Foxp3+; macrophage/microglia/dendritic cells: CD45+ [high/low] /CD11b+) were also evaluated by antibody-staining of spinal cord mononuclear cells followed by FACS analysis.

[000138] The high dose of the test compound significantly reduced the severity of the initial clinical disease episode compared to the control group. The high dose of the test compound prevented mice from attaining a clinical score of 3 or 4 (Figure 2). Figure 3 shows that the high dose of the test compound significantly reduced the relapse rate compared to control treatment. The high dose of the test compound shows efficacy in the EAE model for MS. The high dose of the test compound showed some statistical difference compared to control at the peak of the initial clinical disease episode as well as at the end of the experiment (the relapsing phase of disease).

[000139] The results of the histology, flow cytometry and CNS-TNF results are illustrated in Figures 4 and 5. Figure 4 shows that there was a significant decrease in spinal cord inflammatory cell infiltrate in mice treated with a high dose of the test compound compared to saline control at disease onset/peak. There were no significant differences in spinal cord histology at any of the other time points examined. Figure 5 illustrates that there was a significant reduction in CNS TNF expression in mice treated with a high dose of the test compound compared to controls. Therefore, in mice treated with a high dose of the test compound there was a significant reduction in clinical disease, spinal cord inflammatory cell infiltrate and TNF expression.

[000140] The present invention is not to be limited in scope by the specific embodiments described herein, since such embodiments are intended as but single illustrations of one aspect of the invention and any functionally equivalent embodiments are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

[000141] All publications, patents and patent applications referred to herein are incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety. All publications, patents and patent applications mentioned herein are incorporated herein by reference for the purpose of describing and disclosing the methods etc. which are reported therein which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for treating multiple sclerosis comprising a therapeutically effective amount of N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, excipient or vehicle.
2. A pharmaceutical composition of claim 1 comprising an acid addition salt of N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine.
3. A pharmaceutical composition of claim 2 wherein the salt is N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine.HCl (1:1), N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine.HCl (2:1), N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine.HBr or N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine.H_2SO_4 (2:1).
4. A pharmaceutical composition of claim 1 comprising at least one of N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine.HCl, N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine.HCl (2:1) and N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine.HCl (3:1).
5. A method of treating multiple sclerosis comprising administering a therapeutically effective amount of N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine, or a pharmaceutically acceptable salt thereof.
6. A method of treating a subject exhibiting clinical symptoms of multiple sclerosis comprising administering N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine, or a pharmaceutically acceptable salt thereof to ameliorate the disease.
7. A method of claim 5 or 6, further comprising administering at least one second therapeutic agent at a therapeutically effective dosage in an effective dosage form at a selected interval.
8. A method of claim 5, 6 or 7 wherein the multiple sclerosis is a relapsing remitting form or secondary progressive form of multiple sclerosis.
9. A method of any one of claims 5 to 8 wherein the patient is a female.

10. A method of any one of claims 5 to 9 comprising administering an acid addition salt of N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine.

11. A method of claim 10 wherein the salt comprises at least one of N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine.HCl, N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine.HCl (2:1) and N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine.HCl (3:1).

