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(54) **Title**: R(+)-N-FORMYL-PROPARGYL-AMINOINDAN

(57) **Abstract**: The subject invention provides R (+) -N-formyl-propargyl- aminoindan and a composition containing N-propargyl-1 (R) -aminoindan or a pharmaceutically acceptable salt thereof, and a compound of R (+) -N-formyl-propargyl-aminoindan.

R(+)-N-FORMYL-PROPARGYL-AMINOINDAN

This application claims priority of U.S. Provisional Application No. 61/545,422, filed October 10, 2011, the entire content of which is hereby incorporated by reference herein.

Throughout this application various publications, published patent applications, and patents are referenced. The disclosures of these documents in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

Background of the invention

United States Patents 5,532,415, 5,387,612, 5,453,446, 5,457,133, 5,599,991, 5,744,500, 5,891,923, 5,668,181, 5,576,353, 5,519,061, 5,786,390, 6,316,504, 6,630,514, 7,750,051, and 7,855,233 disclose R(+)-N-propargyl-1-aminoindan ("R-PAI"), also known as rasagiline, and its pharmaceutically acceptable salts. These U.S. patents also disclose that rasagiline is a selective inhibitor of the B-form of the enzyme monoamine oxidase ("MAO-B") and is useful in treating Parkinson's disease and various other conditions by inhibition of MAO-B in the brain.

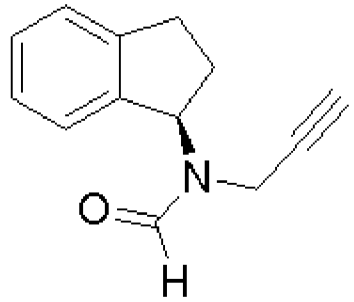
United States Patent Nos. 6,126,968, 7,572,834, and 7,598,420, United States Patent applications 12/283,022, and 12/283,107 and PCT publications WO 95/11016 and WO 2006/014973, hereby incorporated by reference, disclose pharmaceutical compositions comprising rasagiline and processes for their preparation.

AZILECT® is a commercially available rasagiline mesylate immediate release formulation indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease as initial monotherapy and as adjunct therapy to levodopa. The current marketed formulation of rasagiline (Azilect®) is rapidly absorbed, reaching peak plasma concentration (t_{max}) in

approximately 1 hour. The absolute bioavailability of rasagiline is about 36%. (AZILECT® Product Label, May 2006).

Summary of the Invention

The subject invention provides an isolated compound having the structure:



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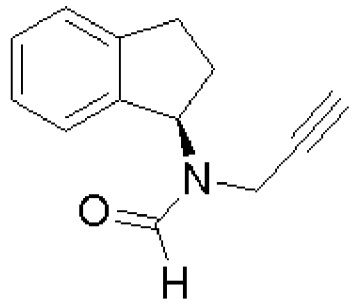
The subject invention also provides a composition comprising a compound having the structure:



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wherein the composition is free of rasagiline or a salt thereof.

The subject invention further provides a process for preparing R(+)-N-formyl-propargyl-aminoindan comprising the steps of:

a) mixing R-(+)-N-Propargyl-1-aminoindan with formic acid in a first solvent at a temperature of less than 30°C;
b) evaporating the first solvent to obtain an oil;
c) dissolving the oil in a second solvent to form a solution; and
d) isolating and obtaining R(+)-N-formyl-propargyl-aminoindan from the solution.

The subject invention yet further provides a pharmaceutical composition comprising rasagiline or a pharmaceutically

acceptable salt thereof, citric acid, R(+)-N-formyl-propargyl-aminoindan, and at least one pharmaceutically acceptable carrier, wherein R(+)-N-formyl-propargyl-aminoindan is present in the pharmaceutical composition in an amount greater than about 0.04% by weight, relative to the amount of rasagiline, based on a determination by a HPLC method.

The subject invention yet further provides a pharmaceutical composition described herein in tablet form.

The subject invention yet further provides a process for preparing a pharmaceutical composition comprising rasagiline or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, comprising:

a) obtaining a batch of rasagiline or a pharmaceutically acceptable salt thereof;
b) analyzing the batch for the presence of R(+)-N-formyl-propargyl-aminoindan by a suitable apparatus; and
c) preparing the pharmaceutical composition from the batch only if the batch is determined to have less than about 0.5% R(+)-N-formyl-propargyl-aminoindan by weight relative to the amount of rasagiline.

The subject invention yet further provides a process for preparing a packaged pharmaceutical composition comprising rasagiline or a pharmaceutically acceptable salt thereof comprising:

a) obtaining a pharmaceutical composition of rasagiline or a pharmaceutically acceptable salt thereof;
b) analyzing the pharmaceutical composition for the presence of R(+)-N-formyl-propargyl-aminoindan by a suitable apparatus; and
c) packaging the pharmaceutical composition only if the amount of R(+)-N-formyl-propargyl-aminoindan is not more than about 0.5% by weight relative to the amount of rasagiline.

The subject invention yet further provides a process of distributing a validated batch of a pharmaceutical composition

comprising rasagiline or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier, comprising:

a) obtaining a batch of the pharmaceutical composition;

b) performing stability testing with a sample of the batch;

c) determining the total amount of R(+)-N-formyl-propargyl-aminoindan in the sample of the batch by a suitable apparatus after stability testing;

d) validating the batch for distribution only if the sample of the batch after stability testing is determined to have not more than about 1.0% by weight of R(+)-N-formyl-propargyl-aminoindan relative to the amount of rasagiline; and

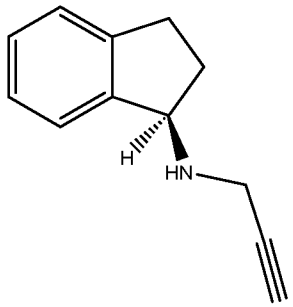
e) distributing the validated batch.

The subject invention yet further provides R(+)-N-formyl-propargyl-aminoindan for use, as a reference standard to detect trace amounts of N R(+)-N-formyl-propargyl-aminoindan in a pharmaceutical composition comprising rasagiline or a pharmaceutically acceptable salt of rasagiline.

