

EXHIBIT EE

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Kramer et al.

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(54) **AMINO ACID COMPOUNDS**

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Dec. 17, 2008, now Pat. No. 8,034,836, which is a
continuation of application No. 11/950,273, filed on
Dec. 4, 2007, now Pat. No. 7,777,074.

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18, 2007.

(51) **Int. Cl.**
A61K 31/195 (2006.01)

(52) **U.S. Cl.** **514/561**; 514/563

(58) **Field of Classification Search** 514/561,
514/563

See application file for complete search history.

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(57) **ABSTRACT**

A method for increasing the bioabsorption of amino acids in
a human or animal is disclosed. The method includes admin-
istering to the human or animal a pharmaceutically effective
amount of an amino acid compound consisting essentially of
a nitrate or nitrite of an amino acid selected from the group
consisting of Arginine, Agmatine, Beta Alanine, Citrulline,
Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Nor-
valine, Ornithine, and Valine.

1 Claim, No Drawings

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AMINO ACID COMPOUNDS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation application of the earlier U.S. Utility patent application to Ronald Kramer, et. al. entitled "Amino Acid Compounds," application Ser. No. 12/336,938, filed Dec. 17, 2008, now pending, which is a continuation application of the earlier U.S. Utility patent application to Ronald Kramer, et. al. entitled "Amino Acid Compounds," application Ser. No. 11/950,273, filed Dec. 4, 2007, now U.S. Pat. No. 7,777,074, which application claims the benefit of the filing date of U.S. Provisional Patent Application 60/973,229 entitled "Amino Acid Compounds" to Ronald Kramer, et. al., filed on Sep. 18, 2007, the disclosures of all of which being hereby incorporated entirely herein by reference.

BACKGROUND

1. Technical Field

Aspects of this document relate generally to amino acid compounds.

2. Background

It is desirable to design new amino acid compounds that have properties lacking in conventional amino acids, conventional nitrates, and conventional nitrites.

SUMMARY

In one aspect, this document features a method for increasing the bioabsorption of amino acids in a human or animal is disclosed. The method includes administering to the human or animal a pharmaceutically effective amount of an amino acid compound consisting essentially of a nitrate or nitrite of an amino acid selected from the group consisting of Arginine, Agmatine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, Ornithine, and Valine.

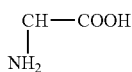
Implementations may comprise one or more of the following. The amino acid compound may further comprise a pharmaceutically acceptable additive, wherein the additive is one of a carrier, excipient, binder, colorant, flavoring agent, preservative, buffer, dilutant, and combinations thereof. The amino acid compound may be in the form of a capsule, tablet, pill, liquid, liquid suspension, vapor, gas, powder, granulate or pulverulence.

The foregoing and other aspects, features, and advantages will be apparent to those artisans of ordinary skill in the art from the DESCRIPTION and DRAWINGS, and from the CLAIMS.

DESCRIPTION

Overview

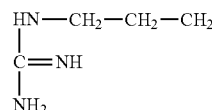
Compounds containing both a carboxyl group and an amino group are typically known as Amino Acids. Amino Acids typically have the basic formula X-R, wherein X is:



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Amino Acids typically differ from one another with respect to the structure of the R group. It is the structure of the R group that typically determines the individuality and character of each Amino Acid.

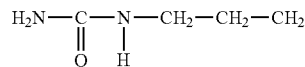
For example, the R group for the Amino Acid Arginine is:



Arginine is characterized as a nonessential Amino Acid. Specifically, Arginine can be independently manufactured by the human body, and does not need to be obtained directly through dietary intake. Arginine plays a significant role in healing, cell division, immune function, the elimination of ammonia from the body and the release of hormones. Arginine is presently used in the dietary supplement industry to supplement Arginine production in the body. Arginine is also presently used in the dietary supplement industry to boost Human Growth Hormone (HGH) production, increase vasodilation, enhance blood circulation, increase oxygen flow to the muscles, and boost Nitric Oxide (NO) production. Various supplemental Arginine forms are available in the consumer marketplace.

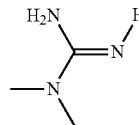
The vasodilating effect of ingested Arginine takes considerable time to manifest since Arginine requires extensive metabolism to yield Nitric Oxide (NO). Additionally, considerable amounts of Arginine are required to produce a significant vasodilating effect, with common doses ranging from eight to twenty-four grams per day.

The R group for the Amino Acid Citrulline is:



Citrulline is an alpha-Amino Acid naturally occurring in the human body, and does not need to be obtained directly through dietary intake. In vivo, Citrulline is made from the Amino Acid Ornithine, along with carbamoyl phosphate in one of the central reactions in the Urea Cycle. Citrulline is also produced during the metabolism of Arginine in the body. Citrulline is presently used in the dietary supplement industry to supplement Citrulline production in the body. By itself, Citrulline has no vasodilating properties. Citrulline is also water insoluble, which reduces its bioavailability and limits the forms in which Citrulline may be effectively used.

The R group for the Amino Acid Creatine is:



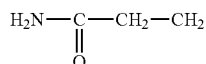
Creatine is a nonessential Amino Acid and is also a nitrogenous organic acid. Creatine is independently manufactured by the human body, and does not need to be obtained directly through dietary intake. Creatine plays a significant role in providing muscles with energy. Creatine is presently used in the dietary supplement industry to supplement Creatine production in the body. Creatine is also presently used in the

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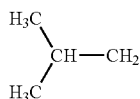
dietary supplement industry to increase muscle-mass gains, improve athletic performance and strength. Creatine, by itself, has no vasodilating properties. Citrulline is also water insoluble, which reduces its bioavailability and limits the forms in which Citrulline may be effectively used.

The R group for the Amino Acid Glutamine is:



Glutamine is a nonessential Amino Acid. Glutamine is the most abundant naturally occurring, non-essential amino acid in the human body and is found circulating in the blood, as well as stored in the skeletal muscles. Glutamine plays a significant role in protein synthesis, muscle growth, and wound healing. Glutamine is presently used in the dietary supplement industry to supplement Glutamine production in the body. Glutamine is also presently used in the dietary supplement industry to maintain the body's Glutamine pool. Glutamine, by itself, has no vasodilating properties. Glutamine is also water insoluble, which reduces its bioavailability and limits the forms in which Glutamine may be effectively used. Additionally, Glutamine inhibits Nitric Acid (NO) production through downregulation of eNOS synthase.

The R group for the Amino Acid Leucine is:



Leucine is an essential Amino Acid, meaning that Leucine is not synthesized in vivo in animals. Accordingly, Leucine must be ingested, usually as a component of proteins consumed directly through dietary intake. Leucine plays a significant role in muscle protein synthesis. Leucine can also inhibit protein degradation in skeletal muscle, as well as in the liver. Leucine is presently used in the dietary supplement industry to supplement dietary Leucine sources. Leucine is also presently used in the dietary supplement industry to promote anabolism and stimulate muscle protein synthesis. Leucine, by itself, has no vasodilating properties. Leucine is also water insoluble, which reduces its bioavailability and limits the forms in which Leucine may be effectively used.

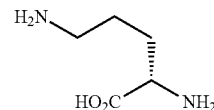
The R group for the Amino Acid Norvaline is:



Norvaline is a nonessential Amino Acid. Specifically, Norvaline can be independently manufactured by the human body, and does not need to be obtained directly through dietary intake. Norvaline is presently used in the dietary supplement industry to supplement Norvaline production in the body. Norvaline is also presently used in the dietary supplement industry to inhibit the enzyme arginase and thus reduce the conversion of Arginine to urea. Norvaline, by itself, has no vasodilating properties, although it enhances the vasodilating properties of Arginine. Norvaline is also water insoluble, which reduces its bioavailability and limits the forms in which Leucine may be effectively used.

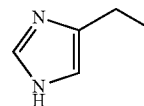
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The R group for the Amino Acid Ornithine is:



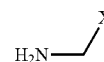
Ornithine is a non-essential Amino Acid. That is, Ornithine is independently manufactured by the human body, and does not need to be obtained directly through dietary intake. Ornithine plays a significant role in the synthesis of polyamines, specifically via the action of Ornithine decarboxylase. Ornithine is presently used in the dietary supplement industry to supplement dietary Ornithine sources. Ornithine is also presently used in the dietary supplement industry to enhance the vasodilating properties in a series of products commonly known as "NO Boosters." Ornithine exerts its vasodilating effect only by in vivo conversion to Arginine and then by following the pathway that converts Arginine to Nitric Acid (NO). Many grams of Ornithine, and a considerable amount of time, are required in order to assert its vasodilating effect.

The R group for the Amino Acid Histidine is:



Histidine is a naturally-occurring Amino Acid and is coded for in DNA. Relatively small shifts in cellular pH will change the electrical charge of Histidine. For this reason, Histidine finds its way into considerable use as a coordinating ligand in metalloproteins, and also as a catalytic site in certain enzymes. Histidine is currently used in the dietary supplement industry to support carnosine production. Histidine, by itself, has no vasodilating properties. Additionally, Histidine is very poorly water soluble, a fact that limits its bioavailability and utility. Histidine is presently used in the dietary supplement industry in the forms of single administration Histidine and Histidine HCl.

The R group for the Amino Acid Beta Alanine is:

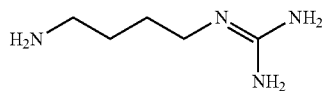


Beta Alanine is the only naturally-occurring Beta Amino Acid. A Beta Amino Acid is one in which the Amino group is located at the beta position (i.e. two atoms away) from the Carboxyl group. Beta Alanine is formed in vivo through the degradation of dihydrouracil and carnosine. Beta Alanine is the rate-limiting precursor of carnosine. Therefore, carnosine levels are limited by the amount of available Beta Alanine. Beta Alanine, by itself, has no vasodilating properties. Additionally, Beta Alanine is poorly water soluble, which limits its bioavailability and utility. Beta Alanine is presently used in the dietary supplement industry to support carnosine production.

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The chemical structure of Agmatine is:



Agmatine is the decarboxylation product of the Amino Acid Arginine and is an intermediate in polyamine biosynthesis. Agmatine is synthesized in the brain and stored in synaptic vesicles in regionally selective neurons. Agmatine is released by depolarization and is inactivated by agmatinase. Agmatine binds to alpha2-adrenoceptors and imidazoline binding sites. Agmatine likewise blocks N-methyl-D-aspartic acid (NMDA) receptor channels and other ligand-gated cationic channels. Additionally, agmatine inhibits nitric oxide synthase, and induces the release of some peptide hormones. Agmatine modulates nitric oxide through various mechanisms. Agmatine stimulates some types of nitric oxide synthase (NOS) while inhibiting others. Agmatine inhibits Nitric Oxide production by inhibiting NOS. Agmatine is presently used in the dietary supplement industry in the forms of single administration Agmatine and Agmatine Sulfate.

Nitrates are a class of compounds that are salts of Nitric Acid (HNO₃) and at least comprise one Nitrogen atoms and three Oxygen atoms (NO₃).

Nitrites are a class of compounds that are salts of Nitrous Acid (HNO₂) and at least comprise one Nitrogen atom and two Oxygen atoms (NO₂).

Nitrates and Nitrites are commercially available in various preparations and are used in various commercial applications. In the case of ingestion by humans, Nitrate (NO₃) is typically reduced to Nitrite (NO₂) in the epithelial cells of blood vessels. In vivo, Nitrite (NO₂) reacts with a thiol donor, principally glutathione, to yield Nitric Oxide (NO).

Terminology and Definitions

In describing implementations of an Amino Acid Compound, the following terminology will be used in accordance with the definitions and explanations set out below. Notwithstanding, other terminology, definitions, and explanations may be found throughout this document, as well.

As used herein, "Amino Acid" is a term used in its broadest sense and may refer to an Amino Acid in its many different chemical forms including a single administration Amino Acid, its physiologically active salts or esters, its combinations with its various salts, its tautomeric, polymeric and/or isomeric forms, its analog forms, its derivative forms, and/or its decarboxylation products. Amino Acids comprise, by way of non-limiting example: Agmatine, Beta Alanine, Arginine, Asparagine, Aspartic Acid, Cysteine, Glutamine, Glutamic Acid, Glycine, Histidine, Isoleucine, Leucine, Lysine, Methionine, PhenylBeta Alanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, and Valine.

As used herein, "Compound" is a term used in its broadest sense and may refer to an Amino Acid in combination with one of a Nitrate and a Nitrite.

As used herein, "Nitrate" is a term used in its broadest sense and may refer to an Nitrate in its many different chemical forms including a salt of Nitric Acid, a single administration Nitrate, its physiologically active salts or esters, its combinations with its various salts, its tautomeric, polymeric and/or isomeric forms, its analog forms, and/or its derivative forms. Nitrate comprises, by way of non-limiting example, many different chemical forms including dinitrate and trinitrate. Nitrates may be salts, or mixed salts, of Nitric Acid and comprise one Nitrogen atom and three Oxygen atoms. For the

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exemplary purposes of this disclosure, Nitrate may comprise salts of Nitrate such as sodium nitrate, potassium nitrate, barium nitrate, calcium nitrate, and the like. For the exemplary purposes of this disclosure, Nitrate may include mixed salts of Nitrate such as nitrate orotate, and the like. Additionally, for the exemplary purposes of this disclosure, Nitrate may comprise nitrate esters such as nitroglycerine, and the like.

As used herein, "Nitrite" is a term used in its broadest sense and may refer to an Nitrite in its many different chemical forms including a salt of Nitrous Acid, a single administration Nitrite, its physiologically active salts or esters, its combinations with its various salts, its tautomeric, polymeric and/or isomeric forms, its analog forms, and its derivative forms. Nitrite comprises, by way of non-limiting example, many different chemical forms including dinitrite and trinitrite. Nitrites may be salts, or mixed salts, of Nitrous Acid and comprise one Nitrogen atom and two Oxygen atoms. For the exemplary purposes of this disclosure, Nitrite may comprise salts of Nitrite such as sodium nitrite, potassium nitrite, barium nitrite, calcium nitrite, and the like. For the exemplary purposes of this disclosure, Nitrite may comprise mixed salts of Nitrite such as nitrite orotate, and the like. Additionally, for the exemplary purposes of this disclosure, Nitrite may comprise nitrite esters such as amyl nitrite, and the like.

As used herein, "pharmaceutically acceptable additive" or "additive" are terms used in their broadest sense. Particular implementations of the compositions described in this document may also comprise an additive (e.g. one of a solubilizer, an enzyme inhibiting agent, an anticoagulant, an antifoaming agent, an antioxidant, a coloring agent, a coolant, a cryoprotectant, a hydrogen bonding agent; a flavoring agent, a plasticizer, a preservative, a sweetener, a thickener, and combinations thereof) and/or a carrier (e.g. one of an excipient, a lubricant, a binder, a disintegrator, a diluent, an extender, a solvent, a suspending agent, a dissolution aid, an isotonicization agent, a buffering agent, a soothing agent, an amphiphilic lipid delivery system, and combinations thereof). These additives may be solids or liquids, and the type of additive may be generally chosen based on the type of administration being used. Those of ordinary skill in the art will be able to readily select suitable pharmaceutically effective additives from the disclosure in this document. In particular implementations, pharmaceutically acceptable additives may include, by non-limiting example, calcium phosphate, cellulose, stearic acid, croscarmellose cellulose, magnesium stearate, and silicon dioxide.

As used in this document, "pharmaceutically effective" is a phrase used in its broadest sense, including, by non-limiting example, effective in a clinical trial, for a specific patient, or only placebo-effective.

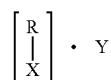
As used in this document, "Pharmaceutically acceptable" is a phrase used in its broadest sense and may describe ingredients of a pharmaceutical composition that meet Food and Drug Administration (FDA) standards, United States Pharmacopeial Standards (USP), US Department of Agriculture (USDA) standards for food-grade materials, commonly accepted standards of the nutritional supplement industry, industry standards, botanical standards, or standards established by any individual. These standards may delineate acceptable ranges of aspects of ingredients of a pharmaceutical composition such as edibility, toxicity, pharmacological effect, or any other aspect of a chemical, composition, or preparation used in implementations of a pharmaceutical composition.

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Compounds/Components

A first implementation is an Arginine compound of the formula:



wherein;

R is the Arginine group identified and defined above;

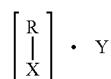
X is the Amino Acid base identified and defined above; and

Y is selected from the group consisting of a Nitrate and a

Nitrite.

Applicants have cost-effectively synthesized Arginine Nitrate by combining nitric acid and Arginine, mixing with water, and leaving to crystallize. Further nitratization can take place, yielding Arginine Dinitrate or Arginine Trinitrate. An alternative implementation may comprise using Nitrous Acid (HNO₂) instead of Nitric Acid (HNO₃), thus yielding Arginine Nitrite. Arginine Nitrite has the same effects as Arginine Nitrate, the only difference being that it requires one less step to yield Nitric Oxide (NO—). Mixed salts may also be used, such as in the non-limiting example of Arginine Nitrate-Orotate.

A second implementation is a Citrulline compound of the formula:



wherein;

R is the Citrulline group identified and defined above;

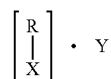
X is the Amino Acid base identified and defined above; and

Y is selected from the group consisting of a Nitrate and a

Nitrite.

Applicants have cost-effectively synthesized Citrulline Nitrate by combining nitric acid and Citrulline, mixing with water, and leaving to crystallize. Further nitratization can take place, yielding Citrulline Dinitrate or Citrulline Trinitrate. An alternative implementation may comprise using Nitrous Acid (HNO₂) instead of Nitric Acid (HNO₃), thus yielding Citrulline Nitrite. Citrulline Nitrite has the same effects as Citrulline Nitrate, the only difference being that it requires one less step to yield Nitric Oxide (NO—). Mixed salts may also be used, such as in the non-limiting example of Citrulline Nitrate-Orotate.

A third implementation is a Creatine compound of the formula:



wherein;

R is the Creatine group identified and defined above;

X is the Amino Acid base identified and defined above; and

Y is selected from the group consisting of a Nitrate and a

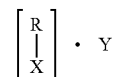
Nitrite.

Applicants have cost-effectively synthesized Creatine Nitrate by combining nitric acid and Creatine, mixing with water, and leaving to crystallize. Further nitratization can take

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place, yielding Creatine Dinitrate or Creatine Trinitrate. An alternative implementation may comprise using Nitrous Acid (HNO₂) instead of Nitric Acid (HNO₃), thus yielding Creatine Nitrite. Creatine Nitrite has the same effects as Creatine Nitrate, the only difference being that it requires one less step to yield Nitric Oxide (NO—). Mixed salts may also be used, such as in the non-limiting example of Creatine Nitrate-Orotate.

A fourth implementation is a Glutamine compound of the formula:



wherein;

R is the Glutamine group identified and defined above;

X is the Amino Acid base identified and defined above; and

Y is selected from the group consisting of a Nitrate and a

Nitrite.

Applicants have cost-effectively synthesized Glutamine Nitrate by combining nitric acid and Glutamine, mixing with water, and leaving to crystallize. Further nitratization can take place, yielding Glutamine Dinitrate or Glutamine Trinitrate. An alternative implementation comprises using Nitrous Acid (HNO₂) instead of Nitric Acid (HNO₃), thus yielding Glutamine Nitrite. Glutamine Nitrite has the same effects as Glutamine Nitrate, the only difference being that it requires one less step to yield Nitric Oxide (NO—). Mixed salts may also be used, such as in the non-limiting example of Glutamine Nitrate-Orotate.

A fifth implementation is a Leucine compound of the formula:



wherein;

R is the Leucine group identified and defined above;

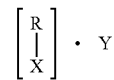
X is the Amino Acid base identified and defined above; and

Y is selected from the group consisting of a Nitrate and a

Nitrite.

Applicants have cost-effectively synthesized Leucine Nitrate by combining nitric acid and Leucine, mixing with water, and leaving to crystallize. Further nitratization can take place, yielding Leucine Dinitrate or Leucine Trinitrate. An alternative implementation comprises substituting the Amino Acids Valine or Isoleucine for Leucine. Another alternative implementation comprises substituting Nitrous Acid (HNO₂) for Nitric Acid (HNO₃), thus yielding Leucine Nitrite. Leucine Nitrite has the same effects as Leucine Nitrate, the only difference being that it requires one less step to yield Nitric Oxide (NO—). Mixed salts may also be used, such as in the non-limiting example of Leucine Nitrate-Orotate.

A sixth implementation is a Norvaline compound of the formula:



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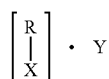
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wherein;

R is the Norvaline group identified and defined above;
X is the Amino Acid base identified and defined above; and
Y is selected from the group consisting of a Nitrate and a Nitrite.

Applicants have cost-effectively synthesized Norvaline Nitrate by combining nitric acid and Norvaline, mixing with water, and leaving to crystallize. Further nitratization can take place, yielding Norvaline Dinitrate or Norvaline Trinitrate. An alternative implementation comprises substituting Nitrous Acid (HNO₂) for Nitric Acid (HNO₃), thus yielding Norvaline Nitrite. Norvaline Nitrite has the same effects as Norvaline Nitrate, the only difference being that it requires one less step to yield Nitric Oxide (NO—). Mixed salts may also be used, such as in the non-limiting example of Norvaline Nitrate-Orotate.

A seventh implementation is an Ornithine compound of the formula:

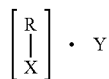


wherein;

R is the Ornithine group identified and defined above;
X is the Amino Acid base identified and defined above; and
Y is selected from the group consisting of a Nitrate and a Nitrite.

Applicants have cost-effectively synthesized Ornithine Nitrate by combining nitric acid and Ornithine, mixing with water, and leaving to crystallize. Further nitratization can take place, yielding Ornithine Dinitrate or Ornithine Trinitrate. An alternative implementation comprises using Nitrous Acid (HNO₂) instead of Nitric Acid (HNO₃), thus yielding Ornithine Nitrite. Ornithine Nitrite has the same effects as Ornithine Nitrate, the only difference being that it requires one less step to yield Nitric Oxide (NO—). Mixed salts may also be used, such as in the non-limiting example of Ornithine Nitrate-Orotate.

An eighth implementation is a Histidine compound of the formula:



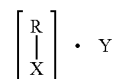
wherein;

R is the Histidine group identified and defined above;
X is the Amino Acid base identified and defined above; and
Y is selected from the group consisting of a Nitrate and a Nitrite.

Applicants have cost-effectively synthesized Histidine Nitrate by combining nitric acid and Histidine, mixing with water, and leaving to crystallize. Further nitratization can take place, yielding Histidine Dinitrate or Histidine Trinitrate. An alternative implementation comprises using Nitrous Acid (HNO₂) instead of Nitric Acid (HNO₃), thus yielding Histidine Nitrite. Histidine Nitrite has the same effects as Histidine Nitrate, the only difference being that it requires one less step to yield Nitric Oxide (NO—). Mixed salts may also be used, such as in the non-limiting example of Histidine Nitrate-Orotate.

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A ninth implementation is a Beta Alanine compound of the formula:

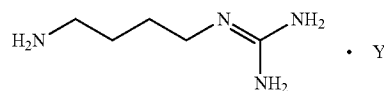


wherein;

R is the Beta Alanine group identified and defined above;
X is the Amino Acid base identified and defined above; and
Y is selected from the group consisting of a Nitrate and a Nitrite.

Applicants have cost-effectively synthesized Beta Alanine Nitrate by combining nitric acid and Beta Alanine, mixing with water, and leaving to crystallize. Further nitratization can take place, yielding Beta Alanine Dinitrate or Beta Alanine Trinitrate. An alternative implementation comprises using Nitrous Acid (HNO₂) instead of Nitric Acid (HNO₃), thus yielding Beta Alanine Nitrite. Beta Alanine Nitrite has the same effects as Beta Alanine Nitrate, the only difference being that it requires one less step to yield Nitric Oxide (NO—). Mixed salts may also be used, such as in the non-limiting example of Beta Alanine Nitrate-Orotate.

A tenth implementation is an Agmatine compound of the formula:



wherein;

Y is selected from the group consisting of a Nitrate and a Nitrite.

Applicants have cost-effectively synthesized Agmatine Nitrate by combining nitric acid and Agmatine, mixing with water, and leaving to crystallize. Further nitratization can take place, yielding Agmatine Dinitrate or Agmatine Trinitrate. An alternative implementation comprises using Nitrous Acid (HNO₂) instead of Nitric Acid (HNO₃), thus yielding Agmatine Nitrite. Agmatine Nitrite has the same effects as Agmatine Nitrate, the only difference being that it requires one less step to yield Nitric Oxide (NO—). Mixed salts may also be used, such as in the non-limiting example of Agmatine Nitrate-Orotate.

Compositions and/or formulations may be administered in any form, including one of a capsule, a cachet, a pill, a tablet, a powder, a granule, a pellet, a bead, a particle, a troche, a lozenge, a pastille, a solution, an elixir, a syrup, a tincture, a suspension, an emulsion, a mouthwash, a spray, a drop, an ointment, a cream, a gel, a paste, a transdermal patch, a suppository, a pessary, cream, a gel, a paste, a foam, and combinations thereof for example. Compositions and/or formulations may also include an acceptable additive (e.g. one of a solubilizer, an enzyme inhibiting agent, an anticoagulant, an antifoaming agent, an antioxidant, a coloring agent, a coolant, a cryoprotectant, a hydrogen bonding agent, a flavoring agent, a plasticizer, a preservative, a sweetener, a thickener, and combinations thereof) and/or an acceptable carrier (e.g. one of an excipient, a lubricant, a binder, a disintegrator, a diluent, an extender, a solvent, a suspending agent, a dissolution aid, an isotonicization agent, a buffering agent, a soothing agent, an amphipathic lipid delivery system, and combinations thereof).

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Implementations of Amino Acid Nitrate and/or Nitrite Compounds may also be synthesized or created in a wide variety of manners, and may be made from a wide variety of materials. Those of ordinary skill in the art will readily be able to select appropriate materials and methods to manufacture and use the compounds disclosed herein.

Dosage Forms

Implementations of Amino Acid Compounds may conveniently be presented in unit dosage form. Unit dosage formulations may be those containing a daily dose or unit, a daily sub-dose, or an appropriate fraction thereof, of the administered components as described herein.

A dosage unit may include an Amino Acid Compound. In addition, a dosage unit may include an Amino Acid Compound admixed with a pharmaceutically acceptable additive(s), and/or any combination thereof.

The dosage units may be in a form suitable for administration by standard routes. In general, the dosage units may be administered, by non-limiting example, by the topical (including buccal and sublingual), transdermal, oral, rectal, ophthalmic (including intravitreal or intracameral), nasal, vaginal, and/or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intratracheal, and epidural) routes.

For the exemplary purposes of this disclosure, oral delivery may be a particularly advantageous delivery route for administration to humans and animals of implementations of a pharmaceutical composition, optionally formulated with appropriate pharmaceutically acceptable additives to facilitate administration.

Manufacture

Implementations of an Amino Acid Compound may be made using conventional or other procedures. Accordingly, although there are a variety of method implementations for producing pharmaceutical compositions, for the exemplary purposes of this disclosure, a method implementation for producing an Amino Acid Compound may comprise: measuring specific quantities of Amino Acid, Nitric or Nitrous Acid and water mixed in a specific order the measured quantities of Amino Acid, Nitric or Nitrous Acid and water, and any additional pharmaceutically acceptable additives or inert ingredients, and then separating the pharmaceutical composition into discrete quantities for distribution and/or administration.

Measuring specific quantities of Amino Acid, Nitric or Nitrous Acid and water, and pharmaceutically acceptable additives or inert ingredients, may involve any number of steps and implementing components, and measuring specific quantities of Amino Acid, Nitric or Nitrous Acid and water, and pharmaceutically acceptable additives or inert ingredients, may be accomplished readily from this disclosure. For the exemplary purposes of this disclosure, measuring specific quantities of Amino Acid, Nitric or Nitrous Acid and water, and pharmaceutically acceptable additives or inert ingredients, may comprise using a scale, a solid or liquid dispensing apparatus, or other measurement device capable of measuring solid mass or liquid volume to produce a desired quantity of Amino Acid, Nitric or Nitrous Acid and water, and pharmaceutically acceptable ingredient.

It should be appreciated that any of the components of particular implementations of an Amino Acid Compound may be used as supplied commercially, or may be preprocessed by, by non-limiting example, any of the methods and techniques of agglomeration, air suspension chilling, air suspension drying, balling, coacervation, comminution, compression, pelletization, cryopelletization, extrusion, granulation, homogenization, inclusion Compoundation,

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lyophilization, melting, mixed, molding, pan coating, solvent dehydration, sonication, spheronization, spray chilling, spray congealing, spray drying, or other processes known in the art depending in part on the dosage form desired. The various components may also be pre-coated or encapsulated as known in the art. It will also be clear to one of ordinary skill in the art that appropriate additives may also be introduced to the composition or during the processes to facilitate the preparation of the dosage forms, depending on the need of the individual process.