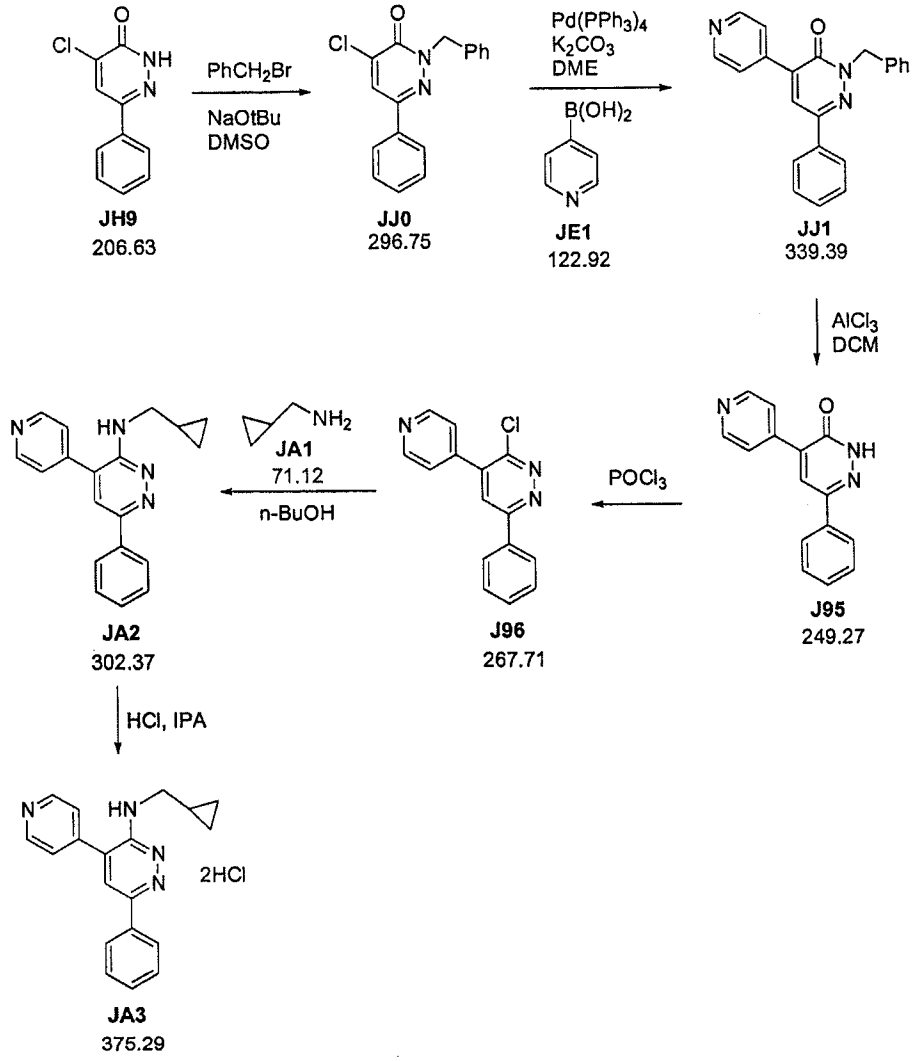
12. A unit dosage form for treating multiple sclerosis comprising 10 to 100 mg of N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine, or a pharmaceutically acceptable salt thereof.

13. Use of N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for treating multiple sclerosis.

14. Use of claim 13 wherein the salt comprises an acid addition salt of N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine.

15. Use of claim 13 wherein the salt comprises at least one of N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine.HCl, N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine.HCl (2:1) and N-(Cyclopropylmethyl)-6-phenyl-4-(pyridin-4-yl)pyridazin-3-amine.HCl (3:1).

FIGURE 1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O
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N
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NaOtBu
DMSO
Ph
Pd(PPh3)4
K2CO3
DME
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JJ0
296.75
JE1
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JJ1
339.39
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DCM
POCl3
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JA2
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JA3
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FIGURE 2

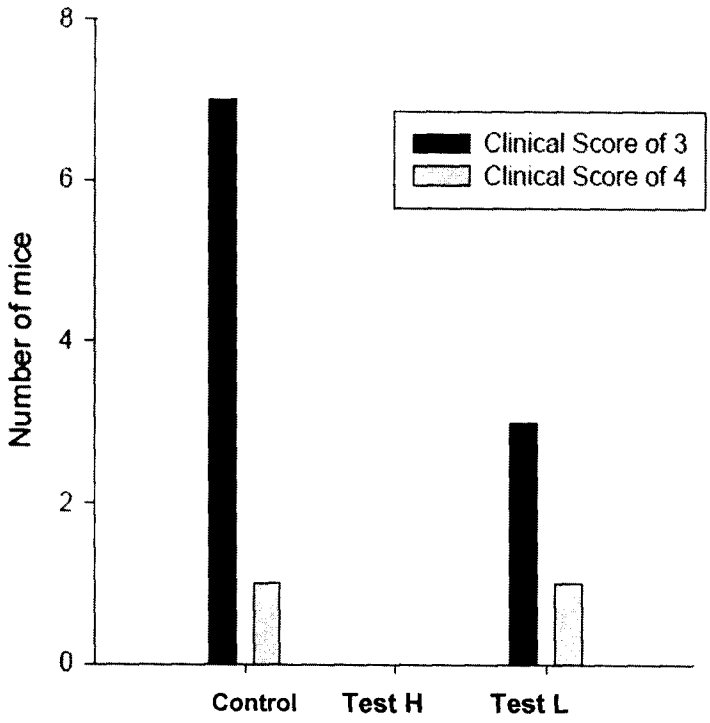

8
6
4
2
0
Number of mice
Clinical Score of 3
Clinical Score of 4
Control
Test H
Test L