The subject invention yet further provides a method for treating Parkinson's disease in a patient comprising administering to the patient an amount of the pharmaceutical compositions disclosed herein effective to treat Parkinson's disease in the patient.

Detailed Description of the Invention

R(+)-N-propargyl-1-aminoindan ("R-PAI"), also known as rasagiline, is a small molecule having the following chemical structure:



Rasagiline

Rasagiline has been reported to be a selective inhibitor of the B-form of the enzyme monoamine oxidase ("MAO-B") and is useful in treating Parkinson's disease and various other conditions by inhibition of MAO-B in the brain.

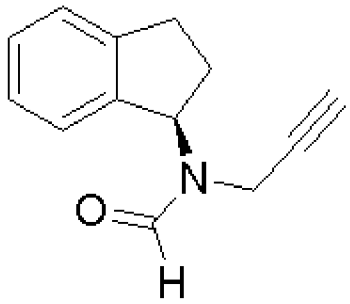
A pharmaceutically acceptable salt of rasagiline, rasagiline citrate, and the process of preparing the same has been described in United States Patent No. 7,855,233, the entire content of which is hereby incorporated by reference.

Crystalline rasagiline, and the process of preparing the same has been described in United States Patent Nos. 7,750,051 and 7,968,749, the entire contents of which are hereby incorporated by reference.

Delayed release rasagiline formulations have been described in United States Application Publication Nos. 2009/0181086, 2010/0189790, 2010/0189788, 2010/0189787, and 2010/0189791, the entire content of each of which is hereby incorporated by reference.

It has been found that when rasagiline drug substance or drug product is exposed to certain extreme conditions, e.g. high temperature, an impurity is formed. This impurity was identified to be R(+)-N-formyl-propargyl-aminoindan, having

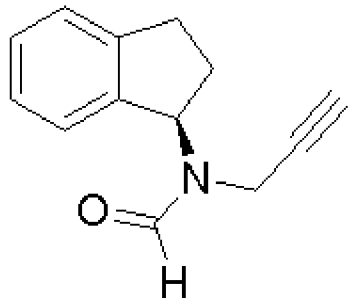
the following structure:



R(+)-N-formyl-propargyl-aminoindan

Other impurities in rasagiline formulations should be avoided, such as rasagiline citramide and R(+)-N-methyl-propargyl-aminoindan.

The subject invention provides an isolated compound having the structure:



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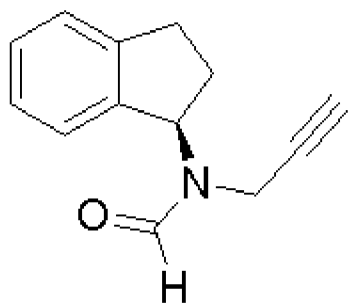
The subject invention also provides a composition comprising a compound having the structure:



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wherein the composition is free of rasagiline or a salt thereof.

The subject invention further provides a process for preparing R(+)-N-formyl-propargyl-aminoindan comprising the steps of:

a) mixing R-(+)-N-Propargyl-1-aminoindan with formic acid in a first solvent at a temperature of less than 30°C;

b) evaporating the first solvent to obtain an oil;

c) dissolving the oil in a second solvent to form a solution; and

d) isolating and obtaining R(+)-N-formyl-propargyl-aminoindan from the solution.

In an embodiment of the process, the first solvent is acetic anhydride.

In another embodiment of the process, the second solvent is ethyl acetate.

The subject invention yet further provides a pharmaceutical composition comprising rasagiline or a pharmaceutically acceptable salt thereof, citric acid, R(+)-N-formyl-propargyl-aminoindan, and at least one pharmaceutically acceptable carrier, wherein R(+)-N-formyl-propargyl-aminoindan is present in the pharmaceutical composition in an amount greater than about 0.04% by weight, relative to the amount of rasagiline, based on a determination by a HPLC method.

In an embodiment of the pharmaceutical composition the amount of R(+)-N-formyl-propargyl-aminoindan is not more than about 0.5% by weight, relative to the amount of rasagiline, based on a determination by a HPLC method.

In another embodiment of the pharmaceutical composition, the pharmaceutical composition is less than one week old, and the temperature during the less than one week did not exceed ambient temperature.

In yet another embodiment of the pharmaceutical composition, the pharmaceutical composition comprises rasagiline as free base.

In yet another embodiment of the pharmaceutical composition, the pharmaceutical composition comprises the pharmaceutically acceptable salt of rasagiline, and which salt is rasagiline citrate.

In yet another embodiment of the pharmaceutical composition, the pharmaceutical composition is a solid pharmaceutical composition.

In yet another embodiment of the pharmaceutical composition, the pharmaceutical composition is in tablet form.

In an embodiment of the pharmaceutical composition in tablet form, the tablet has a core and a coating, wherein the core of the tablet comprises an amount of rasagiline as free base, citric acid and mannitol.

In another embodiment of the pharmaceutical composition in tablet form, the core of the tablet the weight ratio of mannitol to citric acid is between 45 to 1 and 10 to 1.

In yet another embodiment of the pharmaceutical composition in tablet form, the core of the tablet the weight ratio of mannitol to citric acid is between 30 to 1 and 25 to 1.

In yet another embodiment of the pharmaceutical composition in tablet form, the tablet has a core and a coating, wherein the core of the tablet comprises an amount of rasagiline and citric acid, about 59.9% of mannitol, about 0.53% of aerosil, about 6.6% of starch NF, about 26.3% of pregelatinized starch, about 2.0% of stearic acid, and about 2.0% of talc, by weight, relative to the weight of the core of the tablet.

In yet another embodiment of the pharmaceutical composition in tablet form, the core of the tablet comprises an amount of rasagiline and citric acid, 45.5 mg of mannitol, 0.4 mg of aerosil, 5.0 mg of starch NF, 20.0 mg of pregelatinized starch, 1.5 mg of stearic acid, 1.5 mg of talc, and the coating of the tablet comprises two coating layers, of which

the inner of the two coating layers comprises 3.5 mg of hypromellose and the outer of the two coating layers comprises 4.0 mg of methacrylic acid ethyl acrylate copolymer, 0.8 mg of triethyl citrate, and 1.9 mg of talc extra fine.