Mixing the measured quantities of Amino Acid, Nitric or Nitrous Acid and water, and pharmaceutically acceptable additives or inert ingredients, may involve any number of steps and implementing components, and may be accomplished readily from this disclosure. For the exemplary purposes of this disclosure, mixed the measured quantities of Amino Acid, Nitric or Nitrous Acid and water, and pharmaceutically acceptable additives or inert ingredients, may comprise combining the measured quantities of m Amino Acid, Nitric or Nitrous Acid and water, and pharmaceutically acceptable additives or inert ingredients, under the influence of physical, ultrasonic, or electrostatic forces to create a desired degree of intermingling and/or chemical reaction of the Amino Acid, Nitric or Nitrous Acid and water and any pharmaceutically acceptable ingredients. The mixed may be accomplished when the Amino Acid, Nitric or Nitrous Acid and water and/or any pharmaceutically acceptable ingredients are in a solid, liquid, or semisolid state.

Separating the Amino Acid Compound into discrete quantities for distribution may involve any number of steps and implementing components, and separating the Amino Acid Compound into discrete quantities for distribution may be accomplished readily from this disclosure. For the exemplary purposes of this disclosure, separating the Amino Acid Compound into discrete quantities for distribution may involve utilizing a specific piece of equipment, for example, a conventional tablet forming apparatus to shape the formed composition into individual tablets, each containing a desired dose of Amino Acid Compound. The separating process may be accomplished when the Amino Acid Compound is in a solid, liquid, or semisolid state.

Those of ordinary skill in the art will be able to readily select manufacturing equipment and pharmaceutically acceptable additives or inert ingredients to manufacture implementations of an Amino Acid Compound. For the exemplary purposes of this disclosure, some examples of pharmaceutically acceptable additives or inert ingredients and manufacturing process are included below, particularly those that relate to manufacture of implementations of an Amino Acid Compound in tablet form. Notwithstanding the specific examples given, it will be understood that those of ordinary skill in the art will readily appreciate how to manufacture implementations of an Amino Acid Compound according to the other methods of administration and delivery disclosed in this document.

A particular implementation of an Amino Acid Compound may include a lubricant. Lubricants are any anti-sticking agents, glidants, flow promoters, and the like materials that perform a number of functions in tablet manufacture, for example, such as improving the rate of flow of the tablet granulation, preventing adhesion of the tablet material to the surface of the dies and punches, reducing interparticle friction, and facilitating the ejection of the tablets from the die cavity. Lubricants may comprise, for example, magnesium stearate, calcium stearate, talc, and colloidal silica.

Particular implementations of an Amino Acid Compound may also include a binder. Binders are any agents used to

impart cohesive qualities to powdered material through particle-particle bonding. Binders may include, for example, matrix binders (e.g. dry starch, dry sugars), film binders (e.g. celluloses, bentonite, sucrose), and chemical binders (e.g. polymeric cellulose derivatives, such as methyl cellulose, carboxy methyl cellulose, and hydroxy propyl cellulose); and other sugar, gelatin, non-cellulosic binders and the like.

Disintegrators may be used in particular implementations of an Amino Acid Compound to facilitate the breakup or disintegration of tablets after administration. Disintegrators may include, for example, starch, starch derivatives, clays (e.g. bentonite), algins, gums (e.g. guar gum), cellulose, cellulose derivatives (e.g. methyl cellulose, carboxymethyl cellulose), croscarmellose sodium, croscarmellose cellulose, and other organic and inorganic materials.

Implementations of an Amino Acid Compound may include diluents, or any inert substances added to increase the bulk of the Amino Acid Compound to make a tablet a practical size for compression. Diluents may include, for example, calcium phosphate, calcium sulfate, lactose, mannitol, magnesium stearate, potassium chloride, and citric acid, among other organic and inorganic materials.

Buffering agents may be included in an Amino Acid Compound and may be any one of an acid and a base, where the acid is, for example, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, or toluenesulfonic acid, and the base is, for example, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, and other organic and inorganic chemicals.

Implementations of an Amino Acid Compound may also be administered through use of amphipathic lipid delivery systems (such as liposomes and unilamellar vesicles), caplet systems, oral liquid systems, parenteral and/or intravenous systems, topical systems (creams, gels, transdermal patches, etc.), intranasal systems, rectal or vaginal systems, and many other delivery methods and/or systems known to those of ordinary skill in the art. Those of ordinary skill in the art will readily be able to select additional pharmaceutically acceptable additives to enable delivery of implementations of a pharmaceutical composition from the disclosure in this document.

With respect to delivery of particular implementations of an Amino Acid Compound, for the exemplary purposes of this disclosure, tablets may be utilized. Tablets are any solid pharmaceutical dosage form containing a pharmaceutically acceptable active agent or agents to be administered with or without suitable pharmaceutically acceptable additives and prepared either by compression or molding methods well known in the art. Tablets have been in widespread use and remain popular as a dosage form because of the advantages afforded both to the manufacturer (e.g., simplicity and economy of preparation, stability, and convenience in packaging, shipping, and dispensing) and the patient (e.g., accuracy of dosage, compactness, portability, blandness of taste, and ease of administration). Although tablets are most frequently discoid in shape, they may also be round, oval, oblong, cylindrical, rectangular or triangular, for example. The tablets may be optionally scored so that they may be separated into different dosages. They may differ greatly in size and weight depending on the amount of the pharmaceutically acceptable active agent or agents present and the intended route of administration. They are divided into two general classes, (1) compressed tablets, and (2) molded tablets.

Tablets and other orally discrete dosage forms, such as capsules, cachets, pills, granules, pellets, beads, and particles, for example, may optionally be coated with one or more enteric coatings, seal coatings, film coatings, barrier coatings, compress coatings, fast disintegrating coatings, or enzyme degradable coatings for example. Multiple coatings may be applied for desired performance. Further, dosage forms may be designed for, by non-limiting example, immediate release, pulsatile release, controlled release, extended release, delayed release, targeted release, synchronized release, or targeted delayed release. For release/absorption control, carriers may be made of various component types and levels or thicknesses of coats. Such diverse carriers may be blended in a dosage form to achieve a desired performance. In addition, the dosage form release profile may be effected by a polymeric matrix composition, a coated matrix composition, a multi-particulate composition, a coated multi-particulate composition, an ion-exchange resin-based composition, an osmosis-based composition, or a biodegradable polymeric composition.

While manufacture of implementations of an Amino Acid Compound have been described in particular sequences of steps and/or in particular forms, it will be understood that such manufacture is not limited to the specific order of steps or forms as disclosed. Any steps or sequences of steps of manufacture of implementations of an Amino Acid Compound in any form are given as examples of possible steps or sequences of steps or potential forms and not as limitations, since many possible manufacturing processes and sequences of steps may be used to manufacture Amino Acid Compound implementations in a wide variety of forms.

Use

Implementations of an Amino Acid Compound are particularly useful in increasing vasodilation in humans and animals. However, implementations are not limited to uses relating to vasodilation modification, and the like. Rather, any description relating to the foregoing is for the exemplary purposes of this disclosure. It will be understood that implementations of an Amino Acid Compound may encompass a variety of uses and are not limited in their uses. For example, possible uses may be, by non-limiting example, prevention of Nitrate tolerance, enhanced water solubility, increased distribution to muscles, and/or countering Nitric Oxide inhibiting effects of certain Amino Acids.

In conventional preparations of Nitrate compounds, "tolerance," a particular side effect, has been observed in many patients. This is unfortunate because the effectiveness of Nitrate on vasodilation is well documented. "Tolerance" occurs when a subject's reaction to Nitrate decreases so that larger doses are required to achieve the same effect. A Mar. 3, 2000 report in the British Journal of Pharmacology indicates that "tolerance to the dilator effects of nitrates remains a persisting therapeutic problem." Raymond J. MacAllister "Arginine and Nitrate Tolerance" available at <http://www.nature.com/bjp/journal/v130/n2/full/0703340a.html>, the contents of which are hereby incorporated herein by reference.

Empirical studies indicate that Nitrates are useful for their vasodilating effects. Common Nitrates include nitroglycerin and isosorbide dinitrate. Nitrates exert their vasodilating effect through their reduction to Nitrites. In vivo, Nitrates are reduced to Nitrites and, in the blood vessels' epithelial cells, Nitrite reacts with a thiol donor (mainly glutathione) to yield Nitric Oxide. Louis J. Ignarro, "After 130 years, the Molecular Mechanism of Action of Nitroglycerin is Revealed" (Jun. 11, 2002) available at <http://www.pnas.org/cgi/content/full/99/12/7816?ck=nck>, the contents of which are hereby incorporated herein by reference.

The Nitric Oxide inhibiting characteristics of the Amino Acid Glutamine have been well documented in a number of studies. In particular, a Mar. 28, 2006 report in the American Journal of Physiology has found that Glutamine inhibits Nitric Oxide production by downregulation of eNOS synthase. Masao Kakoki, et al. "Amino acids as Modulators of Endothelium-Derived Nitric Oxide." available at <http://ajpre-nal.physiology.org/cgi/content/full/291/2/F297>, the contents of which are hereby incorporated by reference.

A January 2006 *Journal of Nutrition* report indicates that the Amino Acid Leucine promotes anabolism and stimulates muscle protein synthesis. Michael J. Rennie, et al. "Branched-Chain Amino Acids as Fuels and Anabolic Signals in Human Muscle" available at <http://jn.nutrition.org/cgi/content/full/136/1/264S>, the contents of which are hereby incorporated by reference.

Empirical studies indicate that the Amino Acid Norvaline inhibits the enzyme arginase and thus decreases the rate of conversion of the Amino Acid Arginine to urea. Takeyori Saheki, et al. "Regulation of Urea Synthesis in Rat Liver" available at http://jeb.oxfordjournals.org/cgi/content/abstract/86/3/745?ijkey=5d134456b7443ca36c809269462276e532549798&keytype2=tf_ipsecsha, the contents of which are hereby incorporated by reference.

An October 2004 *Journal of Nutrition* report indicates that the Amino Acid Ornithine promotes anabolism and stimulates muscle protein synthesis. Michael J. Rennie, et al. "Branched-Chain Amino Acids as Fuels and Anabolic Signals in Human Muscle" available at <http://jn.nutrition.org/cgi/content/full/136/1/264S>, the contents of which are hereby incorporated by reference.

Empirical studies indicate that the Amino Acids Beta-Beta Alanine and L-Histidine support carnosine production. M. Dunnett, "Influence of Oral Beta-Beta Alanine and L-Histidine Supplementation on the Carnosine Content of the Gluteus Medius" *Equine Veterinary Journal Supplement*, available at <http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=10659307&ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed>. Pubmed, the contents of which are hereby incorporated by reference.

Empirical studies further indicate that the Amino Acids Beta Alanine and L-Histidine increase muscle power, recuperation and stamina. Yoshihiro Suzuki "High Level of Skeletal Muscle Carnosine Contributes to the Latter Half of Exercise Performance During 30-S Maximal Cycle Ergometer Sprinting" in the *Japanese Journal of Physiology*, available at http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12139778&ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum, the contents of which are hereby incorporated by reference.

Accordingly, Applicants have discovered that the Arginine compound according to the first implementation, when ingested, provides enhanced Nitric Oxide (NO—) production while providing improved vasodilation effects over single administration of Arginine, the single administration of Nitrates, or the single administration of Nitrites. Improved vasodilation may, in turn, provide better circulation and distribution of Arginine in the body. Absorption may be improved since Amino Acid salts with inorganic acids are much more water soluble than single administration Amino Acids. Applicants have also discovered that the vasodilating effect of Arginine Nitrate manifests faster than that of single-administration Arginine, and as fast as any nitrate, since the NO₃— group of the salt requires minimal conversion to yield Nitric Oxide. Additionally a much lesser dose may be

required for vasodilation to take place, compared to the single administration of Arginine. Likewise, the development of tolerance to the nitrate component of the molecule may be prevented with the presence of Arginine. Arginine Nitrate may promote vasodilation through production of Nitric Oxide by two different pathways, the Arginine citrullization pathway and the nitrate reduction pathway. Arginine Nitrate may likewise be more water soluble than single administration Arginine.

Accordingly, Applicants have discovered that the Citrulline compound according to the second implementation, when ingested, provides enhanced Nitric Oxide (NO—) production while providing improved vasodilation effects over single administration of Citrulline, the single administration of Nitrates, or the single administration of Nitrites. Improved vasodilation may, in turn, provide better circulation and distribution of Citrulline in the body. Absorption may be improved since Amino Acid salts with inorganic acids are much more water soluble than single administration Amino Acids. Additionally a much lesser dose may be required for vasodilation to take place, compared to the single administration of Citrulline or nitrates. Citrulline Nitrate is likewise more water soluble than single administration Citrulline.

Accordingly, Applicants have discovered that the Creatine compound according to the third implementation, when ingested, provides enhanced Nitric Oxide (NO—) production while providing improved vasodilation effects over single administration of Creatine, the single administration of Nitrates, or the single administration of Nitrites. Improved vasodilation may, in turn, provide better circulation and distribution of Creatine in the body. Absorption may be improved since Amino Acid salts with inorganic acids are much more water soluble than single administration Amino Acids. Additionally a much lesser dose may be required for vasodilation to take place, compared to the single administration of nitrates. Creatine Nitrate is likewise more water soluble than single administration Creatine.

Accordingly, Applicants have discovered that the Glutamine compound according to the fourth implementation, when ingested, counters the Nitric Oxide (NO—) inhibiting characteristics of Glutamine. Absorption of Glutamine may be improved since Amino Acid salts with inorganic acids are much more water soluble than single administration Amino Acids. Additionally a much lesser dose may be required for vasodilation to take place, compared to the single administration of nitrates. Glutamine Nitrate may likewise be more water soluble than single administration Glutamine.

Accordingly, Applicants have discovered that the Leucine compound according to the fifth implementation, when ingested, provides enhanced Nitric Oxide (NO—) production while providing improved vasodilation effects over single administration of Leucine, the single administration of Nitrates, or the single administration of Nitrites. Improved vasodilation may, in turn, provide better circulation and distribution of Leucine in the body. Absorption may be improved since Amino Acid salts with inorganic acids are much more water soluble than single administration Amino Acids. Additionally a much lesser dose may be required for vasodilation to take place, compared to the single administration of nitrates. Leucine Nitrate is likewise more water soluble than single administration Leucine.

Accordingly, Applicants have discovered that the Norvaline compound according to the sixth implementation, when ingested, promotes vasodilation through the inhibition of arginase, while promoting Nitric Oxide formation via the nitrate mechanism. Improved vasodilation may, in turn, provide better circulation and distribution of Norvaline in the

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body. Absorption may be improved since Amino Acid salts with inorganic acids are much more water soluble than single administration Amino Acids. Additionally a much lesser dose may be required for vasodilation to take place, compared to the single administration of nitrates. Norvaline Nitrate may likewise be more water soluble than single administration Norvaline.

Accordingly, Applicants have discovered that the Ornithine compound according to the seventh implementation, when ingested, provides an additional vasodilation mechanism, reducing the amount of Ornithine needed and the amount of time needed for the vasodilating properties to manifest. Improved vasodilation may, in turn, provide better circulation and distribution of Ornithine in the body. Absorption may be improved since Amino Acid salts with inorganic acids are much more water soluble than single administration Amino Acids. Applicants have also discovered that Ornithine Nitrate begins acting as fast as any other nitrate, since the NO_3 — group of the salt requires minimal conversion to yield Nitric Oxide. Additionally, a much lesser dose may be required for vasodilation to take place, compared to the single administration of nitrates. Ornithine Nitrate may likewise be more water soluble than single administration Ornithine.

Accordingly, Applicants have discovered that the Histidine compound according to the eighth implementation, when ingested, provides a vasodilation mechanism. Vasodilation may, in turn, provide better circulation and distribution of Histidine in the body. Applicants have likewise discovered that the Histidine compound according to the ninth implementation, when ingested, promotes carnosine production, thus increasing muscle power, endurance and recuperation. Absorption may be improved since Amino Acid salts with inorganic acids are much more water soluble than single administration Amino Acids. Applicants have also discovered that Histidine Nitrate begins acting as fast as any other nitrate, since the NO_3 — group of the salt requires minimal conversion to yield Nitric Oxide. Additionally, a much lesser dose may be required for vasodilation to take place, compared to the single administration of nitrates. Histidine Nitrate may likewise be more water soluble than single administration Histidine.

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Accordingly, Applicants have discovered that the Beta Alanine compound according to the ninth implementation, when ingested, provides vasodilation. Vasodilation may, in turn, provide better circulation and distribution of Beta Alanine in the body. Applicants have likewise discovered that the Beta Alanine compound according to the tenth implementation, when ingested, promotes carnosine production, thus increasing muscle power, endurance and recuperation. Absorption may be improved since Amino Acid salts with inorganic acids are much more water soluble than single administration Amino Acids. Applicants have also discovered that Beta Alanine Nitrate begins acting as fast as any other nitrate, since the NO_3 — group of the salt requires minimal conversion to yield Nitric Oxide. Additionally, a much lesser dose may be required for vasodilation to take place, compared to the single administration of nitrates. Beta Alanine Nitrate may likewise be more water soluble than single administration Beta Alanine.

Accordingly, Applicants have discovered that the Agmatine compound according to the eighth implementation, when ingested, counteracts the Nitric Oxide inhibiting effect of single administration Agmatine. Absorption may be improved since Amino Acid salts with inorganic acids are much more water soluble than single administration Amino Acids. Applicants have also discovered that Agmatine Nitrate begins acting as fast as any other nitrate, since the NO_3 — group of the salt requires minimal conversion to yield Nitric Oxide. Agmatine Nitrate may likewise be more water soluble than single administration Agmatine.

The invention claimed is:

1. A method for increasing the bioabsorption of amino acids in a human or animal, the method comprising administering to the human or animal a pharmaceutically effective amount of an amino acid compound consisting essentially of a nitrate or nitrite of an amino acid selected from the group consisting of Arginine, Agmatine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, Ornithine, and Valine.

* * * * *

EXHIBIT F



US008952046B1

(12) **United States Patent**
Kramer et al.

(10) **Patent No.:** **US 8,952,046 B1**
(45) **Date of Patent:** ***Feb. 10, 2015**

- (54) **AMINO ACID COMPOSITIONS**
- (71) Applicant: **ThermoLife International, LLC**,
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Alexander Nikolaidis, New Kallikratia
(GR)
- (73) Assignee: **ThermoLife International, LLC**,
Phoenix, AZ (US)
- (*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-
claimer.

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Primary Examiner — Rei-tsang Shiao
(74) *Attorney, Agent, or Firm* — Booth Udall Fuller, PLC

(57) **ABSTRACT**

A composition and a supplement formulation includes: at least one constituent selected from the group consisting of a nitrate salt, a nitrite salt, and both; and at least one constituent amino acid selected from the group consisting of Arginine, Agmatine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, Ornithine, Valine, Aspartic Acid, Cysteine, Glycine, Lysine, Methionine, Proline, Tyrosine, and Phenylalanine.

14 Claims, No Drawings

Related U.S. Application Data

- (63) Continuation of application No. 13/038,615, filed on Mar. 2, 2011, now Pat. No. 8,466,187, which is a continuation-in-part of application No. 12/336,938, filed on Dec. 17, 2008, now Pat. No. 8,034,836, which is a continuation of application No. 11/950,273, filed on Dec. 4, 2007, now Pat. No. 7,777,074.
- (60) Provisional application No. 60/973,229, filed on Sep. 18, 2007.
- (51) **Int. Cl.**
A61K 31/415 (2006.01)
- (52) **U.S. Cl.**
USPC **514/400**
- (58) **Field of Classification Search**
USPC 514/400
See application file for complete search history.

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1

AMINO ACID COMPOSITIONS**CROSS REFERENCE TO RELATED APPLICATIONS**

This application is a continuation application of the earlier U.S. Utility Patent Application to Ronald Kramer, et. al. entitled "Amino Acid Compositions," application Ser. No. 13/038,615, filed Mar. 2, 2011, now pending, which is a continuation-in-part application of the earlier U.S. Utility Patent Application to Ronald Kramer, et. al. entitled "Amino Acid Compounds," application Ser. No. 12/336,938, filed Dec. 17, 2008, now U.S. Pat. No. 8,034,836, which is a continuation application of the earlier U.S. Utility Patent Application to Ronald Kramer, et. al. entitled "Amino Acid Compounds," application Ser. No. 11/950,273, filed Dec. 4, 2007, now U.S. Pat. No. 7,777,074, which application claims the benefit of the filing date of U.S. Provisional Patent Application 60/973,229 entitled "Amino Acid Compounds" to Ronald Kramer, et. al., filed on Sep. 18, 2007, the disclosures of all of which being hereby incorporated entirely herein by reference.

BACKGROUND

1. Technical Field

Aspects of this document relate generally to amino acid compositions.

2. Background

It is desirable to design new amino acid compositions that have properties lacking in conventional amino acids, conventional nitrates, and conventional nitrites alone.

SUMMARY

In one aspect, a composition and a supplement formulation are disclosed, both including: at least one constituent selected from the group consisting of a nitrate salt, a nitrite salt, and both; and at least one constituent amino acid selected from the group consisting of Arginine, Agmatine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, Ornithine, Valine, Aspartic Acid, Cysteine, Glycine, Lysine, Methionine, Proline, Tyrosine, and Phenylalanine.

The composition or supplement formulation may further include an additive. The additive may be a carrier, an excipient, a binder, a colorant, a flavoring agent, a preservative, a buffer, a dilutant, and/or combinations thereof.

The composition or supplement formulation may be in the form of a capsule, a cachet, a pill, a tablet, a powder, a granule, a pellet, a bead, a particle, a troche, a lozenge, and a gel.

The foregoing and other aspects, features, and advantages will be apparent to those artisans of ordinary skill in the art from the DESCRIPTION and DRAWINGS, and from the CLAIMS.

DESCRIPTION

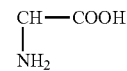
Overview, Terminology and Definitions

In describing implementations of an Amino Acid Compound and Composition, the following terminology will be used in accordance with the definitions and explanations set out below. Notwithstanding, other terminology, definitions, and explanations may be found throughout this document, as well.

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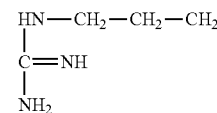
As used herein, "Amino Acid" is a term used in its broadest sense and may refer to an Amino Acid in its many different chemical forms including a single administration Amino Acid, its physiologically active salts or esters, its combinations with its various salts, its tautomeric, polymeric and/or isomeric forms, its analog forms, its derivative forms, its products of biosynthesis, and/or its decarboxylation products. Amino Acids comprise, by way of non-limiting example: Agmatine, Beta Alanine, Arginine, Asparagine, Aspartic Acid, Cysteine, Glutamine, Glutamic Acid, Glycine, Histidine, L-Histidine, Leucine, Isoleucine, Lysine, Methionine, PhenylBeta Alanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, Valine, Citrulline, Creatine, Glutamine, Norvaline, Ornithine, and Phenylalanine.

Compounds containing both a carboxyl group and an amino group are typically known as Amino Acids. Amino Acids typically have the basic formula X—R, wherein X is:



Amino Acids typically differ from one another with respect to the structure of the R group. It is the structure of the R group that typically determines the individuality and character of each Amino Acid.

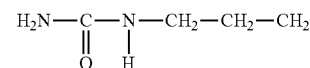
For example, the R group for the Amino Acid Arginine is:



Arginine is characterized as a nonessential Amino Acid. Specifically, Arginine can be independently manufactured by the human body, and does not need to be obtained directly through dietary intake. Arginine plays a significant role in healing, cell division, immune function, the elimination of ammonia from the body and the release of hormones. Arginine is presently used in the dietary supplement industry to supplement Arginine production in the body. Arginine is also presently used in the dietary supplement industry to boost Human Growth Hormone (HGH) production, increase vasodilation, enhance blood circulation, increase oxygen flow to the muscles, and boost Nitric Oxide (NO) production. Various supplemental Arginine forms are available in the consumer marketplace.

The vasodilating effect of ingested Arginine takes considerable time to manifest since Arginine requires extensive metabolism to yield Nitric Oxide (NO). Additionally, considerable amounts of Arginine are required to produce a significant vasodilating effect, with common doses ranging from eight to twenty-four grams per day.

The R group for the Amino Acid Citrulline is:



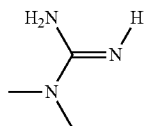
Citrulline is an alpha-Amino Acid naturally occurring in the human body, and does not need to be obtained directly through dietary intake. In vivo, Citrulline is made from the Amino Acid Ornithine, along with carbamoyl phosphate in

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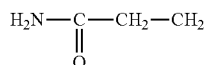
one of the central reactions in the Urea Cycle. Citrulline is also produced during the metabolism of Arginine in the body. Citrulline is presently used in the dietary supplement industry to supplement Citrulline production in the body. By itself, Citrulline has no vasodilating properties. Citrulline is also water insoluble, which reduces its bioavailability and limits the forms in which Citrulline may be effectively used.

The R group for the Amino Acid Creatine is:



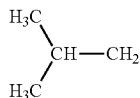
Creatine is a nonessential Amino Acid and is also a nitrogenous organic acid. Creatine is independently manufactured by the human body, and does not need to be obtained directly through dietary intake. Creatine plays a significant role in providing muscles with energy. Creatine is presently used in the dietary supplement industry to supplement Creatine production in the body. Creatine is also presently used in the dietary supplement industry to increase muscle-mass gains, improve athletic performance and strength. Creatine, by itself, has no vasodilating properties. Creatine is also water insoluble, which reduces its bioavailability and limits the forms in which Creatine may be effectively used.

The R group for the Amino Acid Glutamine is:



Glutamine is a nonessential Amino Acid. Glutamine is the most abundant naturally occurring, non-essential amino acid in the human body and is found circulating in the blood, as well as stored in the skeletal muscles. Glutamine plays a significant role in protein synthesis, muscle growth, and wound healing. Glutamine is presently used in the dietary supplement industry to supplement Glutamine production in the body. Glutamine is also presently used in the dietary supplement industry to maintain the body's Glutamine pool. Glutamine, by itself, has no vasodilating properties. Glutamine is also water insoluble, which reduces its bioavailability and limits the forms in which Glutamine may be effectively used. Additionally, Glutamine inhibits Nitric Acid (NO) production through downregulation of eNOS synthase.

The R group for the Amino Acid Leucine is:

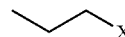


Leucine is an essential Amino Acid, meaning that Leucine is not synthesized in vivo in animals. Accordingly, Leucine must be ingested, usually as a component of proteins consumed directly through dietary intake. Leucine plays a significant role in muscle protein synthesis. Leucine can also inhibit protein degradation in skeletal muscle, as well as in the liver. Leucine is presently used in the dietary supplement industry to supplement dietary Leucine sources. Leucine is also presently used in the dietary supplement industry to promote anabolism and stimulate muscle protein synthesis.

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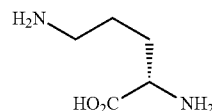
Leucine, by itself, has no vasodilating properties. Leucine is also water insoluble, which reduces its bioavailability and limits the forms in which Leucine may be effectively used.

The R group for the Amino Acid Norvaline is:



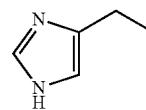
Norvaline is a nonessential Amino Acid. Specifically, Norvaline can be independently manufactured by the human body, and does not need to be obtained directly through dietary intake. Norvaline is presently used in the dietary supplement industry to supplement Norvaline production in the body. Norvaline is also presently used in the dietary supplement industry to inhibit the enzyme arginase and thus reduce the conversion of Arginine to urea. Norvaline, by itself, has no vasodilating properties, although it enhances the vasodilating properties of Arginine. Norvaline is also water insoluble, which reduces its bioavailability and limits the forms in which Leucine may be effectively used.

The R group for the Amino Acid Omithine is:



Omithine is a non-essential Amino Acid. That is, Omithine is independently manufactured by the human body, and does not need to be obtained directly through dietary intake. Omithine plays a significant role in the synthesis of polyamines, specifically via the action of Ornithine decarboxylase. Omithine is presently used in the dietary supplement industry to supplement dietary Omithine sources. Omithine is also presently used in the dietary supplement industry to enhance the vasodilating properties in a series of products commonly known as "NO Boosters." Omithine exerts its vasodilating effect only by in vivo conversion to Arginine and then by following the pathway that converts Arginine to Nitric Acid (NO). Many grams of Omithine, and a considerable amount of time, are required in order to assert its vasodilating effect.