FIGURE 3

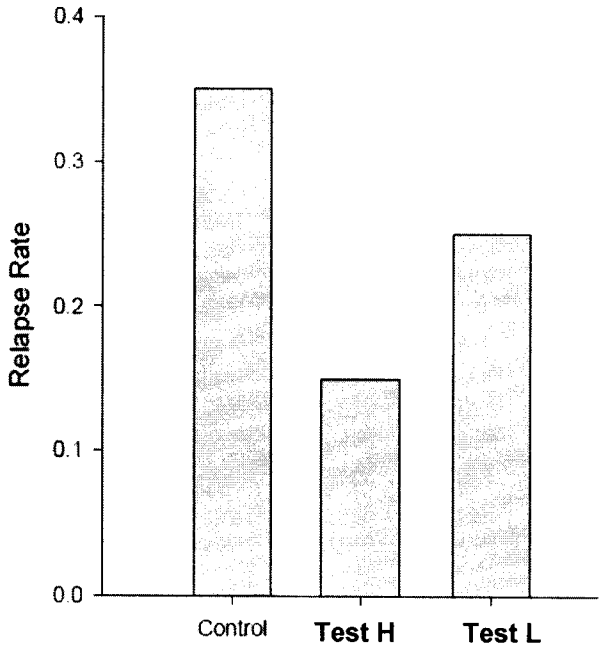
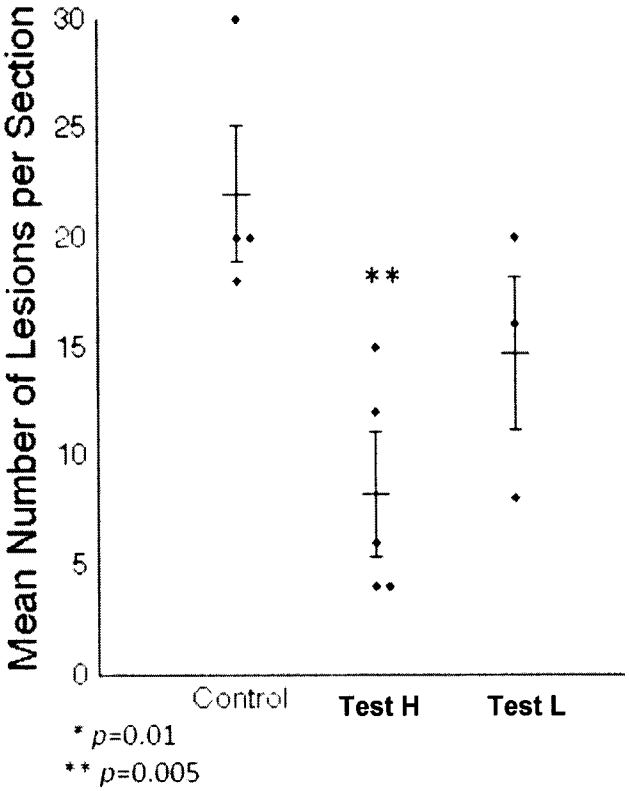


FIGURE 4


Mean Number of Lesions per Section
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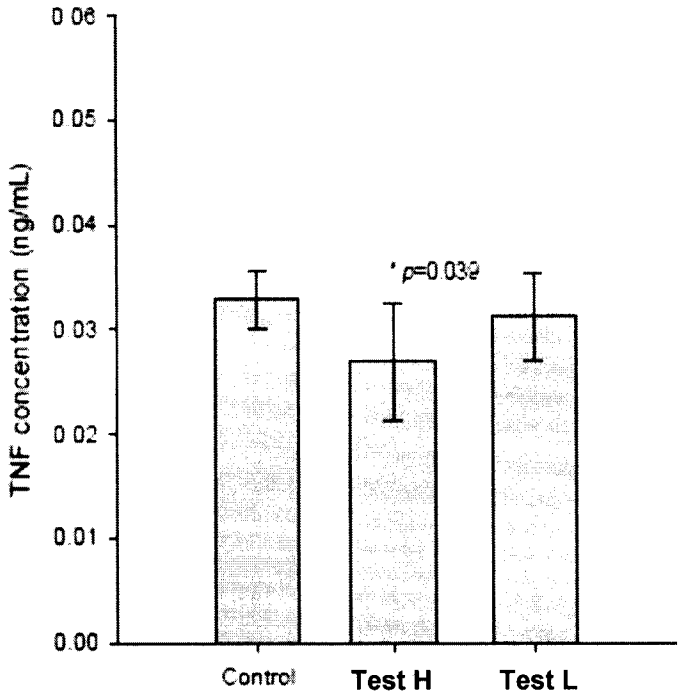
25
20
15
10
5
0
Control
Test H
Test L
**
* p=0.01
** p=0.005

FIGURE 5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0.05
0.04
0.03
0.02
0.01
0.00
TNF concentration (ng/mL)
* p=0.039
Control
Test H
Test L