In yet another embodiment of the pharmaceutical composition in tablet form, the amount of rasagiline in the core is 0.5 mg.

In yet another embodiment of the pharmaceutical composition in tablet form, the tablet has a core and a coating, wherein the core of the tablet comprises an amount of rasagiline and citric acid, about 59.2% of mannitol, about 0.53% of aerosil, about 6.6% of starch NF, about 26.3% of pregelatinized starch, about 2.0% of stearic acid, and about 2.0% of talc, by weight, relative to the weight of the core of the tablet.

In yet another embodiment of the pharmaceutical composition in tablet form, the core of the tablet comprises an amount of rasagiline and citric acid, 45.0 mg of mannitol, 0.4 mg of aerosil, 5.0 mg of starch NF, 20.0 mg of pregelatinized starch, 1.5 mg of stearic acid, 1.5 mg of talc, and the coating of the tablet comprises two coating layers, of which the inner of the two coating layers comprises 3.5 mg of hypromellose and the outer of the two coating layers comprises 4.0 mg of methacrylic acid ethyl acrylate copolymer, 0.8 mg of triethyl citrate, and 1.9 mg of talc extra fine.

In yet another embodiment of the pharmaceutical composition in tablet form, the amount of rasagiline in the core is 1.0 mg.

In yet another embodiment of the pharmaceutical composition, not more than about 1.0% by weight of rasagiline citramide or a salt thereof is in the pharmaceutical composition relative to the amount of rasagiline, based on a determination by a HPLC method.

In yet another embodiment of the pharmaceutical composition, not more than about 1.0% by weight of R(+)-N-methyl-propargyl-aminoindan or a salt thereof is in the pharmaceutical

composition relative to the amount of rasagiline, based on a determination by a HPLC method.

The subject invention yet further provides a process for preparing a pharmaceutical composition comprising rasagiline or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, comprising:

a) obtaining a batch of rasagiline or a pharmaceutically acceptable salt thereof;
b) analyzing the batch for the presence of R(+)-N-formyl-propargyl-aminoindan by a suitable apparatus; and
c) preparing the pharmaceutical composition from the batch only if the batch is determined to have less than about 0.5% R(+)-N-formyl-propargyl-aminoindan by weight relative to the amount of rasagiline.

The subject invention yet further provides a process for preparing a packaged pharmaceutical composition comprising rasagiline or a pharmaceutically acceptable salt thereof comprising:

a) obtaining a pharmaceutical composition of rasagiline or a pharmaceutically acceptable salt thereof;
b) analyzing the pharmaceutical composition for the presence of R(+)-N-formyl-propargyl-aminoindan by a suitable apparatus; and
c) packaging the pharmaceutical composition only if the amount of R(+)-N-formyl-propargyl-aminoindan is not more than about 0.5% by weight relative to the amount of rasagiline.

The subject invention yet further provides a process of distributing a validated batch of a pharmaceutical composition comprising rasagiline or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier, comprising:

a) obtaining a batch of the pharmaceutical composition;
b) performing stability testing with a sample of the batch;
c) determining the total amount of R(+)-N-formyl-propargyl-aminoindan in the sample of the batch by a suitable

apparatus after stability testing;

d) validating the batch for distribution only if the sample of the batch after stability testing is determined to have not more than about 1.0% by weight of R(+)-N-formyl-propargyl-aminoindan relative to the amount of rasagiline; and

e) distributing the validated batch.

In an embodiment of the processes disclosed herein, the pharmaceutical composition comprises rasagiline free base.

In another embodiment of the processes disclosed herein, the pharmaceutical composition comprises rasagiline citrate.

The subject invention yet further provides R(+)-N-formyl-propargyl-aminoindan for use, as a reference standard to detect trace amounts of N R(+)-N-formyl-propargyl-aminoindan in a pharmaceutical composition comprising rasagiline or a pharmaceutically acceptable salt of rasagiline.

The subject invention yet further provides a method for treating Parkinson's disease in a patient comprising administering to the patient an amount of the pharmaceutical compositions disclosed herein effective to treat Parkinson's disease in the patient.

Every embodiment disclosed herein can be combined with every other embodiment of the subject invention, unless specified otherwise.

By any range disclosed herein, it is meant that all hundredth, tenth and integer unit amounts within the range are specifically disclosed as part of the invention. Thus, for example, 0.01 mg to 50 mg means that 0.02, 0.03 ... 0.09; 0.1, 0.2 ... 0.9; and 1, 2 ... 49 mg unit amounts are included as embodiments of this invention.

It will be noted that the structure of the compounds of this invention includes an asymmetric carbon atom and thus the

compounds occur as racemates, racemic mixtures, and isolated single enantiomers. All such isomeric forms of these compounds are expressly included in this invention. Each stereogenic carbon may be of the R or S configuration. It is to be understood accordingly that the isomers arising from such asymmetry (e.g., all enantiomers and diastereomers) are included within the scope of this invention, unless indicated otherwise. Such isomers can be obtained in substantially pure form by classical separation techniques and by stereochemically controlled synthesis, such as those described in "Enantiomers, Racemates and Resolutions" by J. Jacques, A. Collet and S. Wilen, Pub. John Wiley & Sons, NY, 1981. For example, the resolution may be carried out by preparative chromatography on a chiral column.

The subject invention is also intended to include all isotopes of atoms occurring on the compounds disclosed herein. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

It will be noted that any notation of a carbon in structures throughout this application, when used without further notation, are intended to represent all isotopes of carbon, such as ^{12}C, ^{13}C, or ^{14}C. Furthermore, any compounds containing ^{13}C or ^{14}C may specifically have the structure of any of the compounds disclosed herein.