The R group for the Amino Acid Histidine is:

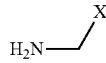


Histidine is a naturally-occurring Amino Acid and is coded for in DNA. Relatively small shifts in cellular pH will change the electrical charge of Histidine. For this reason, Histidine finds its way into considerable use as a coordinating ligand in metalloproteins, and also as a catalytic site in certain enzymes. Histidine is currently used in the dietary supplement industry to support carnosine production. Histidine, by itself, has no vasodilating properties. Additionally, Histidine is very poorly water soluble, a fact that limits its bioavailability and utility. Histidine is presently used in the dietary supplement industry in the forms of single administration Histidine and Histidine HCl.

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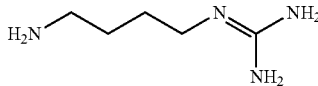
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The R group for the Amino Acid Beta Alanine is:



Beta Alanine is the only naturally-occurring Beta Amino Acid. A Beta Amino Acid is one in which the Amino group is located at the beta position (i.e. two atoms away) from the Carboxyl group. Beta Alanine is formed in vivo through the degradation of dihydrouracil and carnosine. Beta Alanine is the rate-limiting precursor of carnosine. Therefore, carnosine levels are limited by the amount of available Beta Alanine. Beta Alanine, by itself, has no vasodilating properties. Additionally, Beta Alanine is somewhat water soluble, which limits its bioavailability and utility. Beta Alanine is presently used in the dietary supplement industry to support carnosine production.

The chemical structure of Agmatine is:



Agmatine is the decarboxylation product of the Amino Acid Arginine and is an intermediate in polyamine biosynthesis. Agmatine is synthesized in the brain and stored in synaptic vesicles in regionally selective neurons. Agmatine is released by depolarization and is inactivated by agmatinase. Agmatine binds to alpha2-adrenoceptors and imidazoline binding sites. Agmatine likewise blocks N-methyl-D-aspartic acid (NMDA) receptor channels and other ligand-gated cationic channels. Additionally, agmatine inhibits nitric oxide synthase, and induces the release of some peptide hormones. Agmatine modulates nitric oxide through various mechanisms. Agmatine stimulates some types of nitric oxide synthase (NOS) while inhibiting others. Agmatine inhibits Nitric Oxide production by inhibiting NOS. Agmatine is presently used in the dietary supplement industry in the forms of single administration Agmatine and Agmatine Sulfate.

As used herein, "Composition" is a term used in its broadest sense and may refer to a mixture of constituent substances or ingredients. "Mixture" is a term used in its broadest sense and may refer to two or more constituent substances or ingredients (chemical species present in a system) which have been combined (not necessarily in fixed proportions and not necessarily with chemical bonding and not necessarily so that each substance retains its own chemical identity). Mixtures can be the product of a blending or mixing of chemical substances like elements and compounds, without chemical bonding or other chemical change, so that each ingredient substance retains its own chemical properties and makeup. Mixtures can be either homogeneous or heterogeneous. A homogeneous mixture is a type of mixture in which the composition is uniform. A heterogeneous mixture is a type of mixture in which the composition can easily be identified, as there are two or more phases present. A homogeneous mixture in which there is both a solute and solvent present is also a solution.

A "Compound" is a term used in its broadest sense and may refer to a chemical substance comprising two or more different chemically bonded chemical constituent elements or ingredients, with a fixed ratio or proportion by weight. The atoms within a compound can be held together by a variety of

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interactions, ranging from covalent bonds to electrostatic forces in ionic bonds. The physical and chemical properties of compounds are different from those of their constituent elements. This is one of the main criteria for distinguishing a compound from a mixture of elements or other substances because a mixture's properties are generally closely related to and dependent on the properties of its constituents. However, some mixtures are so intimately combined that they have some properties similar to compounds. Another criterion for distinguishing a compound from a mixture is that the constituents of a mixture can usually be separated by simple, mechanical means such as filtering, evaporation, or use of a magnetic force, but the components of a compound can only be separated by a chemical reaction. Conversely, mixtures can be created by mechanical means alone, but a compound can only be created (either from elements or from other compounds, or a combination of the two) by a chemical reaction.

Thus, for purposes of this disclosure, "Composition" may refer to a mixture of at least one Amino Acid in combination with at least a Nitrate, a Nitrite, or both from any source.

As used herein, "Nitrate" is a term used in its broadest sense and may refer to an Nitrate in its many different chemical forms including a salt of Nitric Acid, a single administration Nitrate, its physiologically active salts or esters, its combinations with its various salts, its tautomeric, polymeric and/or isomeric forms, its analog forms, and/or its derivative forms. Nitrate comprises, by way of non-limiting example, many different chemical forms including dinitrate and trinitrate. Nitrates may be salts, or mixed salts, of Nitric Acid (HNO_3) and comprise one Nitrogen atom and three Oxygen atoms (NO_3). For the exemplary purposes of this disclosure, Nitrate may comprise salts of Nitrate such as sodium nitrate, potassium nitrate, barium nitrate, calcium nitrate, and the like. For the exemplary purposes of this disclosure, Nitrate may include mixed salts of Nitrate such as nitrate orotate, and the like. Furthermore, for the exemplary purposes of this disclosure, nitrates that are commonly used in supplement industry are appropriate sources of nitrates, such as juice, extract, powder and the like of Cabbage, Spinach, Beetroot, Artichoke, Asparagus, Broad Bean, Eggplant, Garlic, Onion, Green Bean, Mushroom, Pea, Pepper, Potato, Summer Squash, Sweet Potato, Tomato, Watermelon, Broccoli, Carrot, Cauliflower, Cucumber, Pumpkin, Chicory, Dill, Turnip, Savoy Cabbage, Celeriac, Chinese Cabbage, Endive, Fennel, Kohlrabi, Leek, Parsley, Celery, Cress, Chervil, Lettuce, Rocket (Rucola), and the like.

As used herein, "Nitrite" is a term used in its broadest sense and may refer to an Nitrite in its many different chemical forms including a salt of Nitrous Acid, a single administration Nitrite, its physiologically active salts or esters, its combinations with its various salts, its tautomeric, polymeric and/or isomeric forms, its analog forms, and its derivative forms. Nitrite comprises, by way of non-limiting example, many different chemical forms including dinitrite and trinitrite. Nitrites may be salts, or mixed salts, of Nitrous Acid (HNO_2) and comprise one Nitrogen atom and two Oxygen atoms (NO_2). For the exemplary purposes of this disclosure, Nitrite may comprise salts of Nitrite such as sodium nitrite, potassium nitrite, barium nitrite, calcium nitrite, and the like. For the exemplary purposes of this disclosure, Nitrite may comprise mixed salts of Nitrite such as nitrite orotate, and the like. Additionally, for the exemplary purposes of this disclosure, Nitrite may comprise nitrite esters such as amyl nitrite, and the like. Furthermore, for the exemplary purposes of this disclosure, natural sources of Nitrites that are commonly used in supplement industry are appropriate sources of Nitrites, such as juice, extract, powder and the like of Cabbage, Spin-

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ach, Beetroot, Artichoke, Asparagus, Broad Bean, Eggplant, Garlic, Onion, Green Bean, Mushroom, Pea, Pepper, Potato, Summer Squash, Sweet Potato, Tomato, Watermelon, Broccoli, Carrot, Cauliflower, Cucumber, Pumpkin, Chicory, Dill, Turnip, Savoy Cabbage, Celeriac, Chinese Cabbage, Endive, Fennel, Kohlrabi, Leek, Parsley, Celery, Cress, Chervil, Lettuce, Rocket (Rucola), and the like.

Nitrates and Nitrites are commercially available in various preparations, including natural preparations, and are used in various applications. In the case of ingestion by humans, Nitrate (NO₃) is typically reduced to Nitrite (NO₂) in the epithelial cells of blood vessels. In vivo, Nitrite (NO₂) reacts with a thiol donor, principally glutathione, to yield Nitric Oxide (NO).

As used herein, “acceptable additive” or “additive” are terms used in their broadest sense. Particular implementations of the compositions described in this document may also comprise an additive (e.g. one of a solubilizer, an enzyme inhibiting agent, an anticoagulant, an antifoaming agent, an antioxidant, a coloring agent, a coolant, a cryoprotectant, a hydrogen bonding agent, a flavoring agent, a plasticizer, a preservative, a sweetener, a thickener, and combinations thereof) and/or a carrier (e.g. one of an excipient, a lubricant, a binder, a disintegrator, a diluent, an extender, a solvent, a suspending agent, a dissolution aid, an isotonicization agent, a buffering agent, a soothing agent, an amphipathic lipid delivery system, and combinations thereof). These additives may be solids or liquids, and the type of additive may be generally chosen based on the type of administration being used. Those of ordinary skill in the art will be able to readily select suitable pharmaceutically effective additives from the disclosure in this document. In particular implementations, acceptable additives may include, by non-limiting example, calcium phosphate, cellulose, stearic acid, croscarmellose cellulose, magnesium stearate, and silicon dioxide.

As used in this document, “effective” is a phrase used in its broadest sense, including, by non-limiting example, effective in a clinical trial, for a specific patient, or only placebo-effective.

As used in this document, “acceptable” is a phrase used in its broadest sense and may describe ingredients of a composition that meet Food and Drug Administration (FDA) standards, United States Pharmacopeial Standards (USP), US Department of Agriculture (USDA) standards for food-grade materials, commonly accepted standards of the nutritional supplement industry, industry standards, botanical standards, or standards established by any individual. These standards may delineate acceptable ranges of aspects of ingredients of a composition such as edibility, toxicity, pharmacological effect, or any other aspect of a chemical, composition, or preparation used in implementations of a composition.

Components/Compounds/Compositions

A first implementation is an Arginine compound of the formula:



wherein;

R is the Arginine group identified and defined above;

X is the Amino Acid base identified and defined above; and

Y is selected from the group consisting of a Nitrate and a Nitrite.

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Applicants have cost-effectively synthesized Arginine Nitrate by combining nitric acid and Arginine, mixing with water or another polar, easily evaporated solvent like methanol, alcohol, pyridine, and the like, and leaving to crystallize. Further nitratization can take place, yielding Arginine Dinitrate or Arginine Trinitrate. An alternative implementation may comprise using Nitrous Acid (HNO₂) instead of Nitric Acid (HNO₃), thus yielding Arginine Nitrite. Arginine Nitrite has the same effects as Arginine Nitrate, the only difference being that it requires one less step to yield Nitric Oxide (NO—). Mixed salts may also be used, such as in the non-limiting example of Arginine Nitrate-Orotate.

A second implementation is a Citrulline compound of the formula:



wherein;

R is the Citrulline group identified and defined above;

X is the Amino Acid base identified and defined above; and

Y is selected from the group consisting of a Nitrate and a Nitrite.

Applicants have cost-effectively synthesized Citrulline Nitrate by combining nitric acid and Citrulline, mixing with water or another polar, easily evaporated solvent like methanol, alcohol, pyridine, and the like, and leaving to crystallize. Further nitratization can take place, yielding Citrulline Dinitrate or Citrulline Trinitrate. An alternative implementation may comprise using Nitrous Acid (HNO₂) instead of Nitric Acid (HNO₃), thus yielding Citrulline Nitrite. Citrulline Nitrite has the same effects as Citrulline Nitrate, the only difference being that it requires one less step to yield Nitric Oxide (NO—). Mixed salts may also be used, such as in the non-limiting example of Citrulline Nitrate-Orotate.

A third implementation is a Creatine compound of the formula:



wherein;

R is the Creatine group identified and defined above;

X is the Amino Acid base identified and defined above; and

Y is selected from the group consisting of a Nitrate and a Nitrite.

Applicants have cost-effectively synthesized Creatine Nitrate by combining nitric acid and Creatine, mixing with water or another polar, easily evaporated solvent like methanol, alcohol, pyridine, and the like, and leaving to crystallize. Further nitratization can take place, yielding Creatine Dinitrate or Creatine Trinitrate. An alternative implementation may comprise using Nitrous Acid (HNO₂) instead of Nitric Acid (HNO₃), thus yielding Creatine Nitrite. Creatine Nitrite has the same effects as Creatine Nitrate, the only difference being that it requires one less step to yield Nitric Oxide (NO—). Mixed salts may also be used, such as in the non-limiting example of Creatine Nitrate-Orotate.

A fourth implementation is a Glutamine compound of the formula:

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wherein;

R is the Glutamine group identified and defined above;
X is the Amino Acid base identified and defined above; and
Y is selected from the group consisting of a Nitrate and a Nitrite.

Applicants have cost-effectively synthesized Glutamine Nitrate by combining nitric acid and Glutamine, mixing with water or another polar, easily evaporated solvent like methanol, alcohol, pyridine, and the like, and leaving to crystallize. Further nitratization can take place, yielding Glutamine Dinitrate or Glutamine Trinitrate. An alternative implementation comprises using Nitrous Acid (HNO₂) instead of Nitric Acid (HNO₃), thus yielding Glutamine Nitrite. Glutamine Nitrite has the same effects as Glutamine Nitrate, the only difference being that it requires one less step to yield Nitric Oxide (NO—). Mixed salts may also be used, such as in the non-limiting example of Glutamine Nitrate-Orotate.

A fifth implementation is a Leucine compound of the formula:



wherein;

R is the Leucine group identified and defined above;
X is the Amino Acid base identified and defined above; and
Y is selected from the group consisting of a Nitrate and a Nitrite.

Applicants have cost-effectively synthesized Leucine Nitrate by combining nitric acid and Leucine, mixing with water or another polar, easily evaporated solvent like methanol, alcohol, pyridine, and the like, and leaving to crystallize. Further nitratization can take place, yielding Leucine Dinitrate or Leucine Trinitrate. An alternative implementation comprises substituting the Amino Acids Valine or Isoleucine for Leucine. Another alternative implementation comprises substituting Nitrous Acid (HNO₂) for Nitric Acid (HNO₃), thus yielding Leucine Nitrite. Leucine Nitrite has the same effects as Leucine Nitrate, the only difference being that it requires one less step to yield Nitric Oxide (NO—). Mixed salts may also be used, such as in the non-limiting example of Leucine Nitrate-Orotate.

A sixth implementation is a Norvaline compound of the formula:



wherein;

R is the Norvaline group identified and defined above;
X is the Amino Acid base identified and defined above; and
Y is selected from the group consisting of a Nitrate and a Nitrite.

Applicants have cost-effectively synthesized Norvaline Nitrate by combining nitric acid and Norvaline, mixing with water or another polar, easily evaporated solvent like methanol, alcohol, pyridine, and the like, and leaving to crystallize.

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Further nitratization can take place, yielding Norvaline Dinitrate or Norvaline Trinitrate. An alternative implementation comprises substituting Nitrous Acid (HNO₂) for Nitric Acid (HNO₃), thus yielding Norvaline Nitrite. Norvaline Nitrite has the same effects as Norvaline Nitrate, the only difference being that it requires one less step to yield Nitric Oxide (NO—). Mixed salts may also be used, such as in the non-limiting example of Norvaline Nitrate-Orotate.

A seventh implementation is an Ornithine compound of the formula:



wherein;

R is the Ornithine group identified and defined above;
X is the Amino Acid base identified and defined above; and
Y is selected from the group consisting of a Nitrate and a Nitrite.

Applicants have cost-effectively synthesized Omithine Nitrate by combining nitric acid and Omithine, mixing with water or another polar, easily evaporated solvent like methanol, alcohol, pyridine, and the like, and leaving to crystallize. Further nitratization can take place, yielding Omithine Dinitrate or Omithine Trinitrate. An alternative implementation comprises using Nitrous Acid (HNO₂) instead of Nitric Acid (HNO₃), thus yielding Omithine Nitrite. Omithine Nitrite has the same effects as Omithine Nitrate, the only difference being that it requires one less step to yield Nitric Oxide (NO—). Mixed salts may also be used, such as in the non-limiting example of Omithine Nitrate-Orotate.

An eighth implementation is a Histidine compound of the formula:



wherein;

R is the Histidine group identified and defined above;
X is the Amino Acid base identified and defined above; and
Y is selected from the group consisting of a Nitrate and a Nitrite.

Applicants have cost-effectively synthesized Histidine Nitrate by combining nitric acid and Histidine, mixing with water or another polar, easily evaporated solvent like methanol, alcohol, pyridine, and the like, and leaving to crystallize. Further nitratization can take place, yielding Histidine Dinitrate or Histidine Trinitrate. An alternative implementation comprises using Nitrous Acid (HNO₂) instead of Nitric Acid (HNO₃), thus yielding Histidine Nitrite. Histidine Nitrite has the same effects as Histidine Nitrate, the only difference being that it requires one less step to yield Nitric Oxide (NO—). Mixed salts may also be used, such as in the non-limiting example of Histidine Nitrate-Orotate.

A ninth implementation is a Beta Alanine compound of the formula:



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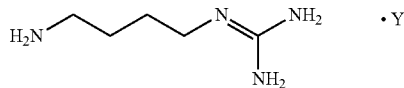
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wherein;

R is the Beta Alanine group identified and defined above;
X is the Amino Acid base identified and defined above; and
Y is selected from the group consisting of a Nitrate and a Nitrite.

Applicants have cost-effectively synthesized Beta Alanine Nitrate by combining nitric acid and Beta Alanine, mixing with water or another polar, easily evaporated solvent like methanol, alcohol, pyridine, and the like, and leaving to crystallize. Further nitratization can take place, yielding Beta Alanine Dinitrate or Beta Alanine Trinitrate. An alternative implementation comprises using Nitrous Acid (HNO₂) instead of Nitric Acid (HNO₃), thus yielding Beta Alanine Nitrite. Beta Alanine Nitrite has the same effects as Beta Alanine Nitrate, the only difference being that it requires one less step to yield Nitric Oxide (NO—). Mixed salts may also be used, such as in the non-limiting example of Beta Alanine Nitrate-Orotate.

A tenth implementation is an Agmatine compound of the formula:



wherein;

Y is selected from the group consisting of a Nitrate and a Nitrite.

Applicants have cost-effectively synthesized Agmatine Nitrate by combining nitric acid and Agmatine, mixing with water or another polar, easily evaporated solvent like methanol, alcohol, pyridine, and the like, and leaving to crystallize. Further nitratization can take place, yielding Agmatine Dinitrate or Agmatine Trinitrate. An alternative implementation comprises using Nitrous Acid (HNO₂) instead of Nitric Acid (HNO₃), thus yielding Agmatine Nitrite. Agmatine Nitrite has the same effects as Agmatine Nitrate, the only difference being that it requires one less step to yield Nitric Oxide (NO—). Mixed salts may also be used, such as in the non-limiting example of Agmatine Nitrate-Orotate.

Other implementations involve compositions instead of compounds. Using an independent source of nitrates and/or nitrites that is mixed with any of the amino acids disclosed in this document to form a composition can obtain substantially the same effects as the amino acid nitrate or nitrite compounds discussed in this document.

Such an amino acid composition might be depicted by the formula X—R+Y. “X—R” represents an amino acid as discussed previously and “Y” represents a Nitrate and/or Nitrite. But instead of forming a compound, they are mixed together (represented by the “+”) to form a composition.

For the exemplary purposes of this disclosure, following is a variety of specific examples of amino acid compositions.

Composition 1: Creatine Nitrate 100-1000 mg in capsules. Dosage is 3 capsules twice daily.

Composition 2 (Powder Form): Serving Size: 4 grams. Creatine Nitrate 3-3.5 grams. Vitamin C 500-1000 mg.

Composition 3 (Sports Drink): 0.5-3 Grams Arginine Nitrate. 0.5-2 Grams Taurine. 1-3 grams Sugar or appropriate Sweetener. Artificial Coloring. Purified Water till 500 ml of total Volume.

Composition 4 (sublingual tablets; amounts are per tablet): Agmatine Nitrate 10-100 mg. Maltulose 200 mg. Artificial Cherry Flavor. Melt Maltulose, add in slowly the Agmatine Nitrate and the flavor, and pour in the tablet machine.

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Composition 5 (Tablets Containing Arginine and Potassium Nitrate for Blood Pressure support). Per tablet: Arginine 250-700 mg. Potassium Nitrate 50-500 mg. Corn Starch till the desired volume for the tablet machine is obtained.

Composition 6 (for healthy blood pressure support): 500-1000 mg Arginine (As arginine nitrate)+250-500 mg Celery Seed Extract+100-300 mg Dried Garlic Powder in airseal Capsules.

Composition 7 (For improved Sexual Performance): 500-1000 mg grams Agmatine+1-2 grams D-aspartic Acid (as D-Aspartic Acid Nitrate)+1-2 grams dried onion powder (onion also increases testosterone) in capsules.

Composition 8 (Improved Strength): Creatine (As Creatine Malate) 2-3 grams and Calcium Nitrate 500 mg.

Composition 9 (Improved Muscle Endurance Sports Drink): Beta Alanine 1-2 grams+Citrulline (As Citrulline Nitrate) 250-500 mg+Potassium Nitrate 100-200 mg+Sodium Nitrate 50-100 mg+Magnesium Nitrate 200 mg Artificial Colouring Sweetener and flavour Purified Water till 500 ml.

Composition 10 (Improved Muscle anabolism and recovery): Leucine 1-5 grams Isoleucine 1-2 grams Valine 1-2 grams Spinach Extract (Standardized for nitrate content and ecdysterone content minimum 1% and 10% respectively) 5 grams.

Composition 11 (Improved Mental Performance): 500-1000 mg Tyrosine+250-500 mg Phenylalanine (as Phenylalanine Nitrate)+1000-2000 mg Glycine+200-300 mg Lithium Nitrate+300-600 mg Hystidine In Time Release Tablets.

Composition 12 (Growth Hormone Support): Arginine 2-4 grams+Ornithine 1-2 grams+Magnesium Nitrate 500 mg.

Composition 13 (Hair Growth Support As External Use Cream): Lysine Nitrite 1 gram Hydroxyproline Nitrate 5 grams Methionine nitrate 5 grams Euserine Cream Base 100 grams.

Composition 14 (Immune Support effervescent tabs): Glutamine 400-800 mg Hystidine (As histidine nitrate) 250-500 mg Cysteine (As N-Acetyl Cysteine) 200-300 mg Parsley Powder (Standardized for Vitamin C and nitrate) 125-250 mg.

Administration and Dosage Forms

Compounds, Compositions and/or formulations may be administered in any form, including one of a capsule, a cachet, a pill, a tablet, a powder, a granule, a pellet, a bead, a particle, a troche, a lozenge, a pastille, a solution, an elixir, a syrup, a tincture, a suspension, an emulsion, a mouthwash, a spray, a drop, an ointment, a cream, a gel, a paste, a transdermal patch, a suppository, a pessary, cream, a foam, and combinations thereof for example.

Implementations of Amino Acid Compounds and Compositions may conveniently be presented in unit dosage form. Unit dosage formulations may be those containing a daily dose or unit, a daily sub-dose, or an appropriate fraction thereof, of the administered components as described herein.

A dosage unit may include an Amino Acid Compound or Composition. In addition, a dosage unit may include an Amino Acid Compound or Composition admixed with a pharmaceutically acceptable additive(s), and/or any combination thereof.

The dosage units may be in a form suitable for administration by standard routes. In general, the dosage units may be administered, by non-limiting example, by the topical (including buccal and sublingual), transdermal, oral, rectal, ophthalmic (including intravitreal or intracameral), nasal, vaginal, and/or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intratracheal, and

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epidural) routes and many other delivery methods and/or systems known to those of ordinary skill in the art. Implementations of an Amino Acid Compound or Composition may also be administered through use of amphipathic lipid delivery systems (such as liposomes and unilamellar vesicles). Those of ordinary skill in the art will readily be able to select additional pharmaceutically acceptable additives to enable delivery of implementations of a pharmaceutical composition from the disclosure in this document.

For the exemplary purposes of this disclosure, oral delivery may be a particularly advantageous delivery route for administration to humans and animals of implementations of a pharmaceutical composition, optionally formulated with appropriate pharmaceutically acceptable additives to facilitate administration.

Manufacture

Implementations of Amino Acid Nitrate and/or Nitrite Compounds or Compositions may be synthesized or created in a wide variety of manners, and may be made from a wide variety of materials. Those of ordinary skill in the art will readily be able to select appropriate materials and methods to manufacture and use the compounds and compositions disclosed herein.

Accordingly, although there are a variety of method implementations for producing pharmaceutical compositions, for the exemplary purposes of this disclosure, a method implementation for producing an Amino Acid Compound may comprise: measuring specific quantities of Amino Acid, Nitric or Nitrous Acid and water or any other polar, easily evaporated solvent such as methanol, alcohol, pyridine, and the like mixed in a specific order the measured quantities of Amino Acid, Nitric or Nitrous Acid and water or solvent, and any additional pharmaceutically acceptable additives or inert ingredients, and then separating the pharmaceutical composition into discrete quantities for distribution and/or administration.

Measuring specific quantities of Amino Acid, Nitric or Nitrous Acid and water or solvent, and pharmaceutically acceptable additives or inert ingredients, may involve any number of steps and implementing components, and measuring specific quantities of Amino Acid, Nitric or Nitrous Acid and water or solvent, and pharmaceutically acceptable additives or inert ingredients, may be accomplished readily from this disclosure. For the exemplary purposes of this disclosure, measuring specific quantities of Amino Acid, Nitric or Nitrous Acid and water or solvent, and pharmaceutically acceptable additives or inert ingredients, may comprise using a scale, a solid or liquid dispensing apparatus, or other measurement device capable of measuring solid mass or liquid volume to produce a desired quantity of Amino Acid, Nitric or Nitrous Acid and water or solvent, and pharmaceutically acceptable ingredient.

It should be appreciated that any of the components of particular implementations of an Amino Acid Compound or Composition may be used as supplied commercially, or may be preprocessed by, by non-limiting example, any of the methods and techniques of agglomeration, air suspension chilling, air suspension drying, balling, coacervation, comminution, compression, pelletization, cryopelletization, extrusion, granulation, homogenization, inclusion Compoundation, lyophilization, melting, mixed, molding, pan coating, solvent dehydration, sonication, spheronization, spray chilling, spray congealing, spray drying, or other processes known in the art depending in part on the dosage form desired. The various components may also be pre-coated or encapsulated as known in the art. It will also be clear to one of ordinary skill in the art that appropriate additives may also be introduced to

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the composition or during the processes to facilitate the preparation of the dosage forms, depending on the need of the individual process.

Mixing the measured quantities of Amino Acid, Nitric or Nitrous Acid and water or solvent, and pharmaceutically acceptable additives or inert ingredients for Compounds, or mixing the measured quantities of Amino Acid, Nitrate and/or Nitrite sources, and pharmaceutically acceptable additives or inert ingredients for Compositions, may involve any number of steps and implementing components, and may be accomplished readily from this disclosure.

For the exemplary purposes of this disclosure, mixing the measured quantities of Amino Acid, Nitric or Nitrous Acid and water or solvent, and pharmaceutically acceptable additives or inert ingredients, may comprise combining the measured quantities of m Amino Acid, Nitric or Nitrous Acid and water or solvent, and pharmaceutically acceptable additives or inert ingredients, under the influence of physical, ultrasonic, or electrostatic forces to create a desired degree of intermingling and/or chemical reaction of the Amino Acid, Nitric or Nitrous Acid and water or solvent and any pharmaceutically acceptable ingredients. The mixed may be accomplished when the Amino Acid, Nitric or Nitrous Acid and water or solvent and/or any pharmaceutically acceptable ingredients are in a solid, liquid, or semisolid state.

Separating the Amino Acid Compound or Composition into discrete quantities for distribution may involve any number of steps and implementing components, and separating the Amino Acid Compound or Composition into discrete quantities for distribution may be accomplished readily from this disclosure. For the exemplary purposes of this disclosure, separating the Amino Acid Compound or Composition into discrete quantities for distribution may involve utilizing a specific piece of equipment, for example, a conventional tablet forming apparatus to shape the formed composition into individual tablets, each containing a desired dose of Amino Acid Compound or Composition. The separating process may be accomplished when the Amino Acid Compound or Composition is in a solid, liquid, or semisolid state.

Those of ordinary skill in the art will be able to readily select manufacturing equipment and pharmaceutically acceptable additives or inert ingredients to manufacture implementations of an Amino Acid Compound or Composition. For the exemplary purposes of this disclosure, some examples of pharmaceutically acceptable additives or inert ingredients and manufacturing process are included below, particularly those that relate to manufacture of implementations of an Amino Acid Compound or Composition in tablet form. Notwithstanding the specific examples given, it will be understood that those of ordinary skill in the art will readily appreciate how to manufacture implementations of an Amino Acid Compound or Composition according to the other methods of administration and delivery disclosed in this document.

Accordingly, compounds and Compositions may include a acceptable additive (e.g. one of a solubilizer, an enzyme inhibiting agent, an anticoagulant, an antifoaming agent, an antioxidant, a coloring agent, a coolant, a cryoprotectant, a hydrogen bonding agent, a flavoring agent, a plasticizer, a preservative, a sweetener, a thickener, and combinations thereof) and/or a acceptable carrier (e.g. one of an excipient, a lubricant, a binder, a disintegrator, a diluent, an extender, a solvent, a suspending agent, a dissolution aid, an isotonicizing agent, a buffering agent, a soothing agent, an amphipathic lipid delivery system, and combinations thereof).