It will also be noted that any notation of a hydrogen in structures throughout this application, when used without further notation, are intended to represent all isotopes of hydrogen, such as ^{1}H, ^{2}H, or ^{3}H. Furthermore, any compounds containing ^{2}H or ^{3}H may specifically have the structure of any of the compounds disclosed herein.

Isotopically-labeled compounds can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples

disclosed herein using an appropriate isotopically-labeled reagents in place of the non-labeled reagents employed.

A characteristic of a compound refers to any quality that a compound exhibits, e.g., peaks or retention times, as determined by 1H nuclear magnetic spectroscopy, mass spectroscopy, infrared, ultraviolet or fluorescence spectrophotometry, gas chromatography, thin layer chromatography, high performance liquid chromatography (HPLC), elemental analysis, Ames test, dissolution, stability and any other quality that can be determined by an analytical method. Once the characteristics of a compound are known, the information can be used to, for example, screen or test for the presence of the compound in a sample. Quantity or weight percentage of a compound present in a sample can be determined by a suitable apparatus, for example, a HPLC.

As used herein, a "pharmaceutically acceptable salt" of rasagiline includes citrate, tannate, malate, mesylate, maleate, fumarate, tartrate, esylate, p-toluenesulfonate, benzoate, acetate, phosphate and sulfate salts. For the preparation of pharmaceutically acceptable acid addition salts of the compounds of the invention, the free base can be reacted with the desired acids in the presence of a suitable solvent by conventional methods.

Rasagiline can also be used in its free base form. A process of manufacture of the rasagiline free base is described in United States Patent Nos. 7,750,051 and 7,968,749, the contents of which are hereby incorporated by reference.

As used herein, "drug substance" refers to the active ingredient in a drug product, which provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or animals.

As used herein, "drug product" refers to the finished dosage form containing the drug substance as well as at least one

pharmaceutically acceptable carrier.

As used herein, an "isolated" compound is a compound isolated from the crude reaction mixture following an affirmative act of isolation. The act of isolation necessarily involves separating the compound from the other known components of the crude reaction mixture, with some impurities, unknown side products and residual amounts of the other known components of the crude reaction mixture permitted to remain. Purification is an example of an affirmative act of isolation.

As used herein, a composition that is "free" of a chemical entity means that the composition contains, if at all, an amount of the chemical entity which cannot be avoided following an affirmative act intended to purify the composition by separating the chemical entity from the composition. A composition which is "free" of a rasagiline of a salt thereof, if present, as used herein, means that the rasagiline or a salt thereof is a minority component relative to the amount of R(+)-N-formyl-propargyl-aminoindan, by weight.

As used herein, "stability testing" refers to tests conducted at specific time intervals and various environmental conditions (e.g., temperature and humidity) to see if and to what extent a drug product degrades over its designated shelf life time. The specific conditions and time of the tests are such that they accelerate the conditions the drug product is expected to encounter over its shelf life. For example, detailed requirements of stability testing for finished pharmaceuticals are codified in 21 C.F.R §211.166, the entire content of which is hereby incorporated by reference.

As used herein, a pharmaceutical composition which is "X weeks old" refers to the period of time, in this case one week, since the pharmaceutical composition was made.

A "detection limit" for an analytical method used in screening or testing for the presence of a compound in a sample is a

threshold under which the compound in a sample cannot be detected by the analytical method, e.g. an HPLC, MS, NMR, or FT-IR method.

As used herein, "ambient temperature" refers to a temperature of from about 20°C to about 30°C.

As used herein, "about" in the context of a measurable numerical value means the numerical value within the standard error of the analytical method used to measure.

A dosage unit may comprise a single compound or mixtures of compounds thereof. A dosage unit can be prepared for oral dosage forms, such as tablets, capsules, pills, powders, and granules.

As used herein, a "pharmaceutically acceptable" carrier or excipient is one that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio.

Specific examples of pharmaceutical acceptable carriers and excipients that may be used to formulate oral dosage forms are described, e.g., in U.S. Pat. No. 6,126,968 to Peskin et al., issued Oct. 3, 2000. Techniques and compositions for making dosage forms useful in the present invention are described-in the following references: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Pharmaceutical Dosage Forms: Tablets (Lieberman et al., 1981); Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976); Remington's Pharmaceutical Sciences, 17th ed. (Mack Publishing Company, Easton, Pa., 1985); Advances in Pharmaceutical Sciences (David Ganderton, Trevor Jones, Eds., 1992); Advances in Pharmaceutical Sciences Vol 7. (David Ganderton, Trevor Jones, James McGinity, Eds., 1995); Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms (Drugs and the Pharmaceutical Sciences, Series 36 (James McGinity, Ed., 1989); Pharmaceutical Particulate Carriers: Therapeutic Applications:

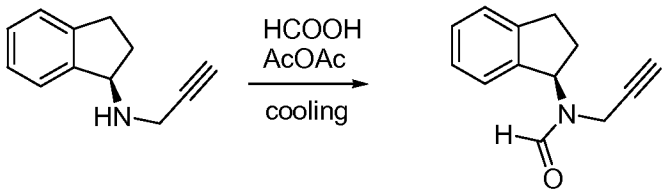
Drugs and the Pharmaceutical Sciences, Vol 61 (Alain Rolland, Ed., 1993); Drug Delivery to the Gastrointestinal Tract (Ellis Horwood Books in the Biological Sciences. Series in Pharmaceutical Technology; J. G. Hardy, S. S. Davis, Clive G. Wilson, Eds.); Modern Pharmaceutics Drugs and the Pharmaceutical Sciences, Vol 40 (Gilbert S. Banker, Christopher T. Rhodes, Eds.).

Tablets may contain suitable binders, lubricants, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, melting agents, stabilizing agents, solubilizing agents, antioxidants, buffering agent, chelating agents, fillers and plasticizers. For instance, for oral administration in the dosage unit form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as gelatin, agar, starch, methyl cellulose, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like. Suitable binders include starch, gelatin, natural sugars such as corn starch, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, povidone, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Antioxidants include ascorbic acid, fumaric acid, citric acid, malic acid, gallic acid and its salts and esters, butylated hydroxyanisole, editic acid. Lubricants used in these dosage forms include sodium oleate, sodium stearate, sodium benzoate, sodium acetate, stearic acid, sodium stearyl fumarate, talc and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, croscarmellose sodium, sodium starch glycolate and the like, suitable plasticizers include triacetin, triethyl citrate, dibutyl sebacate, polyethylene glycol and the like.

This invention will be better understood by reference to the Experimental Details which follow, but those skilled in the art will readily appreciate that the specific experiments detailed are only illustrative of the invention as described more fully in the claims which follow thereafter.

Experimental Details:

Example 1: Preparation of R(+)-N-formyl-propargyl-aminoindan



15.4g (0.09 mole) of rasagiline base (R-(+)-N-Propargyl-1-aminoindan) was added to a mixture of acetic andydride (11.4ml, 0.12mole) and formic acid (5.7ml, 0.15mole) at stirring by portions over 15 min. at cooling. The mixture was stirred at 0-5°C for ½ hr and then at room temperature for 20 hrs.

Reaction mixture was evaporated to dryness under vacuum. The residual oil was dissolved in ethylacetate and transferred to a chromatographic column.

Chromatographic isolation: Column 120.0g, mobile phase EtOAc:Hexane 30:70.

Isolated fraction from the chromatographic column containing R(+)-N-formyl-propargyl-aminoindan was evaporated. The residue (15.2g of oil) was dissolved in 250ml EtOAc and washed with water, 10%$NaHCO_3$ and brine. Organic solution was dried over Na_2SO_4 and evaporated. The residue (oil) was dried under high vacuum (2mbar).

Yield - 12.0g of yellowish oil.

Example 2: Preparation of Racemic N-formyl-N-Propargyl-1-aminoindan

15.4g (0.09 mole) of Racemic PAI base (rac. N-Propargyl-1-aminoindan) was added to a mixture of acetic anhydride (11.4ml, 0.12mole) and formic acid (5.7ml, 0.15mole) at

stirring by portions over 15 min. at cooling. The mixture was stirred at 0-5°C for ½ hr and then at room temperature for 20hrs.

Reaction mixture was evaporated to dryness under vacuum. The residue was dissolved in ethylacetate and transferred to a chromatographic column.

Chromatographic isolation: Column 120.0g, mobile phase EtOAc:Hexane 30:70.

Isolated fraction from the chromatographic column containing racemic N-formyl-propargyl-1-aminoindan was evaporated and a solid product was obtained. The solid was dried under vacuum to constant weight.

Yield - 15.1g of white solid

Elemental analysis:

Element:	C, %	H, %	N, %	O, %
Calculated	78.36	6.58	7.03	8.03
Found	78.42	6.42	7.26	N.A.

Chromatographic purification:
Racemic N-formyl-PAI (9.0g, obtained above) was dissolved in 100ml EtOAc, 30ml silica gel (0.06-0.2mm) was added and solvent evaporated to dryness.

Chromatographic isolation: Column 80.0g, mobile phase EtOAc:Hexane 1:1.

Isolated fraction was evaporated and solid product was obtained. The solid dried under vacuum to constant weight.

Yield - 8.7g of white solid, m.p. 68°C

NMR Spectroscopy

The ^{1}H-NMR and ^{13}C-NMR spectra of R(+)-N-formyl-PAI in $CDCl_3$ were obtained on a Bruker 300 MHz NMR instrument.

NMR peak assignments are listed below in Table 1 for the ^{1}H-NMR spectrum and in Table 2 for the ^{13}C-NMR spectrum.

Structure Of R(+)-N-formyl-PAI With Designations Used For The Attribution Of ^{1}H-NMR Shifts

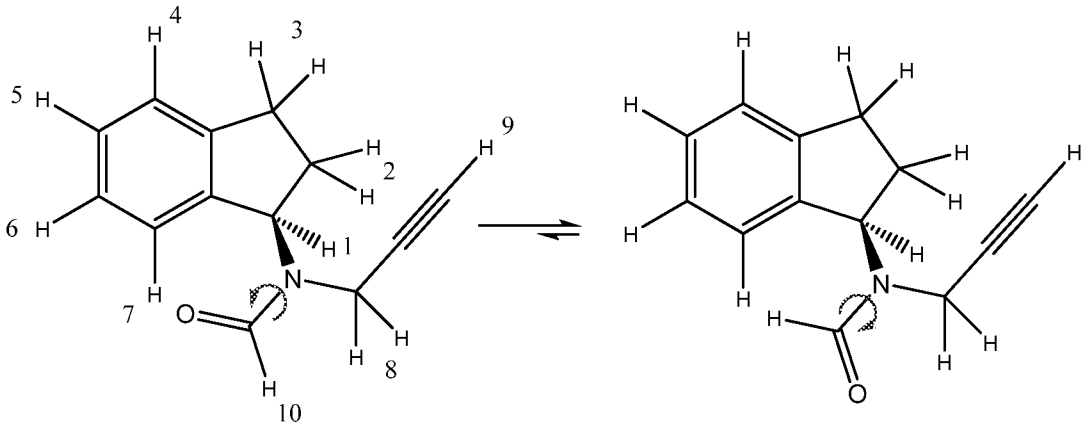


Table 1. ^{1}H-NMR Chemical Shifts of R(+)-N-formyl-PAI in $CDCl_3$

Proton	δ (ppm)	Multiplicity[1]	Coupling Constant (J, Hz)
1 (1H)	Rotamer 1, 5.23 (0.78H) Rotamer 2, 6.06 (0.22H)	t	7.2
2 (2H)	2.18-2.58	m	-
3 (2H)	2.86-1.98, 3.06-3.17	m	-
4, 5, 6, 7 (4H)	7.13-7.33	m	-
8 (2H)	Rotamer 1, 3.58, 4.31 (0.78H) Rotamer 2, 3.67, 3.88 (0.22H)	dd	J_1=17.5, J_2= 2.5
9 (1H)	Rotamer 1, 2.17 (0.78H) Rotamer 2, 2.28 (0.22H)	t	J= 2.5
10 (1H)	Rotamer 1, 8.27 (0.78H) Rotamer 2, 8.45 (0.22H)	s	-