For example, a particular implementation of an Amino Acid Compound or Composition may include a lubricant.

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Lubricants are any anti-sticking agents, glidants, flow promoters, and the like materials that perform a number of functions in tablet manufacture, for example, such as improving the rate of flow of the tablet granulation, preventing adhesion of the tablet material to the surface of the dies and punches, reducing interparticle friction, and facilitating the ejection of the tablets from the die cavity. Lubricants may comprise, for example, magnesium stearate, calcium stearate, talc, and colloidal silica.

Particular implementations of an Amino Acid Compound or Composition may also include a binder. Binders are any agents used to impart cohesive qualities to powdered material through particle-particle bonding. Binders may include, for example, matrix binders (e.g. dry starch, dry sugars), film binders (e.g. celluloses, bentonite, sucrose), and chemical binders (e.g. polymeric cellulose derivatives, such as methyl cellulose, carboxy methyl cellulose, and hydroxy propyl cellulose); and other sugar, gelatin, non-cellulosic binders and the like.

Disintegrators may be used in particular implementations of an Amino Acid Compound or Composition to facilitate the breakup or disintegration of tablets after administration. Disintegrators may include, for example, starch, starch derivatives, clays (e.g. bentonite), algin, gums (e.g. guar gum), cellulose, cellulose derivatives (e.g. methyl cellulose, carboxymethyl cellulose), croscarmellose sodium, croscarmellose cellulose, and other organic and inorganic materials.

Implementations of an Amino Acid Compound or Composition may include diluents, or any inert substances added to increase the bulk of the Amino Acid Compound to make a tablet a practical size for compression. Diluents may include, for example, calcium phosphate, calcium sulfate, lactose, mannitol, magnesium stearate, potassium chloride, and citric acid, among other organic and inorganic materials.

Buffering agents may be included in an Amino Acid Compound or Composition and may be any one of an acid and a base, where the acid is, for example, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, or toluenesulfonic acid, and the base is, for example, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, and other organic and inorganic chemicals.

With respect to delivery of particular implementations of an Amino Acid Compound or Composition, for the exemplary purposes of this disclosure, tablets may be utilized. Tablets are any solid pharmaceutical dosage form containing a pharmaceutically acceptable active agent or agents to be administered with or without suitable pharmaceutically acceptable additives and prepared either by compression or molding methods well known in the art. Tablets have been in widespread use and remain popular as a dosage form because of the advantages afforded both to the manufacturer (e.g., simplicity and economy of preparation, stability, and convenience in packaging, shipping, and dispensing) and the patient (e.g., accuracy of dosage, compactness, portability, blandness of taste, and ease of administration). Although tablets are most frequently discoid in shape, they may also be round, oval, oblong, cylindrical, rectangular or triangular, for example. The tablets may be optionally scored so that they may be separated into different dosages. They may differ greatly in size and weight depending on the amount of the pharmaceutically acceptable active agent or agents present and the intended route of administration. They are divided into two general classes, (1) compressed tablets, and (2) molded tablets.

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Tablets and other orally discrete dosage forms, such as capsules, cachets, pills, granules, pellets, beads, and particles, for example, may optionally be coated with one or more enteric coatings, seal coatings, film coatings, barrier coatings, compress coatings, fast disintegrating coatings, or enzyme degradable coatings for example. Multiple coatings may be applied for desired performance. Further, dosage forms may be designed for, by non-limiting example, immediate release, pulsatile release, controlled release, extended release, delayed release, targeted release, synchronized release, or targeted delayed release. For release/absorption control, carriers may be made of various component types and levels or thicknesses of coats. Such diverse carriers may be blended in a dosage form to achieve a desired performance. In addition, the dosage form release profile may be effected by a polymeric matrix composition, a coated matrix composition, a multi-particulate composition, a coated multi-particulate composition, an ion-exchange resin-based composition, an osmosis-based composition, or a biodegradable polymeric composition.

While manufacture of implementations of an Amino Acid Compound and Composition have been described in particular sequences of steps and/or in particular forms, it will be understood that such manufacture is not limited to the specific order of steps or forms as disclosed. Any steps or sequences of steps of manufacture of implementations of an Amino Acid Compound and Composition in any form are given as examples of possible steps or sequences of steps or potential forms and not as limitations, since many possible manufacturing processes and sequences of steps may be used to manufacture Amino Acid Compound and Composition implementations in a wide variety of forms.

Use

Implementations of an Amino Acid Compound or Composition are particularly useful in increasing bioabsorption and vasodilation in humans and animals. However, implementations are not limited to uses relating to bioabsorption or vasodilation modification, and the like. Rather, any description relating to the foregoing is for the exemplary purposes of this disclosure. It will be understood that implementations of an Amino Acid Compound or Composition may encompass a variety of uses and are not limited in their uses. For example, possible uses may be, by non-limiting example, prevention of Nitrate tolerance, enhanced water solubility, increased distribution to muscles, increased athletic performance, and/or countering Nitric Oxide inhibiting effects of certain Amino Acids.

In conventional preparations of Nitrate compounds, "tolerance," a particular side effect, has been observed in many patients. This is unfortunate because the effectiveness of Nitrate on vasodilation is well documented. "Tolerance" occurs when a subject's reaction to Nitrate decreases so that larger doses are required to achieve the same effect. A Mar. 3, 2000 report in the British Journal of Pharmacology indicates that "tolerance to the dilator effects of nitrates remains a persisting therapeutic problem." Raymond J. MacAllister "Arginine and Nitrate Tolerance" available at <http://www.nature.com/bjpp/journal/v130/n2/full/0703340a.html>, the contents of which are hereby incorporated herein by reference.

Empirical studies indicate that Nitrates are useful for their vasolidating effects. Common Nitrates include nitroglycerin and isosorbide dinitrate. Nitrates exert their vasodilating effect through their reduction to Nitrites. In vivo, Nitrates are reduced to Nitrites and, in the blood vessels' epithelial cells, Nitrite reacts with a thiol donor (mainly glutathione) to yield Nitric Oxide. Louis J. Ignarro, "After 130 years, the Molecular Mechanism of Action of Nitroglycerin is Revealed" (Jun.

11, 2002) available at <http://www.pnas.org/cgi/content/full/99/12/7816?ck=nck>, the contents of which are hereby incorporated herein by reference.

The Nitric Oxide inhibiting characteristics of the Amino Acid Glutamine have been well documented in a number of studies. In particular, a Mar. 28, 2006 report in the American Journal of Physiology has found that Glutamine inhibits Nitric Oxide production by downregulation of eNOS synthase. Masao Kakoki, et al. "Amino acids as Modulators of Endothelium-Derived Nitric Oxide." available at <http://ajprenal.physiology.org/cgi/content/full/291/2/F297>, the contents of which are hereby incorporated by reference.

A January 2006 Journal of Nutrition report indicates that the Amino Acid Leucine promotes anabolism and stimulates muscle protein synthesis. Michael J. Rennie, et al. "Branched-Chain Amino Acids as Fuels and Anabolic Signals in Human Muscle" available at <http://jn.nutrition.org/cgi/content/full/136/1/264S>, the contents of which are hereby incorporated by reference.

Empirical studies indicate that the Amino Acid Norvaline inhibits the enzyme arginase and thus decreases the rate of conversion of the Amino Acid Arginine to urea. Takeyori Saheki, et al. "Regulation of Urea Synthesis in Rat Liver" available at http://jb.oxfordjournals.org/cgi/content/abstract/86/3/745?ijkey=5d134456b7443ca36c809269462276e532549798&keytype2=tf_ipsecsha, the contents of which are hereby incorporated by reference.

An October 2004 *Journal of Nutrition* report indicates that the Amino Acid Ornithine promotes anabolism and stimulates muscle protein synthesis. Michael J. Rennie, et al. "Branched-Chain Amino Acids as Fuels and Anabolic Signals in Human Muscle" available at <http://jn.nutrition.org/cgi/content/full/136/1/264S>, the contents of which are hereby incorporated by reference.

Empirical studies indicate that the Amino Acids Beta-Beta Alanine and L-Histidine support carnosine production. M. Dunnett, "Influence of Oral Beta-Beta Alanine and L-Histidine Supplementation on the Carnosine Content of the Gluteus Medius" *Equine Veterinary Journal Supplement*, available at <http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=10659307&ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed>, the contents of which are hereby incorporated by reference.

Empirical studies further indicate that the Amino Acids Beta Alanine and L-Histidine increase muscle power, recuperation and stamina. Yoshihiro Suzuki "High Level of Skeletal Muscle Carnosine Contributes to the Latter Half of Exercise Performance During 30-S Maximal Cycle Ergometer Sprinting" in the *Japanese Journal of Physiology*, available at http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12139778&ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum, the contents of which are hereby incorporated by reference.

Accordingly, Applicants have discovered that the Arginine compound according to the first implementation, when ingested, provides enhanced Nitric Oxide (NO—) production while providing improved vasodilation effects over single administration of Arginine, the single administration of Nitrates, or the single administration of Nitrites. Improved vasodilation may, in turn, provide better circulation and distribution of Arginine in the body. Absorption may be improved since Amino Acid salts with inorganic acids are much more water soluble than single administration Amino Acids. Applicants have also discovered that the vasodilating effect of Arginine Nitrate manifests faster than that of single-

administration Arginine, and as fast as any nitrate, since the NO₃— group of the salt requires minimal conversion to yield Nitric Oxide. Additionally a much lesser dose may be required for vasodilation to take place, compared to the single administration of Arginine. Likewise, the development of tolerance to the nitrate component of the molecule may be prevented with the presence of Arginine. Arginine Nitrate may promote vasodilation through production of Nitric Oxide by two different pathways, the Arginine citrullization pathway and the nitrate reduction pathway. Arginine Nitrate may likewise be more water soluble than single administration Arginine.

Accordingly, Applicants have discovered that the Citrulline compound according to the second implementation, when ingested, provides enhanced Nitric Oxide (NO—) production while providing improved vasodilation effects over single administration of Citrulline, the single administration of Nitrates, or the single administration of Nitrites. Improved vasodilation may, in turn, provide better circulation and distribution of Citrulline in the body. Absorption may be improved since Amino Acid salts with inorganic acids are much more water soluble than single administration Amino Acids. Additionally a much lesser dose may be required for vasodilation to take place, compared to the single administration of Citrulline or nitrates. Citrulline Nitrate is likewise more water soluble than single administration Citrulline.

Accordingly, Applicants have discovered that the Creatine compound according to the third implementation, when ingested, provides enhanced Nitric Oxide (NO—) production while providing improved vasodilation effects over single administration of Creatine, the single administration of Nitrates, or the single administration of Nitrites. Improved vasodilation may, in turn, provide better circulation and distribution of Creatine in the body. Absorption may be improved since Amino Acid salts with inorganic acids are much more water soluble than single administration Amino Acids. Additionally a much lesser dose may be required for vasodilation to take place, compared to the single administration of nitrates.

Enhancing a molecule's solubility can enhance its bioavailability, rate of absorption by the GI tract, and as a result, its concentration in the muscle tissue and its effectiveness. As we have established, the nitrate salts of creatine and other molecules are exceptionally more soluble than their counterparts. Recent studies on creatine nitrate show 1100% improved solubility over creatine monohydrate.

Study 1

Intrinsic Dissolution Profiles of Creatine Nitrate, Creatine Monohydrate and Buffered Creatine

Objective: The objective of this study was to determine the dissolution characteristics of three different forms of commercially available creatine including creatine nitrate (CN), creatine monohydrate (CM) and buffered creatine (BC) under different temperature and pH. **Methods:** Intrinsic dissolution studies were carried out at 37° C. and room temperature in pH 2.5 and 7.4 buffer using modified Wood's apparatus. CN, CM and BC samples (~0.5 g) were compressed in the dies with constant surface area of 1.21 cm² using a Carver press at 2000 psi with a dwell time of 10 sec. These dies were placed in the USP dissolution apparatus (type II) containing 140 ml of dissolution media, with paddle speed of 50 rpm. Dissolution medium were collected at definite time intervals over a period of 3 hours for CN and 7 hours for both CM and BC and analyzed for creatine using a validated HPLC method. **Results:** A plot of the amount of creatine dissolved (mg)/

surface area (cm²) versus time gives the slope (k') which is directly proportional to the dissolution rate constant. The k' (mg/cm² hr) values for CN, CM and BC in pH 2.5 buffer at room temperature were 293.0±3.48, 59.1±2.06 and 71.1±0.59. At 37° C. these k' (mg/cm² hr) values were 327.3±2.66, 97.9±0.88 and 117.9±1.12, respectively. In pH 7.4 buffer, the k' (mg/cm² hr) values for CN, CM and BC were 278.9±14.6, 52.1±0.22 and 50.6±0.95 at room temperature and 319.5±14.3, 86.0±5.05 and 96.9±9.28 at 37° C., respectively. Conclusions: The dissolution rates of all three creatine forms were higher at 37° C. as compared to at room temperature. CM and BC showed a higher dissolution rate at pH 2.5 than that at pH 7.4, irrespective of temperature. However, the dissolution rate of CN was not affected by the pH of the dissolution media. Comparison of the dissolution profiles for these three creatine forms clearly indicated that CN has the higher intrinsic dissolution rate constant as compared to CM and BC irrespective of temperature and pH of the dissolution media. Results of this study further predict a better bioavailability of CN as compared to CM and BC.

Study 2

Chemical Stability of Creatine Nitrate, Creatine Monohydrate and Buffered Creatine in Solution

Objective: The objective of this study was to determine the chemical stability of creatine nitrate (CN), creatine monohydrate (CM) and buffered creatine (BC) under two different storage conditions (37° C. in pH 2.5 buffer and 40° C. in pH 6.8 buffer). Methods: A known concentration (~10 mg/ml) of CN, CM and BC were prepared in both pH 2.5 and pH 6.8 buffer and stored in stability chambers in screw capped bottles at 37° C. and 40° C., respectively. Samples were collected at predetermined time points and analyzed for creatine and degradation products if any, using a validated HPLC method. Changes in the pH, clarity and color of the samples were also determined. The order of degradation and rate constant were determined by graphical method. Results: The degradation rate constants (k) for CN, CM and BC at 37° C. in pH 2.5 buffer were 0.075±0.001, 0.119±0.011 and 0.108±0.002 (day⁻¹) while that at 40° C. in pH 6.8 buffer were 0.115±0.001, 0.015±0.001 and 0.013±0.002 (day⁻¹), respectively. The pH of CN samples at 40° C. in pH 6.8 buffer changed from 2.83±0.01 to 4.31±0.01 within a period of 12 days. The pH changes noticed at 37° C. in pH 2.5 buffer samples over the same period of time for CM, and BC were 3.08±0.01 to 4.12±0.01 and 3.11±0.01 and 4.16±0.01, respectively. No significant change in pH was observed for the rest of the samples. No change in the color and the clarity was noticed over 12 days. Conclusions: All the creatine samples followed first order degradation kinetics under both these experimental conditions. The k value for CN was found to be higher at 40° C. in pH 6.8 buffer as compared to at 37° C. in pH 2.5 buffer. However, both CM and BC showed a faster rate of degradation at 37° C. in pH 2.5 buffer than at 40° C. in pH 6.8 buffer. The major degradation product detected was creatinine. For CN the increase in pH was higher at 40° C. in pH 6.8 buffer as compared to 37° C. in pH 2.5 buffer. However, opposite effect was noticed for both CM and BC.

Study 3

Equilibrium Solubility Studies of Creatine Nitrate, Creatine Monohydrate and Buffered Creatine

Ambrish Panditl, Pinal Mistryl, Pat Dib2, Alexander Nikolaidis3 Alekha K. Dashl

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Objective: The objective of this study was to determine the equilibrium solubility of creatine nitrate (CN), creatine monohydrate (CM) and buffered creatine (BC) in water at room temperature as well as in pH 2.5 buffer at room temperature and 37° C. Methods: Excess amount of sample was added to the appropriate solvent and temperature was maintained and agitated at 150 rpm. The supernatant was collected after centrifugation at 24, 48, 72 hours till equilibration and analyzed by a HPLC method. Equilibration was confirmed when the solubility values of two consecutive time points were identical. The pH of the solution was monitored and Differential scanning calorimetry (DSC) thermograms of the solid samples before solubility and of the lyophilized sample after solubility studies were compared. Results: The equilibrium solubility of CN, CM and BC in water at room temperature was reached in 44 hours, and was 210.3±4.82 mg/ml, 19.1±0.40 mg/ml and 19.2±0.55 mg/ml, respectively. However, solubility for CN, CM and BC in pH 2.5 buffer at room temperature was 208.2±6.01 mg/ml, 23.8±0.33 mg/ml and 21.2±0.09 mg/ml and achieved within 72 hours for CN and in 48 hours for CM and BC samples, respectively. At 37° C. and in pH 2.5 buffer, the equilibrium solubility was reached within 24 hours for all samples and was 325.9±6.10, 31.5±0.71 and 32.6±0.67 for CN, CM, and BC. The pH of solutions of CN, CM and BC in water at room temperature was 0.44±0.04, 8.24±0.14 and 10.03±0.02 respectively. However, these values in pH 2.5 buffer at room temperature were 1.31±0.02, 3.44±0.02 and 3.68±0.01 and at 37° C. this was 1.13±0.07, 3.86±0.47 and 4.42±0.05, respectively. DSC thermograms of the original samples and lyophilized samples were identical. Conclusions: The solubility of creatine nitrate was around 10 fold higher than that of CM or BC under these experimental conditions studied, where as no significant difference in the solubility of CM and BC were noticed. There was an increase in solubility of each of the creatine forms in pH 2.5 at a higher temperature. DSC analysis confirmed that no phase change was noticed during these solubility studies.

The effectiveness of creatine for increasing athletic performance and improving body composition and muscle anabolism and performance is very well established. Such is also the case for BCAAs (leucine, isoleucine, and valine), taurine and camitine. It is also well established that for these molecules to have these effects, like all drugs, they must reach the site of action, i.e. the muscle.

Creatine Nitrate & the Athlete

Creatine Nitrate excels beyond its superior solubility, stability, and dissolution. That's because Creatine Nitrate overcomes two primary drawbacks of creatine monohydrate. First, creatine monohydrate results in extreme intra and extracellular water and sodium retention. The intracellular water retention is favorable. Cosmetically speaking however, the extracellular water retention is an unfavorable effect, as an athlete's muscles develop a smooth, soft, and bloated appearance. Second and most importantly, the extreme extracellular water retention may restrict muscle growth. Functionally speaking, the extracellular water retention may push back against muscle cells that are attempting to expand in size.

Creatine Nitrate expels excess extracellular water and sodium retention, while simultaneously hydrating and supersaturating muscle cells with creatine. This offers a HUGE benefit to athletes, encouraging muscle cells to expand in size without resistance from extracellular fluid. In addition, athletes using Creatine Nitrate may achieve a leaner, drier, and harder look to their muscle tissue; a stark contrast to the puffy and bloated look created by creatine monohydrate. Creatine

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Nitrate however is more than “Creatine Nitrate,” as the nitrate component offers tremendous functional advantages to athletes.

Nitrates provide substantial benefits to athletes and body-builders, as supported by clinical research. Nitrates are organic anions naturally occurring in the human diet, with close to 80% of dietary nitrates found in vegetables. Fruits and processed meats represent additional sources of nitrates in the human diet. In fact, researchers at Michigan State University have suggested nitrates may be nutritious (13). So what benefit does supplementation with nitrates offer to athletes?

Today, nitric oxide and pre-workout nitric oxide performance enhancing formulas have grown in popularity. Nitric oxide formulas are used to increase muscular “pumps,” vasodilation, and nutrient transport to the muscle to assist in greater aerobic performance and recovery. However, most formulas utilize the amino acid L-arginine, a precursor to nitric oxide, as their base. Recently, L-arginine has been proven to be ineffective for elevating nitric oxide levels. L-arginine has also been proven ineffective at enhancing athletic performance (9, 10, 11). Yet L-arginine is present in nearly every single nitric oxide formula on the market. Contrary to popular belief, most of the “pump” feeling experienced by trainees is derived from an insulin increase following L-arginine supplementation (1).

As recent clinical research confirms, the reduction of inorganic nitrate (NO₃⁻) and nitrite (NO₂⁻) in vivo results in nitric oxide production. Not only does nitrate generate nitric oxide, but nitrate and nitrite are inert end-products of nitric oxide oxidation. That is, nitrate converts into nitric oxide, and once oxidized, nitric oxide is recycled back into nitrate, which then has the potential to convert into nitric oxide once again. And the cycle continues to repeat itself. This creates an exciting alternative to nitric oxide production, and carries profound implications for the bodybuilding community.

A critical problem with nitric oxide is the short lifespan it has in the body. In just a few seconds, the nitric oxide molecule can be metabolized, and the athlete loses any benefit he/she may have received. A pump however must be sustained for several minutes, if not hours, in order to result in those biochemical conditions required to stimulate muscle hypertrophy. And nitrates are capable of elevating nitric oxide production for up to 8 hours.

Thus the use of nitrates represents an important alternative to the classical L-arginine-NO-synthase pathway (2) so commonly attempted in various sports supplement formulations.

The efficacy of nitrates in athletic performance is overwhelming in the clinical research. Nitrate consumption significantly enhances nitric oxide production, resulting in vasodilation, improved nutrient absorption, increased athletic performance (3), and improved energetic function in working muscles during exercise (12). For example, during low and moderate intensity exercise by humans, supplementation with nitrates has been reported to reduce the amount of oxygen required. During high intensity athletic exercise, nitrate supplementation enhances tolerance to high intensity training, effectively extending the “time to exhaustion” (4).

Organic nitrates also function as permeation enhancers. This is beneficial because enhanced permeation increases intestinal absorption of all nutrients coingested. This may allow for a superior quantity of anabolic nutrients to be absorbed and taken up into muscle cells, assisting athletes with the growth and repair of muscle tissue. Nitrates are even able to allow absorption of large macromolecules such as insulin (5, 6, 7).

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For decades, the pharmaceutical industry has used nitrates to induce direct and rapid vasodilation. And today, clinical research is proving that nitrates may produce beneficial effects on blood pressure and cardiovascular health (8). In fact, a recent clinical study investigated the effects of 5 times the amount of nitrates (1,316 mg per day for a 70 kg adult) currently recommended by the World Health Organization (259 mg per day for a 70 kg adult) and showed no adverse health or safety effects. The study results revealed an average reduction in diastolic blood pressure by 4.5 mmHg. Effects on systolic blood pressure were not observed (14, 15).

Nitrates themselves offer many benefits to athletes. Combined with the clinical research behind creatine supporting creatine’s positive benefits to athletes, Creatine Nitrate is the first creatine to solve to the solubility, stability, and dissolution challenges while simultaneously providing up to 8 hours of powerful vasodilation that workout enthusiasts demand!

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Accordingly, Applicants have discovered that the Glutamine compound according to the fourth implementation, when ingested, counters the Nitric Oxide (NO—) inhibiting characteristics of Glutamine. Absorption of Glutamine may be improved since Amino Acid salts with inorganic acids are much more water soluble than single administration Amino Acids. Additionally a much lesser dose may be required for vasodilation to take place, compared to the single administration of nitrates. Glutamine Nitrate may likewise be more water soluble than single administration Glutamine.

Accordingly, Applicants have discovered that the Leucine compound according to the fifth implementation, when ingested, provides enhanced Nitric Oxide (NO—) production while providing improved vasodilation effects over single administration of Leucine, the single administration of Nitrates, or the single administration of Nitrites. Improved vasodilation may, in turn, provide better circulation and distribution of Leucine in the body. Absorption may be improved since Amino Acid salts with inorganic acids are much more water soluble than single administration Amino Acids. Additionally a much lesser dose may be required for vasodilation to take place, compared to the single administration of nitrates. Leucine Nitrate is likewise more water soluble than single administration Leucine.

Accordingly, Applicants have discovered that the Norvaline compound according to the sixth implementation, when ingested, promotes vasodilation through the inhibition of arginase, while promoting Nitric Oxide formation via the nitrate mechanism. Improved vasodilation may, in turn, provide better circulation and distribution of Norvaline in the body. Absorption may be improved since Amino Acid salts with inorganic acids are much more water soluble than single administration Amino Acids. Additionally a much lesser dose may be required for vasodilation to take place, compared to the single administration of nitrates. Norvaline Nitrate may likewise be more water soluble than single administration Norvaline.

Accordingly, Applicants have discovered that the Ornithine compound according to the seventh implementation, when ingested, provides an additional vasodilation mechanism, reducing the amount of Ornithine needed and the amount of time needed for the vasodilating properties to manifest. Improved vasodilation may, in turn, provide better

circulation and distribution of Ornithine in the body. Absorption may be improved since Amino Acid salts with inorganic acids are much more water soluble than single administration Amino Acids. Applicants have also discovered that Ornithine Nitrate begins acting as fast as any other nitrate, since the NO₃— group of the salt requires minimal conversion to yield Nitric Oxide. Additionally, a much lesser dose may be required for vasodilation to take place, compared to the single administration of nitrates. Ornithine Nitrate may likewise be more water soluble than single administration Ornithine.

Accordingly, Applicants have discovered that the Histidine compound according to the eighth implementation, when ingested, provides a vasodilation mechanism. Vasodilation may, in turn, provide better circulation and distribution of Histidine in the body. Applicants have likewise discovered that the Histidine compound according to the ninth implementation, when ingested, promotes carnosine production, thus increasing muscle power, endurance and recuperation.

Absorption may be improved since Amino Acid salts with inorganic acids are much more water soluble than single administration Amino Acids. Applicants have also discovered that Histidine Nitrate begins acting as fast as any other nitrate, since the NO₃— group of the salt requires minimal conversion to yield Nitric Oxide. Additionally, a much lesser dose may be required for vasodilation to take place, compared to the single administration of nitrates. Histidine Nitrate may likewise be more water soluble than single administration Histidine.

Accordingly, Applicants have discovered that the Beta Alanine compound according to the ninth implementation, when ingested, provides vasodilation. Vasodilation may, in turn, provide better circulation and distribution of Beta Alanine in the body. Applicants have likewise discovered that the Beta Alanine compound according to the tenth implementation, when ingested, promotes carnosine production, thus increasing muscle power, endurance and recuperation. Absorption may be improved since Amino Acid salts with inorganic acids are much more water soluble than single administration Amino Acids. Applicants have also discovered that Beta Alanine Nitrate begins acting as fast as any other nitrate, since the NO₃— group of the salt requires minimal conversion to yield Nitric Oxide. Additionally, a much lesser dose may be required for vasodilation to take place, compared to the single administration of nitrates. Beta Alanine Nitrate may likewise be more water soluble than single administration Beta Alanine.

Accordingly, Applicants have discovered that the Agmatine compound according to the eighth implementation, when ingested, counteracts the Nitric Oxide inhibiting effect of single administration Agmatine. Absorption may be improved since Amino Acid salts with inorganic acids are much more water soluble than single administration Amino Acids. Applicants have also discovered that Agmatine Nitrate begins acting as fast as any other nitrate, since the NO₃— group of the salt requires minimal conversion to yield Nitric Oxide. Agmatine Nitrate may likewise be more water soluble than single administration Agmatine.

Accordingly, Applicants have discovered that not only do the foregoing amino acid nitrate or nitrite compounds provide the effects discussed above, but that Amino Acid Compositions (amino acids mixed with independent sources of nitrates and/or nitrites) enhance bioavailability, absorption, vasodilation, water solubility, distribution to muscles, and the like of certain Amino Acids, as well as prevent Nitrate tolerance and counter Nitric Oxide inhibiting effects of certain Amino Acids.

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As demonstrated by Anjali Pradhan and Juan Vera, "Effect of Anions on the Solubility of Zwitterionic Amino Acids", *Journal of Chemical and Engineering data*, Vol 45, 140-143 (2000) (which is hereby incorporated herein by reference), the co-existence of the nitrate ion can enhance the solubility of various amino acids by 300-400%. Although the change in solubility is significantly lower than that of the case of a salt with a nitrate, it is enough to make a difference in absorption in-vivo.

Furthermore, the nitrate ion enhances absorption of compounds by the intestine. Nitrates increase bioavailability by: increasing intestinal absorption of nutrients; and increasing vasodilation and blood flow and blood is the carrier of the nutrients to cells. See for example, the following references which are hereby incorporated herein by reference: Takahashi K et al. "Characterization of the influence of nitric oxide donors on intestinal absorption of macromolecules." *Int J Pharm* 2004; 286:89-97; Fetih G et al. "Nitric oxide donors can enhance the intestinal transport and absorption of insulin and [Asu(1,7)]-eel calcitonin in rats." *J Control Release* 2005; 106:287-97; Fetih G et al. "Excellent absorption enhancing characteristics of NO donors for improving the intestinal absorption of poorly absorbable compound compared with conventional absorption enhancers." *Drug Metab Pharmacokinet* 2006; 21:222-9; and Mitchell, G. E., Little, C. O., Jr. & Greathouse, T. R. (1964). "Influence of nitrate and nitrite, on carotene disappearance from the rat intestine." *Life Sci.* 4, 385.