[1] s = singlet; dd = double doublet; t = triplet; m = multiplet

Structure of R(+)-N-formyl-PAI with Designations Used for the Attribution of ^{13}C-NMR Shifts

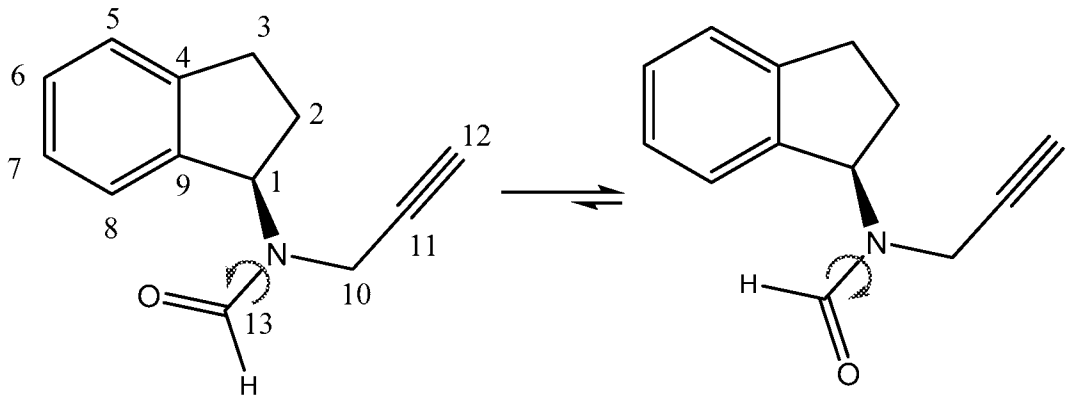


Table 2. ^{13}C-NMR Chemical Shifts of R(+)-N-Formyl-PAI in $CDCl_3$

Carbon	δ (ppm)	
	Rotamer 1 (major)	Rotamer 2 (minor)
1	63.72	57.48
2, 3	30.19, 30.32	29.49, 30.58
4	139.65	139.72
5, 6, 7, 8	124.21, 125.24, 127.08, 128.71	124.37, 125.08, 126.81, 128.29
9	143.77	144.34
10	31.27	33.51
11	79.47	79.34
12	70.91	72.88
13	162.35	163.27

FT-IR Spectrum

The FT-IR (using ATR) spectrum of R(+)-N-formyl-PAI was measured with a Thermo Scientific Nicolet 6700 FT-IR apparatus. The IR spectrum exhibits a typical absorption band of carbonyl vibration at 1658 cm^{-1} and acetylene vibration at 2118 and 3228.

Mass Spectroscopy (MS)

The mass spectrum of R(+)-N-formyl-PAI was performed on a Finnigan 4000 Quadropole Low Resolution Mass Spectrometer operating in the Electrospray Positive mode.

The spectrum exhibits quasi-molecular ions at m/z 200 $[MH^+]^+$ and 222 $[M+Na]^+$. The spectrum is in agreement with the molecular formula of R(+)-N-formyl-PAI.

Example 3 – Stability Study of Rasagiline Base Drug Substance:

Rasagiline base drug substance and delayed release tablets were subject to stability testing under various conditions. Rasagiline base drug substance was prepared according to procedures described in Examples 1-3 of United States Patent No. 7,968,749.

3.1. Degradation of melt Rasagiline base at elevated temperatures

The observed melting point of Rasagiline base is 38-41°C so it appears as a liquid melt at elevated temperatures. This is the reason for performing the degradation study of rasagiline base at 78° - 90°C in melt phase.

Samples of Rasagiline base were introduced into amber glass vials, closed with stoppers and covered with aluminium foil for protection from light. Samples intended to degrade under an inert atmosphere were flushed with nitrogen for 5 minutes before closing with a stopper.

The samples were introduced into a pre-heated oven and held at a constant temperature of 78 and 90°C for 24, 72 or 137 hrs. After completion of the treatment the samples were refrigerated and analyzed. The results are summarized in Table 3 below.

Table 3. Rasagiline base degradation in melt phase

Exp. No.	Atm.	Temp. deg. C	Time hrs	R(+)-N-formyl-PAI, % of Rasagiline
1	N_2	78	24	N.D.
2	N_2	78	72	N.D.

3	Air	78	24	0.14
4	Air	78	72	0.10
5	Air	90	24	0.08
6	Air	90	72	0.07
7	Air	90	137	0.07

N.D. – not detected

3.2. Degradation of Rasagiline base in solutions

3.2.1. Degradation at T=70-78°C

A series of experiments was performed to study formation of R(+)-N-formyl-PAI under intensive degradation of rasagiline base in solutions and to evaluate stability of rasagiline base in organic solvents and aqueous media at different pH at temperatures above 70°C.

Initial concentration of Rasagiline base in all solutions tested was 1 mg/ml. The solutions were exposed to heating in oven under air atmosphere in amber glass vials closed with Teflon stoppers and covered with aluminum foil for protection from light. After completion of the treatment the samples were refrigerated at 2-8°C and analyzed later using HPLC. The results are summarized in Table 4 below.

Table 4. Rasagiline base degradation in solution in air atmosphere, concentration – 1mg rasagiline/ml solution

Exp. No	Solvent	Temperature °C	Time hrs	R(+)-N-formyl-PAI, % of Rasagiline
1	Sulfuric acid 20%	RT	48	N.D.
2	Perchlorate buffer, pH=2.5	70	93	N.D.
		78	168	N.D.
3	Citric acid in water, pH=3.6*	78	168	N.D.
4	Acetate buffer, pH=4.1	70	93	N.D.
		78	168	N.D.
5	Phosphate buffer, pH=6.0	70	93	N.D.
		78	168	N.D.
6	Water, pH~8	70	93	N.D.

		78	168	N.D.
7	Ethanol	70	93	N.D.
		78	168	< 0.04
8	Heptane	70	93	N.D.

N.D. - not detected; *- Rasagiline mono citrate in excess of citric acid

3.2.2. Degradation in aqueous solution at T=90°C

An additional series of degradation experiments was performed at 90°C in order to achieve even higher degradation of Rasagiline in aqueous solutions.

For this series the treatment time was 1 and 2 weeks, and phosphate-citrate buffer (pH=2.6) and phosphate buffer (pH=8.0) were used.

The initial concentration of Rasagiline base in all solutions was 1 mg/ml. The solutions were exposed to heat in an oven under an air atmosphere in amber glass vials closed with Teflon stoppers and covered with aluminum foil for protection from light.

The samples were introduced into an oven pre-heated to 90°C and held at this temperature for 7 or 14 days. After completion of the treatment the samples were refrigerated at 2-8°C and analyzed. The results are summarized in Table 5 below.

Table 5. R(+)-N-formyl-PAI formation in Rasagiline base in aqueous solution at 90°C, air atmosphere, concentration - 1mg rasagiline/ml solution

Exp. No.	Solvent	Time Weeks	R(+)-N-formyl-PAI, % of Rasagiline
1	Phosphate-citrate buffer, pH=2.6	1	0.17
		2	0.26
2	Phosphate-citrate buffer 3.6	1	0.13
		2	0.11

3	Acetate buffer, pH=4.1	1	0.05
		2	N.D.
4	Phosphate buffer, pH=6.0	1	0.07
		2	0.16
5	Phosphate buffer, pH=8.0	1	0.22
		2	0.19

N.D. – not detected

At 90°C, R(+)-N-formyl-PAI was found in the solutions at levels above 0.1% area of Rasagiline. R(+)-N-formyl-PAI is more likely formed at lower pH. At pH=4.1 the rate of formation of R(+)-N-formyl-PAI is the lowest, that may be linked to the acetate buffer used in this solution.

3.2.3. Oxidation with peroxide in aqueous solutions

The concentration of Rasagiline base in all the oxidation experiments was 1 mg/ml.

Acetonitrile was used as co-solvent for fast and complete dissolution of solid rasagiline base in aqueous peroxide. The solutions were prepared in amber glass flasks with 16-20 mg of Rasagiline base and 2-3 ml acetonitrile. Then peroxide and water were added; complete dissolution of solid was achieved by shaking.

After holding at room temperature for 10 minutes to 20 hrs (oxidation time), the solutions were diluted with mobile phase and analyzed by HPLC. The results are summarized in Table 6 below.

Table 6. Rasagiline base oxidation with hydrogen peroxide in aqueous solution at room temperature

Exp. No.	Initial peroxide concentration (%)	Oxidation time hr:min	R(+)-N-formyl-PAI, % of Rasagiline
1	3	5:00	0.17
	3	20:00	0.23
2	1	0:35	N.D.

3	0.1	0:10	N.D.
	0.1	0:50	N.D.

N.D. – not detected

4. Humidity stress

Rasagiline base was exposed to high humidity (RH=100%) at room temperature for 7 days. The samples of the Rasagiline base after humidity stress and initial material (zero-time sample) were analyzed for purity assay. The analytical results showed that R(+)-N-formyl-PAI was not detected.

5. Discussion

The data demonstrates that R(+)-N-formyl-PAI forms when rasagiline base is subject to elevated temperature and not under inert environment.

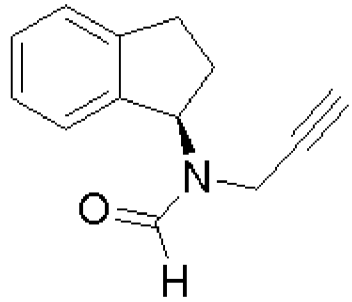
The data also demonstrates that R(+)-N-formyl-PAI is not detected when rasagiline base is present in different solutions at temperature up to 78°C. At 90°C, R(+)-N-formyl-PAI was found in the solutions and R(+)-N-formyl-PAI is more likely formed at lower pH.

It was found that R(+)-N-formyl-PAI also forms when rasagiline base is mixed in solution with oxidizers, such as peroxide at concentration of 3%, for a prolong time.

It was also found that R(+)-N-formyl-PAI does not form when solid rasagiline base is exposed to high humidity at room temperature for a prolong time.

What is claimed is:

1. An isolated compound having the structure:



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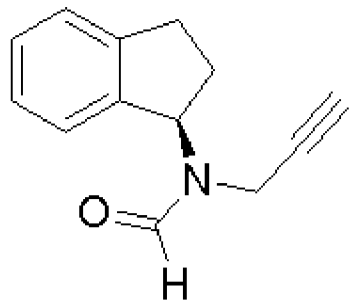
2. A composition comprising a compound having the structure:



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wherein the composition is free of rasagiline or a salt thereof.

3. A process for preparing R(+)-N-formyl-propargyl-aminoindan comprising the steps of:
   e) mixing R-(+)-N-Propargyl-1-aminoindan with formic acid in a first solvent at a temperature of less than 30°C;
   f) evaporating the first solvent to obtain an oil;
   g) dissolving the oil in a second solvent to form a solution; and
   h) isolating and obtaining R(+)-N-formyl-propargyl-aminoindan from the solution.

4. The process of claim 3, wherein the first solvent is acetic anhydride.

5. The process of claim 3 or 4, wherein the second solvent is ethyl acetate.

6. A pharmaceutical composition comprising rasagiline or a pharmaceutically acceptable salt thereof, citric acid, R(+)-N-formyl-propargyl-aminoindan, and at least one pharmaceutically acceptable carrier,
wherein R(+)-N-formyl-propargyl-aminoindan is present in the pharmaceutical composition in an amount greater than about 0.04% by weight, relative to the amount of rasagiline, based on a determination by a HPLC method.

7. The pharmaceutical composition of claim 6, wherein the amount of R(+)-N-formyl-propargyl-aminoindan is not more than about 0.5% by weight, relative to the amount of -rasagiline, based on a determination by a HPLC method.