Also, the nitrate ion can cause vasodilatation after reduction to nitrite and then nitric oxide, improve blood circulation, to the muscles and thus distribution of these compounds to the muscle, as well as oxygen distribution to the muscles. Muscle oxygen is needed to provide energy which is needed for all muscle anabolic actions to take place as well as for the active transport of above nutrients via the cell membrane. See the following references which are hereby incorporated herein by reference—Bailey, Stephen G. et al., "Dietary nitrate supplementation reduces the O₂ cost of low-intensity exercise and enhances tolerance to high-intensity exercise in humans", *PresS. J Appl Physiol* (Aug. 6, 2009) and Bailey, Stephen G. et al., "Dietary nitrate supplementation enhances muscle contractile efficiency during knee-extensor exercise in humans", *J Appl Physiol* 109:135-148, 2010).

In these same references it is also very well described nitrate's positive effect on athletic endurance and muscle strength. Oxygen is needed by the body to produce energy which by itself is needed for all the metabolic processes in the body, including those that Compositions of the present disclosure are involved in. Thus co-administration of nitrate ion with Compositions of the present disclosure furthermore increases their distribution to the muscle and their effectiveness.

Therefore, not only does the binding of nitrate salt with Compounds improve their bioavailability, absorption and effectiveness, but also the co-administration of nitrate through another nitrate salt, acid or a natural source of nitrate in a Composition of the present disclosure shall have similar effects, albeit lower than in the case of nitrate bonded with the molecule.

Via all the above mechanisms, concomitant nitrate or nitrite administration in a composition with an amino acid can substantially increase the concentration of an amino acid in the target muscles (e.g., Neuron cells for the cognitive enhancement properties of phenylalanine, camitine, glycine, and tyrosine, and Muscle cells for the performance enhancing properties of Agmatine Arginine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Nor-

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valine, Ornithine and Taurine). In the case of Creatine, this is further enhanced by the nitrate's ability to preserve muscle Creatine loads.

Therefore, concomitant nitrate or nitrite administration in a composition with an amino acid (just as with amino acid nitrate or nitrite compounds discussed previously) can improve mental focus, cognitive function, athletic and muscle performance, endurance, and strength, and produces much greater synergistic results than the use of only an amino acid alone or a nitrate and a nitrite alone.

The invention claimed is:

1. A composition comprising:

at least one constituent selected from the group consisting of a nitrate salt, a nitrite salt, and both; and

at least one constituent amino acid selected from the group consisting of Arginine, Agmatine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, Ornithine, Valine, Aspartic Acid, Cysteine, Glycine, Lysine, Methionine, Proline, Tyrosine, and Phenylalanine.

2. The composition of claim 1 further comprising one or more additional components selected from the group consisting of a carrier, an excipient, a binder, a colorant, a flavoring agent, a preservative, a buffer, a dilutant, and any combination thereof.

3. The composition of claim 1 in a dosage form selected from the group consisting of a capsule, a cachet, a pill, a tablet, a powder, a granule, a pellet, a bead, a particle, a troche, a lozenge, and a gel.

4. The composition of claim 1, wherein the nitrate salt comprises sodium nitrate, potassium nitrate, barium nitrate, calcium nitrate, and any combination thereof, and the nitrite salt comprises sodium nitrite, potassium nitrite, barium nitrite, calcium nitrite, and any combination thereof.

5. The composition of claim 4, wherein the at least one constituent selected from the group consisting of a nitrate salt, a nitrite salt, and both comprises a nitrate salt.

6. The composition of claim 5, wherein the nitrate salt comprises sodium nitrate.

7. The composition of claim 5, wherein the nitrate salt comprises potassium nitrate.

8. A supplement formulation comprising:

at least one constituent selected from the group consisting of a nitrate salt, a nitrite salt, and both; and

at least one constituent amino acid selected from the group consisting of Arginine, Agmatine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, Ornithine, Valine, Aspartic Acid, Cysteine, Glycine, Lysine, Methionine, Proline, Tyrosine, and Phenylalanine.

9. The supplement formulation of claim 8 further comprising one or more additional components selected from the group consisting of a carrier, an excipient, a binder, a colorant, a flavoring agent, a preservative, a buffer, a dilutant, and any combination thereof.

10. The supplement formulation of claim 8 in a dosage form selected from the group consisting of a capsule, a cachet, a pill, a tablet, a powder, a granule, a pellet, a bead, a particle, a troche, a lozenge, and a gel.

11. The supplement formulation claim 8, wherein the nitrate salt comprises sodium nitrate, potassium nitrate, barium nitrate, calcium nitrate, and any combination thereof, and the nitrite salt comprises sodium nitrite, potassium nitrite, barium nitrite, calcium nitrite, and any combination thereof.

12. The supplement formulation of claim 11, wherein the at least one constituent selected from the group consisting of a nitrate salt, a nitrite salt, and both comprises a nitrate salt.

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13. The supplement formulation of claim 12, wherein the nitrate salt comprises sodium nitrate.

14. The supplement formulation of claim 12, wherein the nitrate salt comprises potassium nitrate.

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EXHIBIT G



US008178572C1

(12) **EX PARTE REEXAMINATION CERTIFICATE** (11004th)
United States Patent
Kramer et al.

(10) **Number:** **US 8,178,572 C1**
(45) **Certificate Issued:** **Dec. 8, 2016**

(54) **AMINO ACID COMPOUNDS**

C07C 279/14 (2006.01)
C07D 233/64 (2006.01)

(75) Inventors: **Ronald Kramer**, Phoenix, AZ (US);
Alexander Nikolaidis, New Kallikratia (GR)

(52) **U.S. Cl.**
CPC *C07C 229/06* (2013.01); *C07C 279/14* (2013.01); *C07D 233/64* (2013.01)

(73) Assignee: **THERMOLIFE INTERNATIONAL, LLC**, Phoenix, AZ (US)

(58) **Field of Classification Search**
None
See application file for complete search history.

Reexamination Request:
No. 90/013,525, Jun. 26, 2015

(56) **References Cited**

Reexamination Certificate for:
Patent No.: **8,178,572**
Issued: **May 15, 2012**
Appl. No.: **12/946,153**
Filed: **Nov. 15, 2010**

To view the complete listing of prior art documents cited during the proceeding for Reexamination Control Number 90/013,525, please refer to the USPTO's public Patent Application Information Retrieval (PAIR) system under the Display References tab.

Related U.S. Application Data

Primary Examiner — Dwayne Jones

(63) Continuation of application No. 12/336,938, filed on Dec. 17, 2008, now Pat. No. 8,034,836, which is a continuation of application No. 11/950,273, filed on Dec. 4, 2007, now Pat. No. 7,777,074.

(60) Provisional application No. 60/973,229, filed on Sep. 18, 2007.

(57) **ABSTRACT**

(51) **Int. Cl.**
A61K 31/415 (2006.01)
C07C 229/06 (2006.01)

A method for increasing the vasodilative characteristics of amino acids in a human or animal is disclosed. The method includes administering to the human or animal a pharmaceutically effective amount of an amino acid compound consisting essentially of a nitrate or nitrite of an amino acid selected from the group consisting of Arginine, Agmatine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, Ornithine, and Valine.

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**EX PARTE
REEXAMINATION CERTIFICATE**

THE PATENT IS HEREBY AMENDED AS
INDICATED BELOW.

Matter enclosed in heavy brackets [] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claims 1 and 2 are determined to be patentable as amended.

New claims 3-13 are added and determined to be patentable.

1. A method for increasing vasodilative characteristics in a human [or animal], the method comprising administering *orally* to the human [or animal] a pharmaceutically effective amount of an amino acid compound consisting essentially of a nitrate [or nitrite] of an amino acid selected from the group consisting of Arginine, Agmatine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, Ornithine, and Valine.

2. The method of claim 1, wherein administering to the human [or animal] a pharmaceutically effective amount of an amino acid compound comprises administering to the human or animal a pharmaceutically effective amount of an amino acid compound consisting essentially of a nitrate [or nitrite] of Ornithine.

3. *The method of claim 1, wherein administering to the human a pharmaceutically effective amount of an amino acid compound comprises administering to the human a pharmaceutically effective amount of an amino acid compound consisting essentially of a nitrate of Arginine.*

4. *The method of claim 1, wherein administering to the human a pharmaceutically effective amount of an amino acid compound comprises administering to the human a pharmaceutically effective amount of an amino acid compound consisting essentially of a nitrate of Agmatine.*

5. *The method of claim 1, wherein administering to the human a pharmaceutically effective amount of an amino acid compound comprises administering to the human a*

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pharmaceutically effective amount of an amino acid compound consisting essentially of a nitrate of Beta Alanine.

6. *The method of claim 1, wherein administering to the human a pharmaceutically effective amount of an amino acid compound comprises administering to the human a pharmaceutically effective amount of an amino acid compound consisting essentially of a nitrate of Citrulline.*

7. *The method of claim 1, wherein administering to the human a pharmaceutically effective amount of an amino acid compound comprises administering to the human a pharmaceutically effective amount of an amino acid compound consisting essentially of a nitrate of Creatine.*

8. *The method of claim 1, wherein administering to the human a pharmaceutically effective amount of an amino acid compound comprises administering to the human a pharmaceutically effective amount of an amino acid compound consisting essentially of a nitrate of Glutamine.*

9. *The method of claim 1, wherein administering to the human a pharmaceutically effective amount of an amino acid compound comprises administering to the human a pharmaceutically effective amount of an amino acid compound consisting essentially of a nitrate of L-Histidine.*

10. *The method of claim 1, wherein administering to the human a pharmaceutically effective amount of an amino acid compound comprises administering to the human a pharmaceutically effective amount of an amino acid compound consisting essentially of a nitrate of Isoleucine.*

11. *The method of claim 1, wherein administering to the human a pharmaceutically effective amount of an amino acid compound comprises administering to the human a pharmaceutically effective amount of an amino acid compound consisting essentially of a nitrate of Leucine.*

12. *The method of claim 1, wherein administering to the human a pharmaceutically effective amount of an amino acid compound comprises administering to the human a pharmaceutically effective amount of an amino acid compound consisting essentially of a nitrate of Norvaline.*

13. *The method of claim 1, wherein administering to the human a pharmaceutically effective amount of an amino acid compound comprises administering to the human a pharmaceutically effective amount of an amino acid compound consisting essentially of a nitrate of Valine.*

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EXHIBIT H



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(12) **EX PARTE REEXAMINATION CERTIFICATE** (11040th)
United States Patent
Kramer et al. (10) **Number: US 8,455,531 C1**
(45) **Certificate Issued: *Jan. 23, 2017**

(54) **AMINO ACID COMPOSITIONS**
(75) Inventors: **Ronald Kramer**, Phoenix, AZ (US);
Alexander Nikolaidis, New Kallikratia (GR)
(73) Assignee: **THERMOLIFE INTERNATIONAL, LLC**, Phoenix, AZ (US)

(52) **U.S. Cl.**
CPC **C07D 233/64** (2013.01); **C07C 279/14** (2013.01)
(58) **Field of Classification Search**
None
See application file for complete search history.

Reexamination Request:
No. 90/013,333, Sep. 2, 2014

(56) **References Cited**
To view the complete listing of prior art documents cited during the proceeding for Reexamination Control Number 90/013,333, please refer to the USPTO's public Patent Application Information Retrieval (PAIR) system under the Display References tab.

Reexamination Certificate for:
Patent No.: **8,455,531**
Issued: **Jun. 4, 2013**
Appl. No.: **13/038,537**
Filed: **Mar. 2, 2011**

Primary Examiner — Gary Kunz

(*) Notice: This patent is subject to a terminal disclaimer.

Related U.S. Application Data

(57) **ABSTRACT**
An amino acid composition is disclosed. The composition includes: at least one constituent selected from the group consisting of a nitrate, a nitrite, and both; and at least one constituent amino acid selected from the group consisting of Arginine, Agmatine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, Ornithine, Valine, Aspartic Acid, Cysteine, Glycine, Lysine, Methionine, Proline, Tyrosine, and Phenylalanine. Also disclosed are a method for increasing the bioabsorption of Amino Acids in a human or animal and a method for increasing vasodilative characteristics of Amino Acids in a human or animal.

(63) Continuation-in-part of application No. 12/336,938, filed on Dec. 17, 2008, now Pat. No. 8,034,836, which is a continuation of application No. 11/950,273, filed on Dec. 4, 2007, now Pat. No. 7,777,074.
(60) Provisional application No. 60/973,229, filed on Sep. 18, 2007.
(51) **Int. Cl.**
A61K 31/425 (2006.01)
C07D 233/64 (2006.01)
C07C 279/14 (2006.01)

US 8,455,531 C1

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**EX PARTE
REEXAMINATION CERTIFICATE**

THE PATENT IS HEREBY AMENDED AS
INDICATED BELOW.

Matter enclosed in heavy brackets [] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claims 1-61 are determined to be patentable as amended. New claims 62-122 are added and determined to be patentable.

1. [An amino acid composition] *A solid supplement formulation* comprising:

at least one [constituent selected from the group consisting of a nitrate, a nitrite, and both] *nitrate salt compound*; and

at least one [constituent] *isolated amino acid compound* selected from the group consisting of [.] Agmatine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, Ornithine, Valine, Aspartic Acid, Cysteine, Glycine, Lysine, Methionine, Proline, Tyrosine, and Phenylalanine,

wherein the at least one isolated amino acid compound is a separate compound than the at least one nitrate salt compound.

2. A method for increasing bioabsorption of Amino Acids in a human [or animal], the method comprising administering to the human [or animal] a pharmaceutically effective amount of [an amino acid composition] *a solid supplement formulation* comprising:

at least one [constituent selected from the group consisting of a nitrate, a nitrite, and both] *nitrate salt compound*; and

at least one [constituent] *isolated amino acid compound* selected from the group consisting of Arginine, Agmatine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, Ornithine, Valine, Aspartic Acid, Cysteine, Glycine, Lysine, Methionine, Proline, Tyrosine, and Phenylalanine,

wherein the at least one isolated amino acid compound is a separate compound than the at least one nitrate salt compound.

3. A method for increasing vasodilative characteristics in a human [or animal], the method comprising administering to the human [or animal] a pharmaceutically effective amount of [an amino acid composition] *a solid supplement formulation* comprising:

at least one [constituent selected from the group consisting of a nitrate, a nitrite, and both] *nitrate salt compound*; and

at least one [constituent] *isolated amino acid compound* selected from the group consisting of Agmatine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, Ornithine, Valine, Aspartic Acid, Cysteine, Glycine, Lysine, Methionine, Proline, Tyrosine, and Phenylalanine,

wherein the at least one isolated amino acid compound is a separate compound than the at least one nitrate salt compound.

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4. [An amino acid composition] *A solid supplement formulation* comprising:

at least one [constituent selected from the group consisting of a nitrate, a nitrite, and both] *nitrate salt compound*; and

an isolated Agmatine compound, wherein the Agmatine compound is a separate compound than the at least one nitrate salt compound.

5. [An amino acid composition] *A solid supplement formulation* comprising:

at least one [constituent selected from the group consisting of a nitrate, a nitrite, and both] *nitrate salt compound*; and

an isolated Beta Alanine compound, wherein the Beta Alanine compound is a separate compound than the at least one nitrate salt compound.

6. [An amino acid composition] *A solid supplement formulation* comprising:

at least one [constituent selected from the group consisting of a nitrate, a nitrite, and both] *nitrate salt compound*; and

an isolated Citrulline compound, wherein the Citrulline compound is a separate compound than the at least one nitrate salt compound.

7. [An amino acid composition] *A solid supplement formulation* comprising:

at least one [constituent selected from the group consisting of a nitrate, a nitrite, and both] *nitrate salt compound*; and

an isolated Creatine compound, wherein the Creatine compound is a separate compound than the at least one nitrate salt compound.

8. [An amino acid composition] *A supplement formulation* comprising:

at least one [constituent selected from the group consisting of a nitrate, a nitrite, and both] *nitrate salt compound*; and

an isolated Glutamine compound, wherein the Glutamine compound is a separate compound than the at least one nitrate salt compound.

9. [An amino acid composition] *A supplement formulation* comprising:

at least one [constituent selected from the group consisting of a nitrate, a nitrite, and both] *nitrate salt compound*; and

an isolated L-Histidine compound, wherein the L-Histidine compound is a separate compound than the at least one nitrate salt compound.

10. [An amino acid composition] *A supplement formulation* comprising:

at least one [constituent selected from the group consisting of a nitrate, a nitrite, and both] *nitrate salt compound*; and

an isolated Isoleucine compound, wherein the Isoleucine compound is a separate compound than the at least one nitrate salt compound.

11. [An amino acid composition] *A supplement formulation* comprising:

at least one [constituent selected from the group consisting of a nitrate, a nitrite, and both] *nitrate salt compound*; and

an isolated Leucine compound, wherein the Leucine compound is a separate compound than the at least one nitrate salt compound.

12. [An amino acid composition] *A supplement formulation* comprising:

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at least one [constituent selected from the group consisting of a nitrate, a nitrite, and both] *nitrate salt compound*; and

an isolated Norvaline compound, wherein the Norvaline compound is a separate compound than the at least one nitrate salt compound.

13. [An amino acid composition] *A supplement formulation* comprising:

at least one [constituent selected from the group consisting of a nitrate, a nitrite, and both] *nitrate salt compound*; and

an isolated Ornithine compound, wherein the Ornithine compound is a separate compound than the at least one nitrate salt compound.

14. [An amino acid composition] *A supplement formulation* comprising:

at least one [constituent selected from the group consisting of a nitrate, a nitrite, and both] *nitrate salt compound*; and

an isolated Valine compound, wherein the Valine compound is a separate compound than the at least one nitrate salt compound.

15. [An amino acid composition] *A supplement formulation* comprising:

at least one [constituent selected from the group consisting of a nitrate, a nitrite, and both] *nitrate salt compound*; and

an isolated Aspartic Acid compound, wherein the Aspartic Acid compound is a separate compound than the at least one nitrate salt compound.

16. [An amino acid composition] *A supplement formulation* comprising:

at least one [constituent selected from the group consisting of a nitrate, a nitrite, and both] *nitrate salt compound*; and

an isolated Cysteine compound, wherein the Cysteine compound is a separate compound than the at least one nitrate salt compound.

17. [An amino acid composition] *A supplement formulation* comprising:

at least one [constituent selected from the group consisting of a nitrate, a nitrite, and both] *nitrate salt compound*; and

an isolated Glycine compound, wherein the Glycine compound is a separate compound than the at least one nitrate salt compound.

18. [An amino acid composition] *A supplement formulation* comprising:

at least one [constituent selected from the group consisting of a nitrate, a nitrite, and both] *nitrate salt compound*; and

an isolated Lysine compound, wherein the Lysine compound is a separate compound than the at least one nitrate salt compound.

19. [An amino acid composition] *A supplement formulation* comprising:

at least one [constituent selected from the group consisting of a nitrate, a nitrite, and both] *nitrate salt compound*; and

an isolated Methionine compound, wherein the Methionine compound is a separate compound than the at least one nitrate salt compound.

20. [An amino acid composition] *A supplement formulation* comprising:

at least one [constituent selected from the group consisting of a nitrate, a nitrite, and both] *nitrate salt compound*; and

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an isolated Proline compound, wherein the Proline compound is a separate compound than the at least one nitrate salt compound.

21. [An amino acid composition] *A supplement formulation* comprising:

at least one [constituent selected from the group consisting of a nitrate, a nitrite, and both] *nitrate salt compound*; and

an isolated Tyrosine compound, wherein the Tyrosine compound is a separate compound than the at least one nitrate salt compound.

22. [An amino acid composition] *A supplement formulation* comprising:

at least one [constituent selected from the group consisting of a nitrate, a nitrite, and both] *nitrate salt compound*; and

an isolated Phenylalanine compound, wherein the Phenylalanine compound is a separate compound than the at least one nitrate salt compound.

23. A method for increasing bioabsorption of Amino Acids in a human [or animal], the method comprising administering to the human [or animal] a pharmaceutically effective amount of [an amino acid composition] *a supplement formulation* comprising [at least one constituent selected from the group consisting of a nitrate, a nitrite, and both;] *at least two separate and isolated compounds, wherein a first compound is a nitrate salt and a second compound is Arginine.*

24. A method for increasing bioabsorption of Amino Acids in a human [or animal], the method comprising administering to the human [or animal] a pharmaceutically effective amount of [an amino acid composition] *a supplement formulation* comprising [at least one constituent selected from the group consisting of a nitrate, a nitrite, and both;] *at least two separate and isolated compounds, wherein a first compound is a nitrate salt and a second compound is Agmatine.*

25. A method for increasing bioabsorption of Amino Acids in a human [or animal], the method comprising administering to the human [or animal] a pharmaceutically effective amount of [an amino acid composition] *a supplement formulation* comprising [at least one constituent selected from the group consisting of a nitrate, a nitrite, and both;] *at least two separate and isolated compounds, wherein a first compound is a nitrate salt and a second compound is Beta Alanine.*

26. A method for increasing bioabsorption of Amino Acids in a human [or animal], the method comprising administering to the human [or animal] a pharmaceutically effective amount of [an amino acid composition] *a supplement formulation* comprising [at least one constituent selected from the group consisting of a nitrate, a nitrite, and both;] *at least two separate and isolated compounds, wherein a first compound is a nitrate salt and a second compound is Citrulline.*

27. A method for increasing bioabsorption of Amino Acids in a human [or animal], the method comprising administering to the human [or animal] a pharmaceutically effective amount of [an amino acid composition] *a supplement formulation* comprising [at least one constituent selected from the group consisting of a nitrate, a nitrite, and both;] *at least two separate and isolated compounds, wherein a first compound is a nitrate salt and a second compound is Creatine.*

28. A method for increasing bioabsorption of Amino Acids in a human [or animal], the method comprising administering to the human [or animal] a pharmaceutically

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59. A method for increasing vasodilative characteristics in a human [or animal], the method comprising administering to the human [or animal] a pharmaceutically effective amount of [an amino acid composition] a supplement formulation comprising [at least one constituent selected from the group consisting of a nitrate, a nitrite, and both:] at least two separate and isolated compounds, wherein a first compound is a nitrate salt and a second compound is Proline.

60. A method for increasing vasodilative characteristics in a human [or animal], the method comprising administering to the human [or animal] a pharmaceutically effective amount of [an amino acid composition] a supplement formulation comprising [at least one constituent selected from the group consisting of a nitrate, a nitrite, and both:] at least two separate and isolated compounds, wherein a first compound is a nitrate salt and a second compound is Tyrosine.

61. A method for increasing vasodilative characteristics in a human [or animal], the method comprising administering to the human [or animal] a pharmaceutically effective amount of [an amino acid composition] a supplement formulation comprising [at least one constituent selected from the group consisting of a nitrate, a nitrite, and both:] at least two separate and isolated compounds, wherein a first compound is a nitrate salt and a second compound is Phenylalanine.

62. A solid supplement formulation comprising:

at least one non-ester nitrate compound; and

at least one isolated amino acid compound selected from the group consisting of Agmatine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, Ornithine, Valine, Aspartic Acid, Cysteine, Glycine, Lysine, Methionine, Proline, Tyrosine, and Phenylalanine,

wherein the at least one isolated amino acid compound is a separate compound than the at least one non-ester nitrate compound.

63. A method for increasing bioabsorption of Amino Acids in a human, the method comprising administering to the human a pharmaceutically effective amount of a solid supplement formulation comprising:

at least one non-ester nitrate compound; and

at least one isolated amino acid compound selected from the group consisting of Arginine, Agmatine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, Ornithine, Valine, Aspartic Acid, Cysteine, Glycine, Lysine, Methionine, Proline, Tyrosine, and Phenylalanine,

wherein the at least one isolated amino acid compound is a separate compound than the at least one non-ester nitrate compound.

64. A method for increasing vasodilative characteristics in a human, the method comprising administering to the human a pharmaceutically effective amount of a solid supplement formulation comprising:

at least one non-ester nitrate compound; and

at least one isolated amino acid compound selected from the group consisting of Agmatine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, Ornithine, Valine, Aspartic Acid, Cysteine, Glycine, Lysine, Methionine, Proline, Tyrosine, and Phenylalanine,

wherein the at least one isolated amino acid compound is a separate compound than the at least one non-ester nitrate compound.

65. The solid supplement formulation of claim 62, wherein the at least one isolated amino acid compound is Agmatine.

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66. The solid supplement formulation of claim 62, wherein the at least one isolated amino acid compound is Beta Alanine.

67. The solid supplement formulation of claim 62, wherein the at least one isolated amino acid compound is Citrulline.

68. The solid supplement formulation of claim 62, wherein the at least one isolated amino acid compound is Creatine.

69. The solid supplement formulation of claim 62, wherein the at least one isolated amino acid compound is Glutamine.

70. The solid supplement formulation of claim 62, wherein the at least one isolated amino acid compound is L-Histidine.

71. The solid supplement formulation of claim 62, wherein the at least one isolated amino acid compound is Isoleucine.

72. The solid supplement formulation of claim 62, wherein the at least one isolated amino acid compound is Leucine.

73. The solid supplement formulation of claim 62, wherein the at least one isolated amino acid compound is Norvaline.

74. The solid supplement formulation of claim 62, wherein the at least one isolated amino acid compound is Ornithine.

75. The solid supplement formulation of claim 62, wherein the at least one isolated amino acid compound is Valine.

76. The solid supplement formulation of claim 62, wherein the at least one isolated amino acid compound is Aspartic Acid.

77. The solid supplement formulation of claim 62, wherein the at least one isolated amino acid compound is Cysteine.

78. The solid supplement formulation of claim 62, wherein the at least one isolated amino acid compound is Glycine.

79. The solid supplement formulation of claim 62, wherein the at least one isolated amino acid compound is Lysine.

80. The solid supplement formulation of claim 62, wherein the at least one isolated amino acid compound is Methionine.

81. The solid supplement formulation of claim 62, wherein the at least one isolated amino acid compound is Proline.

82. The solid supplement formulation of claim 62, wherein the at least one isolated amino acid compound is Tyrosine.

83. The solid supplement formulation of claim 62, wherein the at least one isolated amino acid compound is Phenylalanine.

84. The method of claim 63, wherein the at least one isolated amino acid compound is Arginine.

85. The method of claim 63, wherein the at least one isolated amino acid compound is Agmatine.

86. The method of claim 63, wherein the at least one isolated amino acid compound is Beta Alanine.

87. The method of claim 63, wherein the at least one isolated amino acid compound is Citrulline.

88. The method of claim 63, wherein the at least one isolated amino acid compound is Creatine.

89. The method of claim 63, wherein the at least one isolated amino acid compound is Glutamine.

90. The method of claim 63, wherein the at least one isolated amino acid compound is L-Histidine.

91. The method of claim 63, wherein the at least one isolated amino acid compound is Isoleucine.

92. The method of claim 63, wherein the at least one isolated amino acid compound is Leucine.

93. The method of claim 63, wherein the at least one isolated amino acid compound is Norvaline.

94. The method of claim 63, wherein the at least one isolated amino acid compound is Ornithine.

95. The method of claim 63, wherein the at least one isolated amino acid compound is Valine.

96. The method of claim 63, wherein the at least one isolated amino acid compound is Aspartic Acid.

US 8,455,531 C1

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97. The method of claim 63, wherein the at least one isolated amino acid compound is Cysteine.

98. The method of claim 63, wherein the at least one isolated amino acid compound is Glycine.

99. The method of claim 63, wherein the at least one isolated amino acid compound is Lysine.

100. The method of claim 63, wherein the at least one isolated amino acid compound is Methionine.

101. The method of claim 63, wherein the at least one isolated amino acid compound is Proline.

102. The method of claim 63, wherein the at least one isolated amino acid compound is Tyrosine.

103. The method of claim 63, wherein the at least one isolated amino acid compound is Phenylalanine.

104. The method of claim 64, wherein the at least one isolated amino acid compound is Agmatine.

105. The method of claim 64, wherein the at least one isolated amino acid compound is Beta Alanine.

106. The method of claim 64, wherein the at least one isolated amino acid compound is Citrulline.

107. The method of claim 64, wherein the at least one isolated amino acid compound is Creatine.

108. The method of claim 64, wherein the at least one isolated amino acid compound is Glutamine.

109. The method of claim 64, wherein the at least one isolated amino acid compound is L-Histidine.

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110. The method of claim 64, wherein the at least one isolated amino acid compound is Isoleucine.