8. The pharmaceutical composition of claim 6 or 7, wherein the pharmaceutical composition is less than one week old, and the temperature during the less than one week did not exceed ambient temperature.

9. The pharmaceutical composition of any one of claims 6-8, which comprises rasagiline as free base.

10. The pharmaceutical composition of any one of claims 6-8, which comprises the pharmaceutically acceptable salt of rasagiline, and which salt is rasagiline citrate.

11. The pharmaceutical composition of any one of claims 6-10, wherein the pharmaceutical composition is a solid pharmaceutical composition.

12. The pharmaceutical composition of claim 11, which is in tablet form.

13. The pharmaceutical composition of claim 12 having a core and a coating, wherein the core of the tablet comprises

an amount of rasagiline as free base, citric acid and mannitol.

14. The pharmaceutical composition of claim 13 wherein in the core of the tablet the weight ratio of mannitol to citric acid is between 45 to 1 and 10 to 1.

15. The pharmaceutical composition of claim 14 wherein in the core of the tablet the weight ratio of mannitol to citric acid is between 30 to 1 and 25 to 1.

16. The pharmaceutical composition of any one of claims 12-15 having a core and a coating, wherein the core of the tablet comprises an amount of rasagiline and citric acid, about 59.9% of mannitol, about 0.53% of aerosil, about 6.6% of starch NF, about 26.3% of pregelatinized starch, about 2.0% of stearic acid, and about 2.0% of talc, by weight, relative to the weight of the core of the tablet.

17. The pharmaceutical composition of claim 16, wherein the core of the tablet comprises an amount of rasagiline and citric acid, 45.5 mg of mannitol, 0.4 mg of aerosil, 5.0 mg of starch NF, 20.0 mg of pregelatinized starch, 1.5 mg of stearic acid, 1.5 mg of talc, and the coating of the tablet comprises two coating layers, of which the inner of the two coating layers comprises 3.5 mg of hypromellose and the outer of the two coating layers comprises 4.0 mg of methacrylic acid ethyl acrylate copolymer, 0.8 mg of triethyl citrate, and 1.9 mg of talc extra fine.

18. The pharmaceutical composition of any one of claims 12-17, wherein the amount of rasagiline in the core is 0.5 mg.

19. The pharmaceutical composition of any one of claims 12-15 having a core and a coating, wherein the core of the tablet comprises an amount of rasagiline and citric acid, about 59.2% of mannitol, about 0.53% of aerosil, about 6.6% of starch NF, about 26.3% of pregelatinized starch,

about 2.0% of stearic acid, and about 2.0% of talc, by weight, relative to the weight of the core of the tablet.

20. The pharmaceutical composition of claim 19, wherein the core of the tablet comprises an amount of rasagiline and citric acid, 45.0 mg of mannitol, 0.4 mg of aerosil, 5.0 mg of starch NF, 20.0 mg of pregelatinized starch, 1.5 mg of stearic acid, 1.5 mg of talc, and the coating of the tablet comprises two coating layers, of which the inner of the two coating layers comprises 3.5 mg of hypromellose and the outer of the two coating layers comprises 4.0 mg of methacrylic acid ethyl acrylate copolymer, 0.8 mg of triethyl citrate, and 1.9 mg of talc extra fine.

21. The pharmaceutical composition of any one of claims 12-15, 19 or 20, wherein the amount of rasagiline in the core is 1.0 mg.

22. The pharmaceutical composition of any one of claims 6-21, wherein not more than about 1.0% by weight of rasagiline citramide or a salt thereof is in the pharmaceutical composition relative to the amount of rasagiline, based on a determination by a HPLC method.

23. The pharmaceutical composition of any one of claims 6-22, wherein not more than about 1.0% by weight of R(+)-N-methyl-propargyl-aminoindan or a salt thereof is in the pharmaceutical composition relative to the amount of rasagiline, based on a determination by a HPLC method.

24. A process for preparing a pharmaceutical composition comprising rasagiline or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, comprising:

a) obtaining a batch of rasagiline or a pharmaceutically acceptable salt thereof;

b) analyzing the batch for the presence of R(+)-N-formyl-propargyl-aminoindan by a suitable apparatus;

and

c) preparing the pharmaceutical composition from the batch only if the batch is determined to have less than about 0.5% R(+)-N-formyl-propargyl-aminoindan by weight relative to the amount of rasagiline.

25. A process for preparing a packaged pharmaceutical composition comprising rasagiline or a pharmaceutically acceptable salt thereof comprising:

a) obtaining a pharmaceutical composition of rasagiline or a pharmaceutically acceptable salt thereof;

b) analyzing the pharmaceutical composition for the presence of R(+)-N-formyl-propargyl-aminoindan by a suitable apparatus; and

c) packaging the pharmaceutical composition only if the amount of R(+)-N-formyl-propargyl-aminoindan is not more than about 0.5% by weight relative to the amount of rasagiline.

26. A process of distributing a validated batch of a pharmaceutical composition comprising rasagiline or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier, comprising:

a) obtaining a batch of the pharmaceutical composition;

b) performing stability testing with a sample of the batch;

c) determining the total amount of R(+)-N-formyl-propargyl-aminoindan in the sample of the batch by a suitable apparatus after stability testing;

d) validating the batch for distribution only if the sample of the batch after stability testing is determined to have not more than about 1.0% by weight of R(+)-N-formyl-propargyl-aminoindan relative to the amount of rasagiline; and

e) distributing the validated batch.

27. The process of any one of claims 24-26, wherein the pharmaceutical composition comprises rasagiline free base.

28. The process of any one of claims 24-26, wherein the pharmaceutical composition comprises rasagiline citrate.

29. R(+)-N-formyl-propargyl-aminoindan for use, as a reference standard to detect trace amounts of N R(+)-N-formyl-propargyl-aminoindan in a pharmaceutical composition comprising rasagiline or a pharmaceutically acceptable salt of rasagiline.

30. A method for treating Parkinson's disease in a patient comprising administering to the patient an amount of the pharmaceutical composition of any one of claims 6-23 effective to treat Parkinson's disease in the patient.