111. The method of claim 64, wherein the at least one isolated amino acid compound is Leucine.

112. The method of claim 64, wherein the at least one isolated amino acid compound is Norvaline.

113. The method of claim 64, wherein the at least one isolated amino acid compound is Ornithine.

114. The method of claim 64, wherein the at least one isolated amino acid compound is Valine.

115. The method of claim 64, wherein the at least one isolated amino acid compound is Aspartic Acid.

116. The method of claim 64, wherein the at least one isolated amino acid compound is Cysteine.

117. The method of claim 64, wherein the at least one isolated amino acid compound is Glycine.

118. The method of claim 64, wherein the at least one isolated amino acid compound is Lysine.

119. The method of claim 64, wherein the at least one isolated amino acid compound is Methionine.

120. The method of claim 64, wherein the at least one isolated amino acid compound is Proline.

121. The method of claim 64, wherein the at least one isolated amino acid compound is Tyrosine.

122. The method of claim 64, wherein the at least one isolated amino acid compound is Phenylalanine.

* * * * *

EXHIBIT I



US008466187C1

(12) **EX PARTE REEXAMINATION CERTIFICATE** (11036th)

United States Patent
Kramer et al.

(10) **Number:** **US 8,466,187 C1**
(45) **Certificate Issued:** ***Jan. 18, 2017**

- (54) **AMINO ACID COMPOSITIONS**
- (75) Inventors: **Ronald Kramer**, Phoenix, AZ (US);
Alexander Nikolaidis, New Kallikratia (GR)
- (73) Assignee: **THERMOLIFE INTERNATIONAL LLC**, Phoenix, AZ (US)

Reexamination Request:
No. 90/012,916, Jul. 9, 2013
No. 90/013,539, Jun. 26, 2015

Reexamination Certificate for:
Patent No.: **8,466,187**
Issued: **Jun. 18, 2013**
Appl. No.: **13/038,615**
Filed: **Mar. 2, 2011**

(*) Notice: This patent is subject to a terminal disclaimer.

Related U.S. Application Data

- (63) Continuation-in-part of application No. 12/336,938, filed on Dec. 17, 2008, now Pat. No. 8,034,836, which is a continuation of application No. 11/950,273, filed on Dec. 4, 2007, now Pat. No. 7,777,074.
- (60) Provisional application No. 60/973,229, filed on Sep. 18, 2007.

- (51) **Int. Cl.**
A61K 31/415 (2006.01)
C07D 233/64 (2006.01)
- (52) **U.S. Cl.**
CPC *C07D 233/64* (2013.01)
- (58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

To view the complete listing of prior art documents cited during the proceeding for Reexamination Control Numbers 90/012,916 and 90/013,539, please refer to the USPTO's public Patent Application Information Retrieval (PAIR) system under the Display References tab.

Primary Examiner — Dwayne Jones

(57) **ABSTRACT**

Methods for increasing athletic performance, distribution of various Amino Acids to muscles, and solubility of various Amino Acids in a human or animal by administering an amino acid composition that includes: at least one constituent selected from the group consisting of a nitrate, a nitrite, and both; and at least one constituent amino acid selected from the group consisting of Arginine, Agmatine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, Ornithine, Valine, Aspartic Acid, Cysteine, Glycine, Lysine, Methionine, Proline, Tyrosine, and Phenylalanine.

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**EX PARTE
REEXAMINATION CERTIFICATE**

THE PATENT IS HEREBY AMENDED AS
INDICATED BELOW.

Matter enclosed in heavy brackets [] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claims 1-60 are determined to be patentable as amended.

New claims 61-69 are added and determined to be patentable.

1. A method for increasing athletic performance in a human or animal, the method comprising administering to the human or animal a pharmaceutically effective amount of an amino acid composition comprising [at least one constituent selected from the group consisting of a nitrate, a nitrite, and both, and] Arginine and at least one constituent selected from the group consisting of a salt of a nitrate (NO_3^-) and a mixed salt of a nitrate (NO_3^-).

2. A method for increasing distribution of Amino Acids to muscles in a human or animal, the method comprising administering to the human or animal a pharmaceutically effective amount of an amino acid composition comprising [at least one constituent selected from the group consisting of a nitrate, a nitrite, and both, and] Arginine and at least one constituent selected from the group consisting of a salt of a nitrate (NO_3^-) and a mixed salt of a nitrate (NO_3^-).

3. A method for increasing solubility of Amino Acids in a human or animal, the method comprising administering to the human or animal a pharmaceutically effective amount of an amino acid composition comprising [at least one constituent selected from the group consisting of a nitrate, a nitrite, and both, and] Arginine and at least one constituent selected from the group consisting of a salt of a nitrate (NO_3^-) and a mixed salt of a nitrate (NO_3^-).

4. A method for increasing athletic performance in a human or animal, the method comprising administering to the human or animal a pharmaceutically effective amount of an amino acid composition comprising at least one constituent selected from the group consisting of a salt of a nitrate (NO_3^-), a mixed salt of a nitrate (NO_3^-), a salt of a nitrite [, and both,] (NO_2^-), and a mixed salt of a nitrite (NO_2^-); and Agmatine.

5. A method for increasing athletic performance in a human or animal, the method comprising administering to the human or animal a pharmaceutically effective amount of an amino acid composition comprising at least one constituent selected from the group consisting of a salt of a nitrate (NO_3^-), a mixed salt of a nitrate (NO_3^-), a salt of a nitrite [, and both,] (NO_2^-), and a mixed salt of a nitrite (NO_2^-); and Beta Alanine.

6. A method for increasing athletic performance in a human or animal, the method comprising administering to the human or animal a pharmaceutically effective amount of an amino acid composition comprising at least one constituent selected from the group consisting of a salt of a nitrate (NO_3^-), a mixed salt of a nitrate (NO_3^-), a salt of a nitrite [, and both,] (NO_2^-), and a mixed salt of a nitrite (NO_2^-); and Citrulline.

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7. A method for increasing athletic performance in a human or animal, the method comprising administering to the human or animal a pharmaceutically effective amount of an amino acid composition comprising at least one constituent selected from the group consisting of a salt of a nitrate (NO_3^-), a mixed salt of a nitrate (NO_3^-), a salt of a nitrite [and both,] (NO_2^-), and a mixed salt of a nitrite (NO_2^-); and Creatine.

8. A method for increasing athletic performance in a human or animal, the method comprising administering to the human or animal a pharmaceutically effective amount of an amino acid composition comprising at least one constituent selected from the group consisting of a salt of a nitrate (NO_3^-), a mixed salt of a nitrate (NO_3^-), a salt of a nitrite [, and both,] (NO_2^-), and a mixed salt of a nitrite (NO_2^-); and Glutamine.

9. A method for increasing athletic performance in a human or animal, the method comprising administering to the human or animal a pharmaceutically effective amount of an amino acid composition comprising at least one constituent selected from the group consisting of a salt of a nitrate (NO_3^-), a mixed salt of a nitrate (NO_3^-), a salt of a nitrite [, and both,] (NO_2^-), and a mixed salt of a nitrite (NO_2^-); and L-Histidine.

10. A method for increasing athletic performance in a human or animal, the method comprising administering to the human or animal a pharmaceutically effective amount of an amino acid composition comprising at least one constituent selected from the group consisting of a salt of a nitrate (NO_3^-), a mixed salt of a nitrate (NO_3^-), a salt of a nitrite [, and both,] (NO_2^-), and a mixed salt of a nitrite (NO_2^-); and Isoleucine.

11. A method for increasing athletic performance in a human or animal, the method comprising administering to the human or animal a pharmaceutically effective amount of an amino acid composition comprising at least one constituent selected from the group consisting of a salt of a nitrate (NO_3^-), a mixed salt of a nitrate (NO_3^-), a salt of a nitrite [, and both,] (NO_2^-), and a mixed salt of a nitrite (NO_2^-); and Leucine.

12. A method for increasing athletic performance in a human or animal, the method comprising administering to the human or animal a pharmaceutically effective amount of an amino acid composition comprising at least one constituent selected from the group consisting of a salt of a nitrate (NO_3^-), a mixed salt of a nitrate (NO_3^-), a salt of a nitrite [, and both,] (NO_2^-), and a mixed salt of a nitrite (NO_2^-); and Norvaline.

13. A method for increasing athletic performance in a human or animal, the method comprising administering to the human or animal a pharmaceutically effective amount of an amino acid composition comprising at least one constituent selected from the group consisting of a salt of a nitrate (NO_3^-), a mixed salt of a nitrate (NO_3^-), a salt of a nitrite [, and both,] (NO_2^-), and a mixed salt of a nitrite (NO_2^-); and Ornithine.

14. A method for increasing athletic performance in a human or animal, the method comprising administering to the human or animal a pharmaceutically effective amount of an amino acid composition comprising at least one constituent selected from the group consisting of a salt of a nitrate (NO_3^-), a mixed salt of a nitrate (NO_3^-), a salt of a nitrite [, and both,] (NO_2^-), and a mixed salt of a nitrite (NO_2^-); and Valine.

15. A method for increasing athletic performance in a human or animal, the method comprising administering to the human or animal a pharmaceutically effective amount of

Arginine and at least one constituent selected from the group consisting of a salt of a nitrate (NO_3^-) and a mixed salt of a nitrate (NO_3^-), wherein the increased distribution of amino acid to muscles in the human or animal is mediated by a thiol donor. 5

67. *The method of claim 66, wherein the thiol donor is glutathione.*

68. *A method for increasing solubility of Amino Acids in a human or animal, the method comprising administering to the human or animal a pharmaceutically effective amount of an amino acid composition comprising Arginine and at least one constituent selected from the group consisting of a salt of a nitrate (NO_3^-) and a mixed salt of a nitrate (NO_3^-), wherein the increased solubility of Amino Acids in the human or animal is mediated by a thiol donor.* 10 15

69. *The method of claim 68, wherein the thiol donor is glutathione.*

* * * * *

EXHIBIT II

(12) **EX PARTE REEXAMINATION CERTIFICATE** (11013th)
United States Patent
Kramer et al.

(10) **Number:** **US 8,183,288 C1**

(45) **Certificate Issued:** ***Dec. 22, 2016**

(54) **AMINO ACID COMPOUNDS**

(75) Inventors: **Ronald Kramer**, Phoenix, AZ (US);
Alexander Nikolaidis, New Kallikratia
 (GR)

(73) Assignee: **THERMOLIFE INTERNATIONAL,
 LLC**, Phoenix, AZ (US)

Reexamination Request:

No. 90/013,526, Jun. 26, 2015

Reexamination Certificate for:

Patent No.: **8,183,288**
 Issued: **May 22, 2012**
 Appl. No.: **12/946,114**
 Filed: **Nov. 15, 2010**

(*) Notice: This patent is subject to a terminal disclaimer.

Related U.S. Application Data

(63) Continuation of application No. 12/336,938, filed on Dec. 17, 2008, now Pat. No. 8,034,836, which is a continuation of application No. 11/950,273, filed on Dec. 4, 2007, now Pat. No. 7,777,074.

(60) Provisional application No. 60/973,229, filed on Sep. 18, 2007.

(51) **Int. Cl.**

A61K 31/195 (2006.01)

C07C 229/06 (2006.01)

C07D 233/64 (2006.01)

C07C 279/14 (2006.01)

(52) **U.S. Cl.**

CPC **C07C 229/06** (2013.01); **C07C 279/14**
 (2013.01); **C07D 233/64** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

(56)

References Cited

To view the complete listing of prior art documents cited during the proceeding for Reexamination Control Number 90/013,526, please refer to the USPTO's public Patent Application Information Retrieval (PAIR) system under the Display References tab.

Primary Examiner — Dwayne Jones

(57)

ABSTRACT

A method for increasing the bioabsorption of amino acids in a human or animal is disclosed. The method includes administering to the human or animal a pharmaceutically effective amount of an amino acid compound consisting essentially of a nitrate or nitrite of an amino acid selected from the group consisting of Arginine, Agmatine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Iso-leucine, Leucine, Norvaline, Ornithine, and Valine.

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**EX PARTE
REEXAMINATION CERTIFICATE**

THE PATENT IS HEREBY AMENDED AS
INDICATED BELOW.

Matter enclosed in heavy brackets [] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claim 1 is determined to be patentable as amended.

New claims 2-13 are added and determined to be patentable.

1. A method for increasing the bioabsorption of amino acids in a human [or animal], the method comprising administering *orally* to the human [or animal] a pharmaceutically effective amount of an amino acid compound consisting essentially of a nitrate [or nitrite] of an amino acid selected from the group consisting of Arginine, Agmatine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, Ornithine, and Valine.

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2. *The method of claim 1, wherein the amino acid compound consists essentially of a nitrate of Arginine.*

3. *The method of claim 1, wherein the amino acid compound consists essentially of a nitrate of Agmatine.*

5 4. *The method of claim 1, wherein the amino acid compound consists essentially of a nitrate of Beta Alanine.*

5. *The method of claim 1, wherein the amino acid compound consists essentially of a nitrate of Citrulline.*

10 6. *The method of claim 1, wherein the amino acid compound consists essentially of a nitrate of Creatine.*

7. *The method of claim 1, wherein the amino acid compound consists essentially of a nitrate of Glutamine.*

8. *The method of claim 1, wherein the amino acid compound consists essentially of a nitrate of L-Histidine.*

15 9. *The method of claim 1, wherein the amino acid compound consists essentially of a nitrate of Isoleucine.*

10. *The method of claim 1, wherein the amino acid compound consists essentially of a nitrate of Leucine.*

20 11. *The method of claim 1, wherein the amino acid compound consists essentially of a nitrate of Norvaline.*

12. *The method of claim 1, wherein the amino acid compound consists essentially of a nitrate of Ornithine.*

13. *The method of claim 1, wherein the amino acid compound consists essentially of a nitrate of Valine.*

* * * * *

EXHIBIT J



US008952046C1

(12) **EX PARTE REEXAMINATION CERTIFICATE** (11042nd)
United States Patent
Kramer et al.

(10) **Number:** **US 8,952,046 C1**
(45) **Certificate Issued:** ***Jan. 23, 2017**

- (54) **AMINO ACID COMPOSITIONS**
- (71) Applicant: **ThermoLife International, LLC**,
Phoenix, AZ (US)
- (72) Inventors: **Ronald Kramer**, Phoenix, AZ (US);
Alexander Nikolaidis, New Kallikratia
(GR)
- (73) Assignee: **THERMOLIFE INTERNATIONAL,**
LLC, Phoenix, AZ (US)

- (60) Provisional application No. 60/973,229, filed on Sep. 18, 2007.
- (51) **Int. Cl.**
A61K 31/415 (2006.01)
C07D 233/64 (2006.01)
- (52) **U.S. Cl.**
CPC **C07D 233/64** (2013.01)
- (58) **Field of Classification Search**
None
See application file for complete search history.

Reexamination Request:
No. 90/013,519, Jun. 16, 2015

Reexamination Certificate for:
Patent No.: **8,952,046**
Issued: **Feb. 10, 2015**
Appl. No.: **13/920,081**
Filed: **Jun. 17, 2013**

(*) Notice: This patent is subject to a terminal disclaimer.

Related U.S. Application Data

- (63) Continuation of application No. 13/038,615, filed on Mar. 2, 2011, now Pat. No. 8,466,187, which is a continuation-in-part of application No. 12/336,938, filed on Dec. 17, 2008, now Pat. No. 8,034,836, which is a continuation of application No. 11/950,273, filed on Dec. 4, 2007, now Pat. No. 7,777,074.

(56) **References Cited**

To view the complete listing of prior art documents cited during the proceedings for Reexamination Control Numbers 90/013,519, please refer to the USPTO's public Patent Application Information Retrieval (PAIR) system under the Display References tab.

Primary Examiner — Gary Kunz

(57) **ABSTRACT**

A composition and a supplement formulation includes: at least one constituent selected from the group consisting of a nitrate salt, a nitrite salt, and both, and at least one constituent amino acid selected from the group consisting of Arginine, Agmatine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, Ornithine, Valine, Aspartic Acid, Cysteine, Glycine, Lysine, Methione, Proline, Tyhrosine, and Phenylalainine.

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EX PARTE

REEXAMINATION CERTIFICATE

THE PATENT IS HEREBY AMENDED AS
INDICATED BELOW.

Matter enclosed in heavy brackets [] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claims 5 and 12 are cancelled.

Claims 1-4, 6-11 and 13-14 are determined to be patentable as amended.

New claims 15-54 are added and determined to be patentable.

1. A *solid* composition comprising:

at least one [constituent selected from the group consisting of a nitrate, a nitrite, and both] *isolated nitrate salt compound*; and

at least one [constituent] *isolated amino acid compound* selected from the group consisting of Arginine, Agmatine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, Ornithine, Valine, Aspartic Acid, Cysteine, Glycine, Lysine, Methionine, Proline, Tyrosine, and Phenylalanine,

wherein the at least one *isolated amino acid compound* is a separate compound than the at least one *isolated nitrate salt compound*.

2. The *solid* composition of claim 1 further comprising one or more additional components selected from the group consisting of a carrier, an excipient, a binder, a colorant, a flavoring agent, a preservative, a buffer, a dilutant, and any combination thereof.

3. The *solid* composition of claim 1 in a dosage form selected from the group consisting of a capsule, a cachet, a pill, a tablet, a powder, a granule, a pellet, a bead, a particle, a troche, and a lozenge[, and a gel].

4. The *solid* composition of claim 1, wherein the at least one nitrate salt comprises sodium nitrate, potassium nitrate, barium nitrate, calcium nitrate, and any combination thereof[, and the nitrite salt comprises sodium nitrite, potassium nitrite, barium nitrite, calcium nitrite, and any combination thereof].

6. The *solid* composition of claim [5] 4, wherein the at least one nitrate salt *compound* comprises sodium nitrate.

7. The composition of claim [5] 4, wherein the at least one nitrate salt *compound* comprises potassium nitrate.

8. A *solid* supplement formulation comprising:

at least one *isolated nitrate salt* compound [constituent selected from the group consisting of a nitrate salt, a nitrite salt, and both]; and

at least one [constituent] *isolated amino acid compound* selected from the group consisting of Arginine, Agmatine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, Ornithine, Valine, Aspartic Acid, Cysteine, Glycine, Lysine, Methionine, Proline, Tyrosine, and Phenylalanine,

wherein the at least one *isolated amino acid compound* is a separate compound than the at least one *isolated nitrate salt compound*.

9. The *solid* supplement formulation of claim 8 further comprising one or more additional components selected

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from the group consisting of a carrier, an excipient, a binder, a colorant, a flavoring agent, a preservative, a buffer, a dilutant, and any combination thereof.

10. The *solid* supplement formulation of claim 8 in a dosage form selected from the group consisting of a capsule, a cachet, a pill, a tablet, a powder, a granule, a pellet, a bead, a particle, a troche, and a lozenge[, and a gel].

11. The *solid* supplement formulation of claim 8, wherein at least one *isolated* nitrate salt comprises sodium nitrate, potassium nitrate, barium nitrate, calcium nitrate, and any combination thereof[, and the nitrite salt comprises sodium nitrite, potassium nitrite, barium nitrite, calcium nitrite, and any combination thereof].

13. The *solid* supplement formulation of claim [12] 11, wherein the *isolated* nitrate salt comprises sodium nitrate.

14. The *solid* supplement formulation of claim [12] 11, wherein the *isolated* nitrate salt comprises potassium nitrate.

15. The *solid* composition of claim 1, wherein the at least one *isolated amino acid compound* is Arginine.

16. The *solid* composition of claim 1, wherein the at least one *isolated amino acid compound* is Agmatine.

17. The *solid* composition of claim 1, wherein the at least one *isolated amino acid compound* is Beta Alanine.

18. The *solid* composition of claim 1, wherein the at least one *isolated amino acid compound* is Citrulline.

19. The *solid* composition of claim 1, wherein the at least one *isolated amino acid compound* is Creatine.

20. The *solid* composition of claim 1, wherein the at least one *isolated amino acid compound* is Glutamine.

21. The *solid* composition of claim 1, wherein the at least one *isolated amino acid compound* is L-Histidine.

22. The *solid* composition of claim 1, wherein the at least one *isolated amino acid compound* is Isoleucine.

23. The *solid* composition of claim 1, wherein the at least one *isolated amino acid compound* is Leucine.

24. The *solid* composition of claim 1, wherein the at least one *isolated amino acid compound* is Norvaline.

25. The *solid* composition of claim 1, wherein the at least one *isolated amino acid compound* is Ornithine.

26. The *solid* composition of claim 1, wherein the at least one *isolated amino acid compound* is Valine.

27. The *solid* composition of claim 1, wherein the at least one *isolated amino acid compound* is Aspartic Acid.

28. The *solid* composition of claim 1, wherein the at least one *isolated amino acid compound* is Cysteine.

29. The *solid* composition of claim 1, wherein the at least one *isolated amino acid compound* is Glycine.

30. The *solid* composition of claim 1, wherein the at least one *isolated amino acid compound* is Lysine.

31. The *solid* composition of claim 1, wherein the at least one *isolated amino acid compound* is Methionine.

32. The *solid* composition of claim 1, wherein the at least one *isolated amino acid compound* is Proline.

33. The *solid* composition of claim 1, wherein the at least one *isolated amino acid compound* is Tyrosine.

34. The *solid* composition of claim 1, wherein the at least one *isolated amino acid compound* is Phenylalanine.

35. The *solid* supplement formulation of claim 8, wherein the at least one *isolated amino acid compound* is Arginine.

36. The *solid* supplement formulation of claim 8, wherein the at least one *isolated amino acid compound* is Agmatine.

37. The *solid* supplement formulation of claim 8, wherein the at least one *isolated amino acid compound* is Beta Alanine.

38. The *solid* supplement formulation of claim 8, wherein the at least one *isolated amino acid compound* is Citrulline.

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39. The solid supplement formulation of claim 8, wherein the at least one isolated amino acid compound is Creatine.

40. The solid supplement formulation of claim 8, wherein the at least one isolated amino acid compound is Glutamine.

41. The solid supplement formulation of claim 8, wherein the at least one isolated amino acid compound is L-Histidine.

42. The solid supplement formulation of claim 8, wherein the at least one isolated amino acid compound is Isoleucine.

43. The solid supplement formulation of claim 8, wherein the at least one isolated amino acid compound is Leucine.

44. The solid supplement formulation of claim 8, wherein the at least one isolated amino acid compound is Norvaline.

45. The solid supplement formulation of claim 8, wherein the at least one isolated amino acid compound is Ornithine.

46. The solid supplement formulation of claim 8, wherein the at least one isolated amino acid compound is Valine.

47. The solid supplement formulation of claim 8, wherein the at least one isolated amino acid compound is Aspartic Acid.

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48. The solid supplement formulation of claim 8, wherein the at least one isolated amino acid compound is Cysteine.

49. The solid supplement formulation of claim 8, wherein the at least one isolated amino acid compound is Glycine.

50. The solid supplement formulation of claim 8, wherein the at least one isolated amino acid compound is Lysine.

51. The solid supplement formulation of claim 8, wherein the at least one isolated amino acid compound is Methionine.

52. The solid supplement formulation of claim 8, wherein the at least one isolated amino acid compound is Proline.

53. The solid supplement formulation of claim 8, wherein the at least one isolated amino acid compound is Tyrosine.

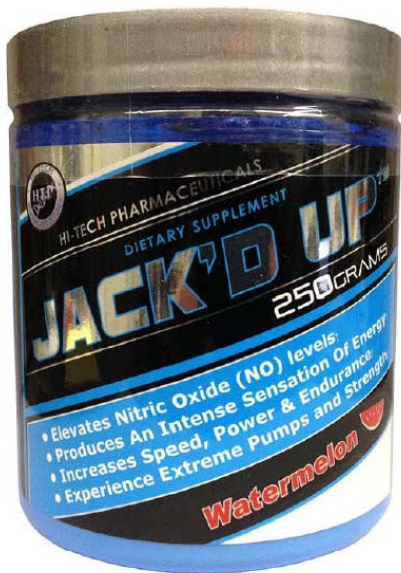
54. The solid supplement formulation of claim 8, wherein the at least one isolated amino acid compound is Phenylalanine.

* * * * *

EXHIBIT K



Supplement Facts		
Serving Size: 4 Capsules	Servings Per Container: 50	
Amount Per Serving	% Daily Value	
Proprietary Blend: 3000mg	*	
Creatine Nitrate, Dicalcium Phosphate, Vitamin C		
* Daily Value not established.		
Other Ingredients: Gelatin, Titanium Dioxide, FD&C Red #40, FD&C Blue #1		



Supplement Facts		
Serving Size: 1 Scoop (2.55grams)	Servings Per Container: 50	
Amount Per Servings	% Daily Value	
Proprietary Blend	4145mg	
L-Arginine Alpha-Ketoglutarate 2:1, Creatine Monohydrate, Beta Alanine, Creatine HCl, Creatine Nitrate, Disodium Creatine Phosphate, Caffeine, 1,3-Dimethylamylamine HCl, Agmatine Sulphate (AgmaPure®), Schisandra Chinensis (Berry) Extract.		
* Daily value not established		
Other Ingredients: Citric Acid, Natural Flavors, Acesulfame-K, Sucralose, Silicon Dioxide, Grape Skin Extract.		
Directions For JACK'D UP: Stir 3 Ultra-Concentrated scoops with 4-8 ounces of cold water and consume 30-45 minutes before beginning activity. Due to extreme potency, it's highly recommended to assess tolerance by using a 1.5 scoop serving before consuming full dose, especially if you are sensitive to stimulants. Some individuals may find 1, 1.5 or 2 scoops per serving is the ideal dose for extremely intense workouts. DO NOT EXCEED 3 SCOOPS IN ANY 24 HOUR PERIOD		
JACK'D UP is a product specifically formulated to help fuel your body through your workout. Maximize the benefits of your workout with higher energy levels, performance, and stamina.		



**AGGRESSION YOU DESIRE
LIFT MORE WEIGHT
LONG-LASTING ENERGY**



**7.9
OVERALL
RATING**

JACK'D UP™



**EXTREME
STRENGTH
& PUMP!**

**INTENSE
ENERGY**

**THE MOST INTENSE
PRE-WORKOUT
EVER CREATED**



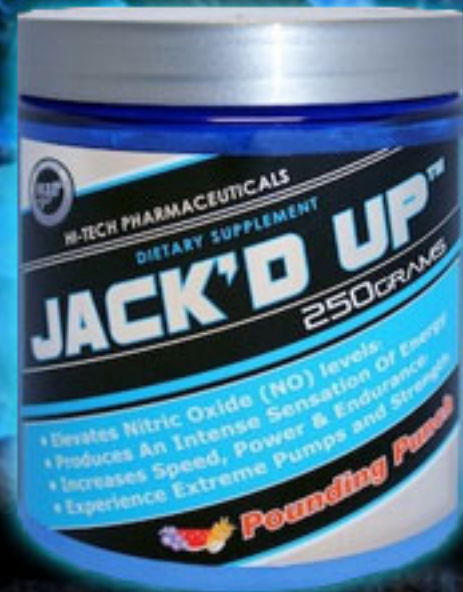
THE ULTIMATE PRE-WORKOUT FORMULA!



JACK'D UP™

250 GRAMS

- Elevates Nitric Oxide (NO) levels
- Produces An Intense Sensation of Energy
- Increases Speed, Power & Endurance
- Experience Extreme Pumps and Strength



GET IT NOW

***Compared to a new and improved version of the original Jack 3D by USP Labs**



Supplement Facts		
Serving Size: 15.5 grams (one rounded scoop)		
Servings Per Container: 25		
	Amount Per Serving	% Daily Value
SYNTHENOX-CARNOSINE/NITRIC OXIDE COMPLEX: 6,500mg *		
Beta Alanine, I-Citruline DL-Malate 2:1, Arginine Alpha Ketoglutarate		
MESOSWELL-CELL VOLUMIZING		
ATP MATRIX: 4,500mg *		
Di-Creatine Malate, L-Taurine, Creatine Nitrate, Ascorbic Acid, Creatinol-O-Phosphate, Agmatine Sulfate.		
NEUROMORPH-NEURO ENERGIZED		
STIMULANT MATRIX: 1,860mg *		
Glucoronolactone, Methylxanthine Anhydrous, Acacia Rigidula Extract (leaves), Theobromine, Naringin, Isopropylorsynephrine HCl		
* Daily value not established.		
Other Ingredients: Malic Acid, Natural & Artificial Flavors, Acesulfame-K, Sucralose, Silicon Dioxide, FD&C Red #40.		



Supplement Facts		
Serving Size: 15.5 grams (one rounded scoop)		
Servings Per Container: 25		
	Amount Per Serving	% Daily Value
SYNTHENOX-CARNOSINE/NITRIC OXIDE COMPLEX: 6,500mg *		
Beta Alanine, I-Citruline DL-Malate 2:1, Arginine Alpha Ketoglutarate		
MESOSWELL-CELL VOLUMIZING		
ATP MATRIX: 4,500mg *		
Di-Creatine Malate, L-Taurine, Creatine Nitrate, Ascorbic Acid, Creatinol-O-Phosphate, Agmatine Sulfate		
NEUROMORPH-NEURO ENERGIZED		
STIMULANT MATRIX: 1,870mg *		
Glucoronolactone, Methylxanthine Anhydrous, 3,7-Dihydro-3,7-Dimethyl-1H-Purine-2,6-Dione, Naringin, Geranaburn (geranium oil extract)		
* Daily value not established.		
Other Ingredients: Malic Acid, Natural & Artificial Flavors, Acesulfame-K, Sucralose, Silicon Dioxide, FD&C Red #40.		



THE KING OF PREWORKOUTS

MESOMORPH™

ULTIMATE PRE-WORKOUT COMPLEX



25
servings

NO
fillers

**UNLEASH YOUR TRUE
GENETIC POTENTIAL**





APS

**NOW
AVAILABLE!**

MESOMORPH™

THE KING
OF PREWORKOUTS

MESOMORPH

THE ULTIMATE PREWORKOUT



SUPERCHARGED ENERGY
ULTIMATE PREWORKOUT
UNLEASH YOUR TRUE
GENETIC POTENTIAL!



In the early 1990s, EAS introduced its original brand of creatine monohydrate and thus sparked the first great revolution into the sports nutrition market. Since the release of Phosphagen, Hi-Tech has worked diligently to develop a creatine product that would represent the same quantum leap in nutritional technology and consumer value that EAS' Phosphagen did. Now, nearly twenty years after EAS launched Phosphagen, Hi-Tech Pharmaceuticals is launching a new and improved Phosphagen™!

The new Phosphagen™ optimizes the benefits of creatine supplementation because it doesn't just stop with incorporating the finest ingredients to enhance creatine availability for utilization in the phosphagen system. The new Phosphagen™ also incorporates ingredients that create a synergistic effect with creatine by enhancing creatine uptake and by delaying the onset of muscular fatigue during intense muscular contraction. This provides the creatine ingredients in Phosphagen™ with the opportunity to continue to perform longer in the phosphagen system, which extends the duration and intensity of muscular contraction to elicit a greater hypertrophic response. Thus, the bodybuilder who wisely chooses Phosphagen™ over another typical creatine product will have the extra amount of muscle fuel available to complete the one additional rep required to pull the trigger for muscles to grow.

Phosphagen™ is back to maximize the creatine endgame with renewed thinking outside the creatine box, which represents what creatine supplementation is capable of achieving in its most aggressive and comprehensive form. Phosphagen™, by Hi-Tech Pharmaceuticals... more weight... more reps... more muscle!

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to treat, cure, diagnose or prevent any disease.



PHOSPHAGEN™

HPLC Pure Creatine Complex

Dietary Supplement

500 grams




Supplement Facts

Serving Size: 1 heaping scoop (15 grams) Servings Per Container: 33

	Amount Per Serving	% Daily Value
Proprietary Blend with Micro-Rx™ and Extend-Rx™ Technologies:		
Creatine HCL, Creatine Nitrate, Disodium Creatine Phosphate Tetrahydrate, Beta-alanine, CreatPhos™ Creatine Phosphate, Guanidinopropionic acid	12.5 grams	*

*Daily Value Not Established

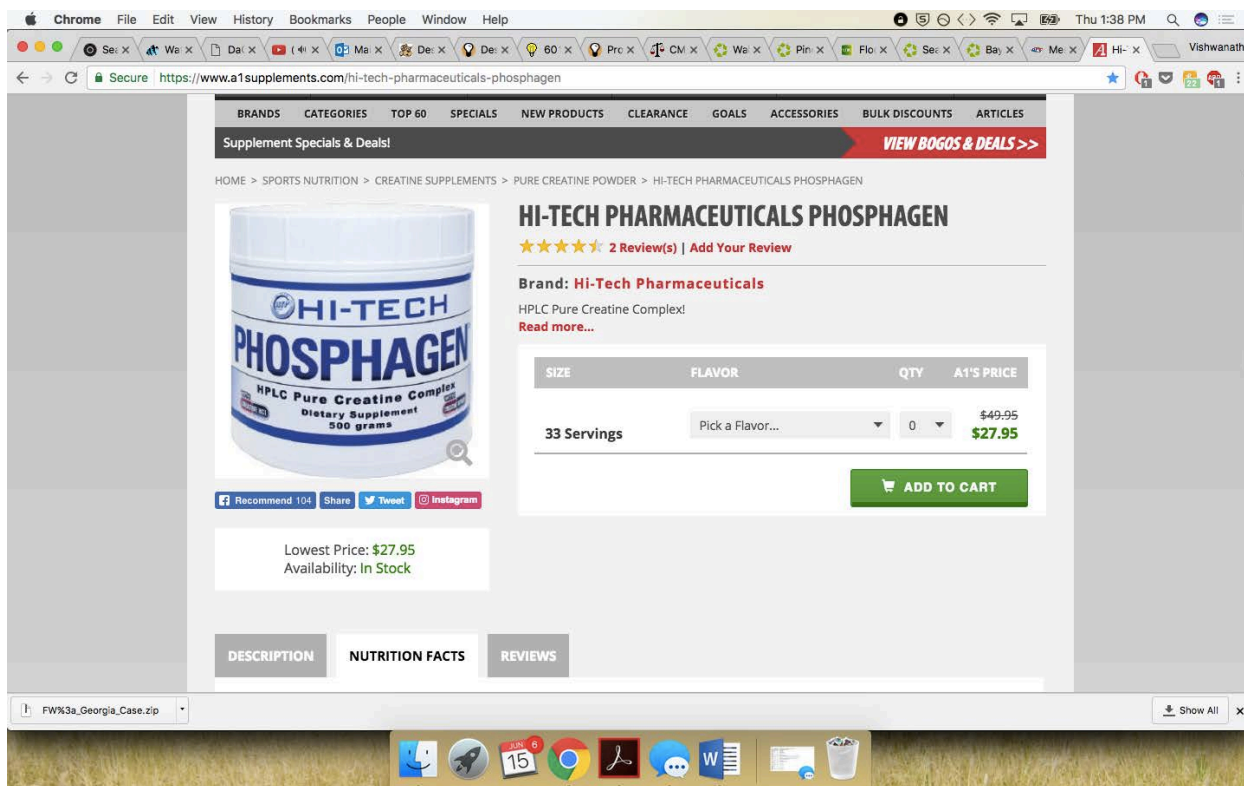
Other Ingredients: Malic Acid, Citric Acid, Stearic Acid, Naturally Sweet™ (Erythritol, Maltitol, Maltodextrin, Xylitol, Tagatose, Sucralose), Silica, Natural and Artificial Flavors

Suggested Use: On training days: To optimize creatine uptake and PCR deposition for enhanced muscle work performance and muscular development, take 1 scoop of Phosphagen™ with 8-10 ounces of water 20-30 minutes prior to training. On non-training days: To volumize muscle cells, speed recovery, and maximize saturation of PCR stores, take 1 scoop of Phosphagen™ with 8-10 ounces of water anytime as desired during the day.



HI-TECH PHARMACEUTICALS, INC.
 6015-G Unity Drive • Norcross, GA 30071
 www.hitechpharma.com • 1.888.855.7919





The screenshot shows a Chrome browser window with the URL <https://www.a1supplements.com/hi-tech-pharmaceuticals-phosphagen>. The page features a navigation bar with categories like BRANDS, CATEGORIES, TOP 60, SPECIALS, NEW PRODUCTS, CLEARANCE, GOALS, ACCESSORIES, BULK DISCOUNTS, and ARTICLES. Below the navigation is a banner for 'Supplement Specials & Deals!' with a 'VIEW BOGOS & DEALS >>' button. The main content area displays the product 'HI-TECH PHARMACEUTICALS PHOSPHAGEN' with a 2-star rating and '2 Review(s) | Add Your Review'. The brand is identified as 'Hi-Tech Pharmaceuticals' and the product is 'HPLC Pure Creatine Complex'. A table shows the product size as '33 Servings' and the price as '\$27.95' (original price '\$49.95'). There is an 'ADD TO CART' button. At the bottom, there are tabs for 'DESCRIPTION', 'NUTRITION FACTS', and 'REVIEWS'. The browser's taskbar at the bottom shows various application icons and the system clock.

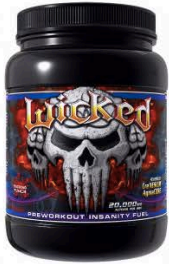
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Seas W: X Da X W: X Me X Desic De X 60 X Pr X Cl X We X Pinec Flc X Se X Ba X Me X Hi X Vishwanath

Secure https://www.a1supplements.com/innovative-laboratories-wicked

Supplement Specials & Deals! **VIEW BOGOS & DEALS >>**

HOME > SPORTS NUTRITION > PRE-WORKOUT SUPPLEMENTS > INNOVATIVE LABORATORIES WICKED



Tweet 

Lowest Price: **\$37.95**
Availability: **In Stock**

INNOVATIVE LABORATORIES WICKED

★★★★☆ 12 Review(s) | [Add Your Review](#)

Brand: Innovative Laboratories

Wicked Is Simply A Pre-Workout Putting Your Body In "Beast Mode" And Causes You To Have Wicked Energy, Skin Tearing Pumps & Freaky Vascularity!
[Read more...](#)

BUY 1, GET 1 50% OFF!
Buy 1 Innovative Laboratories Wicked - 30 Servings, Get 1 50% OFF!

SIZE	FLAVOR	QTY	AT'S PRICE
BUY 1, GET 1 50% OFF!	Pick a Flavor...	0	\$64.95
30 Servings			\$37.95

ADD TO CART

DESCRIPTION NUTRITION FACTS REVIEWS

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Secure https://www.a1supplements.com/innovative-laboratories-wicked

DESCRIPTION NUTRITION FACTS REVIEWS

30 Servings Grueling Grape

Supplement Facts

Serving Size: 2 Scoops (11g)
Servings Per Container: 30

- Vitamin C 250mg
- Niacin 400mg
- Vitamin B6 20mg
- Inositol 100mg
- N.O. Amplification Matrix 5,000mg
- Beta-Alanine, L-Citrulline Silicate, Red Wine Extract
- Anabolic Cell Volumizer 4,010mg
- Creatine Nitrate, 2-Aminoethanesulfonic acid Silicate,
- Agmatine Silicate, D-Ribose, Creatinol-O Phosphate
- eurogenic Energizers 390mg
- Caffeine Anhydrous, Methylhexamine Hd, Histidine,
- Rauwolfia serpentina extract

Other Ingredients: Maltodextrin, Natural and Artificial Flavors, Citric Acids, Malic Acid, Sucralose, FD&C Red #40.

Directions

Directions:

ON TRAINING DAYS:

Take one heaping scoop to assess personal tolerance. Once tolerance has been assessed, users may increase dosage to 2 scoops in 6-8oz (depending on taste preference) of ice cold water. Do not take with food.

ON NON-TRAINING DAYS:

Take one scoop in the morning to maintain increased Nitric Oxide, ATP and energy levels while assisting in reducing body fat and fatigue.

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Wicked™

GRUELING
GRAPE

POWERED BY
CREATINE NITRATE
AGMATINE SILICATE

DIETARY SUPPLEMENT

PREWORKOUT INSANITY FUEL

30 SERVINGS (330 GR)

PREWORKOUT INSANITY FUEL

Wicked



**EXTREME CAUTION
NOT FOR THE WEAK**

PUMP

**YOUR MUSCLES
WITH THE ONLY
SKIN SPLITTING
FUEL FIT TO FEED
THE BEAST OF
BODYBUILDING!**

INNOVATIVE™
LABORATORIES



RAPIDCUTS SHREDDED BUY 1, GET 1 FREE! ALLMAX

FREE SHIPPING* SIGN UP FOR DISCOUNTS & DEALS Like 191K people like this. Be the first of your friends.

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A1 Supplements - America's Favorite Supplement Store.®

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PROTEIN SPORTS NUTRITION DIET & LIFESTYLE HEALTH & WELLNESS VITAMINS & MINERALS HERBS

BRANDS CATEGORIES TOP 60 SPECIALS NEW PRODUCTS CLEARANCE GOALS ACCESSORIES BULK DISCOUNTS ARTICLES

Supplement Specials & Deals! **VIEW BOGOS & DEALS >>**

HOME > SPORTS NUTRITION > MUSCLE BUILDERS > HI-TECH PHARMACEUTICALS ANAVAR

HI-TECH PHARMACEUTICALS ANAVAR
★★★★☆ 48 Review(s) | Add Your Review

Brand: Hi-Tech Pharmaceuticals

Anavar - Extraordinary Profile Of Muscle-Building Agents And Strength Increasing Compounds! Revolutionary Muscle Builder Designed To Increase Strength And Size!

Read more...

FREE ARIMPLEX!
Buy Hi-Tech Pharmaceuticals Anavar - 180 Tablets, Get Arimiplex - 60 Tablets FREE!

Search results for "anavar+creatine+nitrate" showing product images and a snippet of the product information.

Serving Size: 3 Tablets Serving Per Container: 60

Proprietary Blend with Extend-Rx™ Technology: 1,900mg

S-(2-Boronoethyl) L-Cysteine HCl [BEC], 2-(S)-Amino-6-Boronohexanoic Acid [ABH], Creatine Nitrate, Creatine HCl, L-Arginine HCl, Inosine Ethyl Ester, Adenosine Triphosphate, 25-R-Spirostan-5A-Diol-6-One-3-One, Dehydroepiandrosterone Acetate, Dehydroepiandrosterone Propionate, Dehydroepiandrosterone Enanthate, 5a Hydroxy Laxogenin Acetate, 6-Keto Diosgenin Acetate, 20-Hydroxyecdysone Decanoate, 1-Androstenedione, 4-Androstenedione, Epandrosterone, Naringin, 6,7-Dihydroxybergamottin, Quebracho Blanco HCl

Supplement Facts

Serving Size: 3 Tablets Serving Per Container: 60

Amount Per Serving % Daily Value

Proprietary Blend with Extend-Rx™ Technology: 1,900mg *

S-(2-Boronoethyl) L-Cysteine HCl [BEC], 2-(S)-Amino-6-Boronohexanoic Acid [ABH], Creatine Nitrate, Creatine HCl, L-Arginine HCl, Inosine Ethyl Ester, Adenosine Triphosphate, 25-R-Spirostan-5A-Diol-6-One-3-One, Dehydroepiandrosterone Acetate, Dehydroepiandrosterone Propionate, Dehydroepiandrosterone Enanthate, 5a Hydroxy Laxogenin Acetate, 6-Keto Diosgenin Acetate, 20-Hydroxyecdysone Decanoate, 1-Androstenedione, 4-Androstenedione, Epandrosterone, Naringin, 6,7-Dihydroxybergamottin, Quebracho Blanco HCl

https://supplementwarehouse.com/products/anavar

Anavar® - Bodybuilding Supplement for Muscle & Strength - Supplement Warehouse

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**BUY AN
ANAVAR**

A1 Supplements



**GET A FREE
ARIMIPLEX**



Supplement Facts

Supplement Facts:

Serving Size: 3 Tablets
Servings Per Container: 60

Amount Per Serving:
Proprietary Blend With Extend-Rx Technology: 1900mg
S-(2 Boronethyl) L-Cysteine HCL, 2-(S)-Amino-6-Borohexanoic Acid, Creatine Ethyl Ester, Creatine Monohydrate, L-Arginine HCL, Inosine Ethyl Ester, Adenosine Triphosphate, 25R Spirosten-5A-Diol-6-One-3-One, Dehydroepiandrosterone Acetate, Dehydroepiandrosterone Cypionate, Dehydroepiandrosterone Propionate, Dehydroepiandrosterone Enanthate, Smilagenin, Hecogenin Acetate, 6-Keto-Diosgenin Cypionate, 6-Keto-Diosgenin Propionate, 6-Keto Diosgenin Acetate 20-HydroxyEcdysone Deconate, Naringen, 6,7 Dihydroxy Bergamottin, Quebracho Blanco HCL.

Other Ingredients:
Agglomerated Dextrose, Microcrystalline Cellulose, Hydroxypropylcellulose (Klucel HXF And HF Brand), Hydroxypropylmethylcellulose (Beneceel Brand), Di-Calcium Phosphate, Sodium Starch Glycolate, Starch, Magnesium Stearate, Stearic Acid, Povidone, Silica

Directions

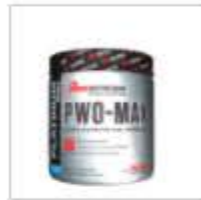
Directions: Take 3 tablets twice daily. Take 3 tablets in the morning and 3 tablets in the afternoon or evening. Do not exceed recommended dosage as Anavar is a potent anabolic agent.

Warning: Not for use of persons under the age of 18. Do not use if you are currently breast feeding, pregnant or plan to become pregnant. Keep out of reach of children. Consult your doctor prior to use if you have any medical conditions or if you are taking any other medications. Discontinue use immediately if you experience rapid heartbeat, dizziness, vomiting or other similar symptoms.

Buy Hi-Tech Pharmaceuticals Anavar and Save With A1's Everyday Low Pricing!

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Supplement Facts

Serving Size: 1 Scoop (30g)	
Servings Per Container: 30	
Amount Per Serving	
Total Calories 100	
Total Fat 0g	
Total Carbohydrate 0g	
Total Protein 0g	
Total Sugar 0g	
Total Fiber 0g	
Total DMAA 75mg	
Total Agmatine Sulfate 100mg	
Total Caffeine 300mg	
Total Stevia 0g	
Total Natural Flavors 0g	
Total Artificial Flavors 0g	
Total Artificial Colors 0g	
Total Proprietary Blends 0g	
Total Other Ingredients 0g	



Prime Nutrition PWO-MAX™ Pre-Workout

★★★★★ 11 reviews

\$ 39.99

PNPWSK30SVG

Flavor

Kiwi Strawberry ▾

Quantity

1

Add to Cart

[Ask us a question](#)

PWO-MAX™

- 75 mg of DMAA per serving for Intense and Focused Energy
- Agmatine Sulfate for Monster Vasodilation
- 300mg of caffeine per serving
- Push Past Mental Barriers With Incredible Focus
- 30 Minutes to Crazy Intensity'
- Scientifically Developed and Tested
- 3 Delicious Flavors, Naturally Sweetened With Stevia

Pre-workout fans get ready. **PWO-MAX™**, the big bully on the block, is **back** and this time packed with 75mg of DMAA, the industry's most sought after pre-workout ingredient. We aren't asking for you to have good workouts, PWO-MAX™ will drag it out of you kicking and screaming.



Supplement Facts	
Serving Size: 1 Rounded Scoop (12 Grams)	
Servings Per Container: 30	
Amount Per Serving	
Sodium (as Sodium Nitrate)	270mg
Beta Alanine	3.2g
Agmatine Sulfate	2g
Sodium Nitrate	1g
N-Acetyl L-Tyrosine	750mg
Choline Bitartrate	500mg
DMAE (Dimethylaminoethanol)	500mg
Caffeine Citrate	200mg
Caffeine Anhydrous	100mg
1,3-Dimethylamylamine	75mg

Supplement Facts

Serving Size: 1 Rounded Scoop (12 Grams)

Servings Per Container: 30

	Amount Per Serving	% DV
Sodium (as Sodium Nitrate)	270mg	11%*
Beta Alanine	3.2g	**
Agmatine Sulfate	2g	**
Sodium Nitrate	1g	**
N-Acetyl L-Tyrosine	750mg	**
Choline Bitartrate	500mg	**
DMAE (Dimethylaminoethanol)	500mg	**
Caffeine Citrate	200mg	**
Caffeine Anhydrous	100mg	**
1,3-Dimethylamylamine	75mg	**

* Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs.

** Daily Value (DV) Not Established

- **75 mg of DMAA per serving for Intense and Focused Energy**
- **Agmatine Sulfate for Monster Vasodilation**
- **300mg of caffeine per serving**
- **Push Past Mental Barriers With Incredible Focus**
- **30 Minutes to Crazy Intensity'**
- **Scientifically Developed and Tested**
- **3 Delicious Flavors, Naturally Sweetened With Stevia**

Pre-workout fans get ready. **PWO-MAX™**, the big bully on the block, is **back** and this time packed with 75mg of DMAA, the industry's most sought after pre-workout ingredient. We aren't asking for you to have good workouts, PWO-MAX™ will drag it out of you kicking and screaming.

If you are looking for that clear, focused energy that you used to get when you had that first coffee, this is it... but even better. With a host of stimulants and focus ingredients, our pre-workout creates a feeling not often, if ever felt. Praised by IFBB pros and your typical gym rats, **PWO-MAX™ is taking the fitness industry by storm** as people realize its ability to enhance workouts to a whole other level than normally seen.

Ignite each workout with a highly potent dose of beta alanine, a widely researched lactic acid buffering molecule proven to increase athletic performance. You will be able to train longer and with more intensity than you have ever thought possible. Also included is a scientifically backed dose of Agmatine Sulfate, a vasodilator with the ability to greatly expand blood vessels, allowing for nutrients to flow fast and freely throughout the body. This high rate of circulation has been shown to speed recovery time between workouts and enhance muscle pump.

Once you take **PWO-MAX™** 30 minutes prior to your workout, it's time to start kicking your mind into gear. You have half an hour or even less to prepare for the workout of your life. When you take a pre-workout that brings the intensity like **PWO-MAX™** you really only have one choice - take no prisoners. And we promise, once you try **PWO-MAX™** you'll realize what you've been missing all this time. The days of little energy, no focus, and terrible workouts are over. Seriously, this is that one addition to your workout you don't want to miss.

TruPump

\$ 44.95

Flavor

GREEN APPLE CANDY

Quantity

1

ADD TO CART



Product Info

Supplement Facts

Suggested Use

Warnings

Reviews

SUPPLEMENT FACTS

Serving Size: 1 scoop (9.5g)
Servings Per Container: 30

	Amount Per Serving	%DV
L-Citrulline	3000mg	†
HydroMax™ Glycerol	1000mg	†
Agmatine Sulfate	500mg	†
Rhodiola Rosea	300mg	†
Alpha-GPC	300mg	†
L-Norvaline	250mg	†
Sodium Nitrate	250mg	†
L-Leucine	375mg	†
L-Isoleucine	187mg	†
L-Valine	187mg	†

† Daily Value (DV) Not Established

TruPump: STIM-FREE PUMP AND MUSCLE VOLUMIZER

Overview:

TruPump is a stimulant free preworkout that is optimized for the best pumps and muscle volumizing effects on the market. TruPump combines several proven ingredients to increase blood flow to working muscles and pull water into your cells. This leads to engorged cells and muscles that give you those skin-tightening pumps. All our products are non-proprietary, full disclosure so you can take a look below at our ingredient profile to see exactly what and how much we put into TruPump. To give you a little preview, we've got the industry renowned Hydromax Glycerol, a hefty dose of L-Citrulline, along with Alpha GPC and nitric oxide boosters L-Valine and Arginine Sulfate. We've even got a little bit of BCAA, why? Because 1. Why not? and 2. our formulation is so hydrophilic (strongly absorbs water from the atmosphere), we had to have some BCAA to help reduce clumping. Our product is so good at pulling in water (that's what gives you the best pumps!) that it even pulls water from the surrounding environment.

TruPump is ideal for those who work out late in the day or close to bed time as it does not contain any stimulants. This is also a great product to cycle in with other stimulant based preworkouts so you can give your adrenergic receptor a break and lower your stimulant tolerance. TruPump can be used by itself or for more advanced users, it can be used in tandem with any other preworkout for a custom blend tailored to your specific needs.

Targeted Uses:

Ingredient Profile:

L-Citrulline - A well studied amino acid that increases training volume, blood flow and nitric oxide production, leading to better pumps. Also has shown to reduce fatigue during exercise as well as muscle soreness.

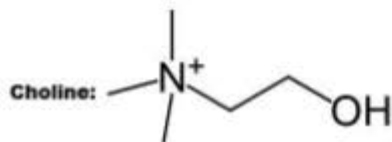
HydroMax - A highly concentrated version of a blended glycerol and silica that readily absorbs water and distributes throughout the body. This temporary increase in fluid in the blood and muscles increases endurance and stamina while also promoting blood flow during resistance training and improving hydration.

Agmatine Sulfate - A derivative of L-arginine, agmatine sulfate enhances blood flow to allow more nutrients and oxygen to be shuttled into your muscles. This results in better pumps, increased endurance and quicker recovery.

Rhodiola Rosea - An extract that significantly decreases fatigue and reducing muscle damage while also increasing cognition and the feeling of well-being. An increase in athletic performance is also seen when taking rhodiola rosea.

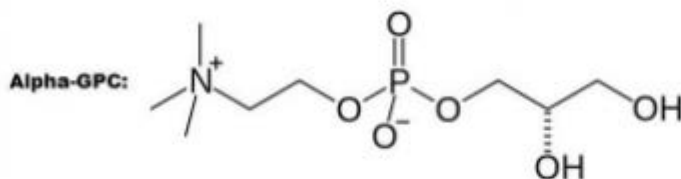
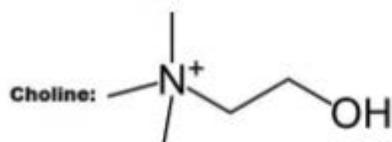
SUPPLEMENT FACTS		
Serving Size: 1 scoop (9.5g)		
Servings Per Container: 30		
	Amount Per Serving	%DV
L-Citrulline	3000mg	†
HydroMax™ Glycerol	1000mg	†
Agmatine Sulfate	500mg	†
Rhodiola Rosea	300mg	†
Alpha-GPC	300mg	†
L-Norvaline	250mg	†
Sodium Nitrate	250mg	†
L-Leucine	375mg	†
L-Isoleucine	187mg	†
L-Valine	187mg	†

† Daily Value (DV) Not Established



Alpha-GPC - A choline containing compound that increases mental focus and enhances power output

while also increasing cognition and the feeling of well-being. An increase in athletic performance is also seen when taking rhodiola rosea.



Alpha-GPC - A choline containing compound that increases mental focus and enhances power output during athletic performance. Alpha-GPC is one of the best, and most expensive, forms of dietary choline.

L-Norvaline - L-norvaline works by inhibiting arginase. The enzyme arginase prevents you from creating more nitric oxide from arginine, cutting your pump short. By inhibiting arginase, L-Norvaline allows you to achieve longer, stronger pumps that give more power and recovery ability

Sodium Nitrate - A precursor for the production of nitric oxide, leads to increased nitric oxide levels in the body which leads to increase blood flow, and a better pump. Notable also found in some processed food as a preservative, so we kept this dosage relatively low.

BCAA's (Branched Chain Amino Acids) - Deserves an entire article to itself, click here for article. One of the reasons we put into this formulation is that it helps reduce clumping due to moisture (ingredients pulls water from the environment and forms clumps).

Suggested Use:

As a dietary supplement mix 1 scoop in 8-12 oz. and sip throughout your workout or it can be taken all at once prior to workout. New users may wish to assess tolerance with ½ scoop. Experienced users may take additional scoops if necessary. To avoid building a tolerance, cycle this product on a 2 week basis or as necessary. This product is to be used as needed for physical fitness only. DO NOT OVERUSE.

Can be used by itself or stacked with other preworkouts for added benefits. Can be used close to

EXHIBIT L

Infringement of the '531 Patent

Claim	Jack'd Up	Mesomorph	Mesomorph v. 2.0	Anavar	Phosphagen	Creatine Nitrate	TruePump,	PWO-MAX	Wicked
1. A solid supplement formulation comprising:	Yes - Powder formulation	Yes – Powder formulation	Yes – Powder formulation	Yes – Tablet formulation	Yes – Powder formulation	Yes – Tablet formulation	Yes – Powder formulation	Yes – Powder formulation	Yes – Powder formulation
at least one nitrate salt compound;	Includes at least Creatine Nitrate, which is a nitrate salt compound.	Includes at least Creatine Nitrate, which is a nitrate salt compound.	Includes at least Creatine Nitrate, which is a nitrate salt compound.	Includes at least Creatine Nitrate, which is a nitrate salt compound.	Includes at least Creatine Nitrate, which is a nitrate salt compound.	Includes at least Creatine Nitrate, which is a nitrate salt compound.	Includes at least sodium nitrate, which is a nitrate salt compound.	Includes at least sodium nitrate, which is a nitrate salt compound.	Includes at least Creatine Nitrate, which is a nitrate salt compound.
and at least one isolated amino acid compound selected from the group consisting of Agmatine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, Omithine, Valine, Aspartic Acid, Cysteine, Glycine, Lysine, Methionine, Praline, Tyrosine, and Phenylalanine,	Includes at least one isolated amino acid compound comprising at least agmatine sulfate and beta alanine	Includes at least one isolated amino acid compound comprising at least agmatine sulfate and beta alanine	Includes at least one isolated amino acid compound comprising at least agmatine sulfate and beta alanine	Includes at least one isolated amino acid compound comprising at least creatine HCl and L-cysteine HCl	Includes at least one isolated amino acid compound comprising at least creatine HCl and beta alanine	Includes at least one isolated amino acid compound comprising at least dicreatine malate, which is a compound of malic acid and creatine	Includes at least one isolated amino acid compound comprising at least agmatine sulfate, histidine, L-citrulline, L-norvaline, and L-valine	Includes at least one isolated amino acid compound comprising at least agmatine sulfate and beta alanine	Includes at least one isolated amino acid compound comprising at least agmatine silicate, histidine, L-citrulline silicate, and beta alanine
wherein the at least one isolated amino acid compound is a separate compound than the at least one nitrate salt compound.	The agmatine sulfate and beta alanine are each separate from the creatine nitrate	The agmatine sulfate and beta alanine are each separate from the creatine nitrate	The agmatine sulfate and beta alanine are each separate from the creatine nitrate	The creatine HCl and L-cysteine HCl are each separate from the creatine nitrate	The creatine HCl and beta alanine are each separate from the creatine nitrate	The dicreatine malate is separate from the creatine nitrate	Includes agmatine sulfate, histidine, L-citrulline, L-norvaline, and L-valine are each separate from the sodium nitrate	The agmatine sulfate and beta alanine are each separate from the sodium nitrate	The agmatine silicate, histidine, L-citrulline silicate, and beta alanine are each separate from the creatine nitrate

Infringement of the '187 Patent

Claim	Jack'd Up	Mesomorph	Mesomorph v. 2.0	TruePump	PWO-MAX	Wicked
4. A method for increasing athletic performance in a human or animal,	The product is designed and intended to and – on information and belief – in fact does increase athletic performance. Defendants tout this advantage, explaining that - for example - the product “Elevates Nitric Oxide (NO) levels for Extreme Muscle Pumps Produces An Intense Sensation Of Energy,” “Increases Speed, Power & Endurance,” and “Experience Extreme Pumps and Strength”	The product is designed and intended to and – on information and belief – in fact does increase athletic performance. Defendants tout this advantage, explaining that - for example - the product is “guaranteed to deliver eye opening energy, focus, and stamina like nothing you’ve ever experienced before,” “Will Help Athletes with the Following: ... Unleash Your True Genetic Potential! Greater Muscle Gains and Enhanced Athletic Performance.”	The product is designed and intended to and – on information and belief – in fact does increase athletic performance. Defendants tout this advantage, explaining that - for example - the product has a “cutting edge preworkout formula that will cause you to experience out of this world pumps, and tons of extra energy and unleash your true muscle building and genetic potential,” and “Will Help Athletes with the Following: ... Unleash Your True Genetic Potential! Greater Muscle Gains and Enhanced Athletic Performance.”	The product is designed and intended to and – on information and belief – in fact does increase athletic performance. Defendants tout this advantage, explaining that - for example - the product “enhances blood flow to allow more nutrients and oxygen to be shuttled into your muscles. This results in better pumps, increased endurance and quicker recovery.”	The product is designed and intended to and – on information and belief – in fact does increase athletic performance. Defendants tout this advantage, explaining that - for example - the product will “[i]gnite each workout with a highly potent dose beta alanine, a widely researched lactic acid buffering molecule proven to increase athletic performance. You will be able to train longer and with more intensity than you have ever thought possible ... [and] speed recovery time between workouts and enhance muscle pump.”	The product is designed and intended to and – on information and belief – in fact does increase athletic performance. Defendants tout this advantage, explaining that - for example - the product “provides explosive energy, long-lasting endurance, increased strength and power, road-map vascularity, and razor-sharp mental focus,” and “will help you to have the best workouts of your life!”
the method comprising orally administering to the human or animal a pharmaceutically effective amount of an amino acid composition comprising at least one constituent	Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid composition comprising creatine nitrate, which is a salt of nitrate. The amino acid composition further includes agmatine in the	Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid composition comprising creatine nitrate, which is a salt of nitrate. The amino acid composition further includes agmatine in the form of agmatine sulfate.	Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid composition comprising creatine nitrate, which is a salt of nitrate. The amino acid composition further includes agmatine in the form of agmatine sulfate. Product also includes beta	Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid composition comprising sodium nitrate, which is a salt of nitrate. The amino acid composition further includes agmatine in the form of agmatine sulfate. The product further includes	Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid composition comprising sodium nitrate, which is a salt of nitrate. The amino acid composition further includes agmatine in the form of agmatine sulfate. The product further includes	Product is administered orally to a human. Product further includes a pharmaceutically effective amount of an amino acid composition comprising creatine nitrate, which is a salt of nitrate. The amino acid composition further includes agmatine silicate.

Claim	Jack'd Up	Mesomorph	Mesomorph v. 2.0	TruePump	PWO-MAX	Wicked
selected from the group consisting of a salt of a nitrate (NO 3-), a mixed salt of a nitrate (NO 3-), a salt of a nitrate (NO 2-), and a mixed salt of a nitrate (NO 2-); and agmatine.	form of agmatine sulfate. Product also includes beta alanine and arginine (Arginine Alpha-Ketoglutarate)..	Product also includes beta alanine, di-creatine malate, and arginine (Arginine Alpha-Ketoglutarate).	alanine, di-creatine malate, and arginine (Arginine Alpha-Ketoglutarate).	histidine, L-citruline, L-norvaline, and L-valine	beta alanine.	The product further includes beta alanine, histidine, and L-citruline silicate

Infringement of the '187 Patent (cont.)

Claim	Jack'd Up	Mesomorph	Mesomorph v. 2.0	Phosphagen	PWO-MAX	Wicked
5. A method for increasing athletic performance in a human or animal,	The product is designed and intended to and – on information and belief – in fact does increase athletic performance. Defendants tout this advantage, explaining that - for example - the product “Elevates Nitric Oxide (NO) levels for Extreme Muscle Pumps Produces An Intense Sensation Of Energy,” “Increases Speed, Power & Endurance,” and “Experience Extreme Pumps and Strength”	The product is designed and intended to and – on information and belief – in fact does increase athletic performance. Defendants tout this advantage, explaining that - for example - the product is “guaranteed to deliver eye opening energy, focus, and stamina like nothing you’ve ever experienced before,” “Will Help Athletes with the Following: ... Unleash Your True Genetic Potential! Greater Muscle Gains and Enhanced Athletic Performance.”	The product is designed and intended to and – on information and belief – in fact does increase athletic performance. Defendants tout this advantage, explaining that - for example - the product has a “cutting edge preworkout formula that will cause you to experience out of this world pumps, and tons of extra energy and unleash your true muscle building and genetic potential,” and “Will Help Athletes ... Unleash Your True Genetic Potential! Greater Muscle Gains and Enhanced Athletic Performance.”	The product is designed and intended to and – on information and belief – in fact does increase athletic performance. Defendants tout this advantage, explaining that - for example - the product encourages “enhanced muscle work performance and muscular development,” and “the bodybuilder ... will have the extra amount of muscle fuel available to complete the one additional rep required to pull the trigger for muscles to grow.”	The product is designed and intended to and – on information and belief – in fact does increase athletic performance. Defendants tout this advantage, explaining that - for example - the product will “[i]gnite each workout with a highly potent dose beta alanine, a widely researched lactic acid buffering molecule proven to increase athletic performance. You will be able to train longer and with more intensity than you have ever thought possible ... [and] speed recovery time between workouts and enhance muscle pump.”	The product is designed and intended to and – on information and belief – in fact does increase athletic performance. Defendants tout this advantage, explaining that - for example - the product “provides explosive energy, long-lasting endurance, increased strength and power, road-map vascularity, and razor-sharp mental focus,” and “will help you to have the best workouts of your life!”
the method comprising orally administering to the human or animal a pharmaceutically effective amount of an amino acid composition comprising at least one constituent selected from the group consisting	Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid composition comprising creatine nitrate, which is a salt of nitrate. The amino acid composition further includes beta alanine. Product also includes	Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid composition comprising creatine nitrate, which is a salt of nitrate. The amino acid composition further includes beta alanine. Product also includes agmatine sulfate, di-creatine malate, and	Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid composition comprising creatine nitrate, which is a salt of nitrate. The amino acid composition further includes beta alanine. Product also includes agmatine sulfate, di-creatine malate, and arginine (Arginine Alpha-Ketoglutarate).	Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid composition comprising creatine nitrate, which is a salt of nitrate. The amino acid composition further includes beta alanine. Product further include creatine HCl.	Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid composition comprising sodium nitrate, which is a salt of nitrate. The amino acid composition further includes beta alanine. The product further includes agmatine sulfate.	Product is administered orally to a human. Product further includes a pharmaceutically effective amount of an amino acid composition comprising creatine nitrate, which is a salt of nitrate. The amino acid composition further includes beta alanine. The product further includes agmatine silicate, histidine, and L-citrulline silicate

Claim	Jack'd Up	Mesomorph	Mesomorph v. 2.0	Phosphagen	PWO-MAX	Wicked
of a salt of a nitrate (NO 3-), a mixed salt of a nitrate (NO 3-), a salt of a nitrate (NO 2-), and a mixed salt of a nitrate (NO 2-); and beta alanine.	agmatine sulfate and arginine (Arginine Alpha-Ketoglutarate)..	arginine (Arginine Alpha-Ketoglutarate).				

Infringement of the '187 Patent (cont.)

Claim	Jack'd Up	Mesomorph	Mesomorph v. 2.0	Anavar	Phosphagen	Creatine Nitrate
7. A method for increasing athletic performance in a human or animal,	The product is designed and intended to and – on information and belief – in fact does increase athletic performance. Defendants tout this advantage, explaining that - for example - the product “Elevates Nitric Oxide (NO) levels for Extreme Muscle Pumps Produces An Intense Sensation Of Energy,” “Increases Speed, Power & Endurance,” and “Experience Extreme Pumps and Strength”	The product is designed and intended to and – on information and belief – in fact does increase athletic performance. Defendants tout this advantage, explaining that - for example - the product is “guaranteed to deliver eye opening energy, focus, and stamina like nothing you’ve ever experienced before,” “Will Help Athletes with the Following: ... Unleash Your True Genetic Potential! Greater Muscle Gains and Enhanced Athletic Performance.”	The product is designed and intended to and – on information and belief – in fact does increase athletic performance. Defendants tout this advantage, explaining that - for example - the product has a “cutting edge preworkout formula that will cause you to experience out of this world pumps, and tons of extra energy and unleash your true muscle building and genetic potential,” and “Will Help Athletes with the Following: ... Unleash Your True Genetic Potential! Greater Muscle Gains and Enhanced Athletic Performance.”	The product is designed and intended to and – on information and belief – in fact does increase athletic performance. Defendants tout this advantage, explaining that - for example - the product has an “Extraordinary Profile of Muscle-Building Agents and Strength Increasing Compounds,” and “the bodybuilder ... will have the extra amount of muscle fuel available to complete the additional reps required to pull the trigger for muscles to grow.”	The product is designed and intended to and – on information and belief – in fact does increase athletic performance. Defendants tout this advantage, explaining that - for example - the product encourages “enhanced muscle work performance and muscular development,” and “the bodybuilder ... will have the extra amount of muscle fuel available to complete the one additional rep required to pull the trigger for muscles to grow.”	The product is designed and intended to and – on information and belief – in fact does increase athletic performance. Defendants tout this advantage, explaining that - for example - the product increases “Vascularity, Strength, ATP Elevation And Recovery!” and that the user “will experience full, swollen muscle bellies complimented by road map vascularity.”

Claim	Jack'd Up	Mesomorph	Mesomorph v. 2.0	Anavar	Phosphagen	Creatine Nitrate
the method comprising orally administering to the human or animal a pharmaceutically effective amount of an amino acid composition comprising at least one constituent selected from the group consisting of a salt of a nitrate (NO 3-), a mixed salt of a nitrate (NO 3-), a salt of a nitrate (NO 2-), and a mixed salt of a nitrate (NO 2-); and creatine.	<p>Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid composition comprising creatine nitrate, which is a salt of nitrate.</p> <p>The amino acid composition further includes creatine in the form of creatine monohydrate.</p> <p>Product also includes agmatine sulfate and arginine (Arginine Alpha-Ketoglutarate)..</p>	<p>Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid composition comprising creatine nitrate, which is a salt of nitrate.</p> <p>The amino acid composition further includes creatine in the form of di-creatine malate</p> <p>Product also includes beta alanine, agmatine sulfate, di-creatine malate, and arginine (Arginine Alpha-Ketoglutarate).</p>	<p>Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid composition comprising creatine nitrate, which is a salt of nitrate.</p> <p>The amino acid composition further includes creatine in the form of di-creatine malate</p> <p>Product also includes beta alanine, agmatine sulfate, di-creatine malate, and arginine (Arginine Alpha-Ketoglutarate).</p>	<p>Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid composition comprising creatine nitrate, which is a salt of nitrate.</p> <p>The amino acid composition further includes creatine in the form of creatine HCl.</p> <p>Product further includes L-cysteine HCl</p>	<p>Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid composition comprising creatine nitrate, which is a salt of nitrate.</p> <p>The amino acid composition further includes creatine in the form of creatine HCl, creatine phosphate, and disodium creatine phosphate tetrahydrate.</p> <p>Product further includes beta alanine</p>	<p>Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid composition comprising creatine nitrate, which is a salt of nitrate.</p> <p>The amino acid composition further includes creatine in the form of di-creatine malate.</p>

Infringement of the '187 Patent (cont.)

Claim	Jack'd Up	Mesomorph	Mesomorph v. 2.0	Anavar
61. A method for increasing athletic performance in a human or animal,	The product is designed and intended to and – on information and belief – in fact does increase athletic performance. Defendants tout this advantage, explaining that - for example - the product “Elevates Nitric Oxide (NO) levels for Extreme Muscle Pumps Produces An Intense Sensation Of Energy,” “Increases Speed, Power & Endurance,” and “Experience Extreme Pumps and Strength”	The product is designed and intended to and – on information and belief – in fact does increase athletic performance. Defendants tout this advantage, explaining that - for example - the product is “guaranteed to deliver eye opening energy, focus, and stamina like nothing you’ve ever experienced before,” “Will Help Athletes with the Following: ... Unleash Your True Genetic Potential! Greater Muscle Gains and Enhanced Athletic Performance.”	The product is designed and intended to and – on information and belief – in fact does increase athletic performance. Defendants tout this advantage, explaining that - for example - the product has a “cutting edge preworkout formula that will cause you to experience out of this world pumps, and tons of extra energy and unleash your true muscle building and genetic potential,” and “Will Help Athletes with the Following: ... Unleash Your True Genetic Potential! Greater Muscle Gains and Enhanced Athletic Performance.”	The product is designed and intended to and – on information and belief – in fact does increase athletic performance. Defendants tout this advantage, explaining that - for example - the product has an “Extraordinary Profile of Muscle-Building Agents and Strength Increasing Compounds,” and “the bodybuilder who wisely chooses Anavar® will have the extra amount of muscle fuel available to complete the additional reps required to pull the trigger for muscles to grow.”
the method comprising orally administering to the human or animal a pharmaceutically effective amount of an amino acid composition comprising Arginine and at least one constituent selected from the group consisting of a salt of a nitrate (NO ₃ ⁻) and a mixed salt of a nitrate (NO ₃ ⁻).	Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid composition comprising Arginine in the form of L-Arginine Alpha-Ketoglutarate. The amino acid composition also includes at least Creatine Nitrate, which is a salt of Nitrate.	Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid composition comprising Arginine in the form of Arginine Alpha-Ketoglutarate. The amino acid composition also includes at least Creatine Nitrate, which is a salt of Nitrate.	Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid composition comprising Arginine in the form of Arginine Alpha-Ketoglutarate. The amino acid composition also includes at least Creatine Nitrate, which is a salt of Nitrate.	Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid composition comprising Arginine in the form of L-Arginine HCl. The amino acid composition also includes at least Creatine Nitrate, which is a salt of Nitrate.

Infringement of the '046 Patent

Claim	Jack'd Up	Mesomorph	Mesomorph v. 2.0	Anavar	Phosphagen	Creatine Nitrate	TruePump	PWO-MAX	Wicked
1. A solid composition comprising:	Yes - Powder formulation	Yes – Powder formulation	Yes – Powder formulation	Yes – Tablet formulation	Yes – Powder formulation	Yes – Tablet formulation	Yes – Powder formulation	Yes – Powder formulation	Yes – Powder formulation
at least one isolated nitrate salt compound;	Includes at least Creatine Nitrate, which is an isolated nitrate salt compound.	Includes at least Creatine Nitrate, which is an isolated nitrate salt compound.	Includes at least Creatine Nitrate, which is an isolated nitrate salt compound.	Includes at least Creatine Nitrate, which is an isolated nitrate salt compound.	Includes at least Creatine Nitrate, which is an isolated nitrate salt compound.	Includes at least Creatine Nitrate, which is an isolated nitrate salt compound.	Includes at least sodium nitrate, which is an isolated nitrate salt compound.	Includes at least sodium nitrate, which is an isolated nitrate salt compound.	Includes at least Creatine Nitrate, which is an isolated nitrate salt compound.
and at least one isolated amino acid compound selected from the group consisting of Arginine, Agmatine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, Omithine, Valine, Aspartic Acid, Cysteine, Glycine, Lysine, Methionine, Praline, Tyrosine, and Phenylalanine,	Includes L-arginine alpha-ketoglutarate, creatine monohydrate, agmatine sulfate, and beta alanine	Includes arginine alpha ketoglutarate, agmatine sulfate, l-citrulline DL-malate, di-creatine malate, and beta alanine	Includes arginine alpha ketoglutarate, agmatine sulfate, l-citrulline DL-malate, di-creatine malate, and beta alanine	Includes at least creatine HCl, L-arginine HCl, and L-cysteine HCl	Includes creatine HCl, creatine phosphate, disodium creatine phosphate tetrahydrate, and beta alanine	Includes dicreatine malate, which is a compound of malic acid and creatine	Includes agmatine sulfate, histidine, L-citrulline, L-leucine, L-norvaline, and L-valine	Includes N-acetyl L-tyrosine, agmatine sulfate, and beta alanine	Includes agmatine silicate, histidine, L-citrulline silicate, and beta alanine.

Infringement of the '572 Patent

Claim	Jack'd Up	Mesomorph	Mesomorph v. 2.0	Anavar	Phosphagen	Creatine Nitrate	TruePump	PWO-MAX	Wicked
1. A method for increasing vasodilative characteristics in a human,	The product is designed and intended to and – on information and belief – in fact does increase vasodilative characteristics in a human. Defendants tout this advantage, explaining that - for example - the product produces “Extreme Pumps and Strength,” “muscle-engorging pumps,” and “pumps and vascularity are out of this world.”	The product is designed and intended to and – on information and belief – in fact does increase vasodilative characteristics in a human. Defendants tout this advantage, explaining that - for example - the product produces “vein blasting” performance and “out of this world pumps.”	The product is designed and intended to and – on information and belief – in fact does increase vasodilative characteristics in a human. Defendants tout this advantage, explaining that - for example - the product produces “vein blasting” performance, as well as “mind blowing” and “out of this world pumps.”	The product is designed and intended to and – on information and belief – in fact does increase vasodilative characteristics in a human. Defendants tout this advantage, explaining that - for example - the product “Contains L-Arginine and the Arginase Inhibitors ABH and BEC for Maximum Muscle Vasodilation.”	The product is designed and intended to and – on information and belief – in fact does increase vasodilative characteristics in a human. Defendants tout this advantage, explaining that - for example - the product “volumize[s] muscle cells,” and “enhance[s] the anabolic effect of greater muscle cell volumization.”	The product is designed and intended to and – on information and belief – in fact does increase vasodilative characteristics in a human. Defendants tout this advantage, explaining that - for example - the product “provide[s] more vasodilation and vascularity than ANY current Nitric Oxide/pump product.”	The product is designed and intended to and – on information and belief – in fact does increase vasodilative characteristics in a human. Defendants tout this advantage, explaining that - for example - the product “increases training volume, blood flow and nitric oxide production, leading to better pumps,” and “promot[es] blood flow during resistance training”	The product is designed and intended to and – on information and belief – in fact does increase vasodilative characteristics in a human. Defendants tout this advantage, explaining that - for example - the product includes a “scientifically backed dose of Agmatine Sulfate, a vasodilator with the ability to greatly expand blood vessels, allowing for nutrients to flow fast and freely throughout the body ... to speed recovery time between workouts and enhance muscle pump.”	The product is designed and intended to and – on information and belief – in fact does increase athletic performance. Defendants tout this advantage, explaining that - for example - the product provides “road-map vascularity,” and “skin tearing pumps and freaky vascularity.”

Claim	Jack'd Up	Mesomorph	Mesomorph v. 2.0	Anavar	Phosphagen	Creatine Nitrate	TruePump	PWO-MAX	Wicked
the method comprising administering orally to the human a pharmaceutically effective amount of an amino acid compound consisting essentially of a nitrate of an amino acid selected from the group consisting of Arginine, Agmatine, Beta Alanine, Citrulline, Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, Ornithine, and Valine.	Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid compound, including at least L-arginine alpha-ketoglutarate, creatine monohydrate, agmatine sulfate, and beta alanine	Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid compound, including at least arginine alpha ketoglutarate, agmatine sulfate, l-citrulline DL-malate, di-creatine malate, and beta alanine	Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid compound, including at least arginine alpha ketoglutarate, agmatine sulfate, l-citrulline DL-malate, di-creatine malate, and beta alanine	Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid compound, including at least creatine HCl, L-arginine HCl, and L-cysteine HCl	Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid compound, including at least creatine HCl, creatine phosphate, disodium creatine phosphate tetrahydrate, and beta alanine	Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid compound, including at least dicreatine malate, which is a compound of malic acid and creatine	Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid compound, including at least agmatine sulfate, histidine, L-citrulline, L-leucine, L-norvaline, and L-valine	Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid compound, including at least N-acetyl L-tyrosine, agmatine sulfate, and beta alanine	Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid compound, including at least agmatine silicate, histidine, L-citrulline silicate, and beta alanine.

Infringement of the '288 Patent

Claim	Jack'd Up	Mesomorph	Mesomorph v. 2.0	Anavar	Phosphagen	Creatine Nitrate	TruePump	PWO-MAX	Wicked
1. A method for increasing the bioabsorption of amino acids in a human,	The product is designed and intended to and – on information and belief – in fact does increase bioabsorption of amino acids in a human. Indeed, this specific benefit of Plaintiff's invention has recently become generally recognized by both Defendants as well as others in the industry. See, e.g., http://www.livestrong.com/article/516485-how-to-increase-your-absorption-of-arginine/ (“[s]upplements with a high quality L-glutamine product as this will enhance the absorption rate of nutrients in the small intestine where amino acids, including arginine is absorbed.”); see also https://thefeed.com/blogs/news/10-benefits-of-amino-acid-supplements (“[A]mino acids	The product is designed and intended to and – on information and belief – in fact does increase bioabsorption of amino acids in a human. Indeed, this specific benefit of Plaintiff's invention has recently become generally recognized by both Defendants as well as others in the industry. See, e.g., http://www.livestrong.com/article/516485-how-to-increase-your-absorption-of-arginine/ ; see also https://thefeed.com/blogs/news/10-benefits-of-amino-acid-supplements ; https://www.mysupplementstore.com/hi-tech-pharmaceuticals-phosphagen-500-grams.html	The product is designed and intended to and – on information and belief – in fact does increase bioabsorption of amino acids in a human. Indeed, this specific benefit of Plaintiff's invention has recently become generally recognized by both Defendants as well as others in the industry. See, e.g., http://www.livestrong.com/article/516485-how-to-increase-your-absorption-of-arginine/ ; see also https://thefeed.com/blogs/news/10-benefits-of-amino-acid-supplements ; https://www.mysupplementstore.com/hi-tech-pharmaceuticals-phosphagen-500-grams.html	The product is designed and intended to and – on information and belief – in fact does increase bioabsorption of amino acids in a human. Indeed, this specific benefit of Plaintiff's invention has recently become generally recognized by both Defendants as well as others in the industry. See, e.g., http://www.livestrong.com/article/516485-how-to-increase-your-absorption-of-arginine/ ; see also https://thefeed.com/blogs/news/10-benefits-of-amino-acid-supplements ; https://www.mysupplementstore.com/hi-tech-pharmaceuticals-phosphagen-500-grams.html	The product is designed and intended to and – on information and belief – in fact does increase bioabsorption of amino acids in a human. Indeed, this specific benefit of Plaintiff's invention has recently become generally recognized by both Defendants as well as others in the industry. See, e.g., http://www.livestrong.com/article/516485-how-to-increase-your-absorption-of-arginine/ ; see also https://thefeed.com/blogs/news/10-benefits-of-amino-acid-supplements ; https://www.mysupplementstore.com/hi-tech-pharmaceuticals-phosphagen-500-grams.html	The product is designed and intended to and – on information and belief – in fact does increase bioabsorption of amino acids in a human. Indeed, this specific benefit of Plaintiff's invention has recently become generally recognized by both Defendants as well as others in the industry. See, e.g., http://www.livestrong.com/article/516485-how-to-increase-your-absorption-of-arginine/ ; see also https://thefeed.com/blogs/news/10-benefits-of-amino-acid-supplements ; https://www.mysupplementstore.com/hi-tech-pharmaceuticals-phosphagen-500-grams.html	The product is designed and intended to and – on information and belief – in fact does increase bioabsorption of amino acids in a human. Indeed, this specific benefit of Plaintiff's invention has recently become generally recognized by both Defendants as well as others in the industry. See, e.g., http://www.livestrong.com/article/516485-how-to-increase-your-absorption-of-arginine/ ; see also https://thefeed.com/blogs/news/10-benefits-of-amino-acid-supplements ; https://www.mysupplementstore.com/hi-tech-pharmaceuticals-phosphagen-500-grams.html	The product is designed and intended to and – on information and belief – in fact does increase bioabsorption of amino acids in a human. 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Claim	Jack'd Up	Mesomorph	Mesomorph v. 2.0	Anavar	Phosphagen	Creatine Nitrate	TruePump	PWO-MAX	Wicked
	<p>compete for absorption with each other. To get the full benefit of BCAAs, then, a dedicated amino acid supplement, such as Klean BCAA, is needed.”);</p> <p>https://www.mysupplementstore.com/hi-tech-pharmaceuticals-phosphagen-500-grams.html (Phosphagen “Increases Creatine Absorption”)</p>								
the method comprising administering orally to the human a pharmaceutically effective amount of an amino acid compound	<p>Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid compound, including at least L-arginine alpha-ketoglutarate, creatine monohydrate, agmatine sulfate, and beta alanine</p>	<p>Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid compound, including at least arginine alpha ketoglutarate, agmatine sulfate, l-citrulline DL-malate, di-creatine malate, and beta alanine</p>	<p>Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid compound, including at least arginine alpha ketoglutarate, agmatine sulfate, l-citrulline DL-malate, di-creatine malate, and beta alanine</p>	<p>Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid compound, including at least at least creatine HCl, L-arginine HCl, and L-cysteine HCl</p>	<p>Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid compound, including at least creatine HCl, creatine phosphate, disodium creatine phosphate tetrahydrate, and beta alanine</p>	<p>Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid compound, including at least dicreatine malate, which is a compound of malic acid and creatine</p>	<p>Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid compound, including at least agmatine sulfate, histidine, L-citrulline, L-leucine, L-norvaline, and L-valine</p>	<p>Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid compound, including at least N-acetyl L-tyrosine, agmatine sulfate, and beta alanine</p>	<p>Product is administered orally to a human. Product includes a pharmaceutically effective amount of an amino acid compound, including at least agmatine silicate, histidine, L-citrulline silicate, and beta alanine.</p>

Claim	Jack'd Up	Mesomorph	Mesomorph v. 2.0	Anavar	Phosphagen	Creatine Nitrate	TruePump	PWO-MAX	Wicked
consist- ing essen- tially of a nitrate of an amino acid selected from the group consist- ing of Arginin- e, Agmati- ne, Beta Alanine , Citrulli- ne, Creatin- e, Glutami- ne, L- Histidin- e, Isoleuci- ne, Leucine , Norvali- ne, Omithin- e, and Valine.									

EXHIBIT M

BakerHostetler

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March 17, 2015

VIA UPS NEXT DAY AIR

Mr. Jared Wheat
Hi-Tech Pharmaceuticals
APS Nutrition
6015 Unity Drive
Norcross, GA 30071

Re: Infringement of ThermoLife International, LLC's Patents

Dear Mr. Wheat:

Baker & Hostetler represents ThermoLife International, LLC ("ThermoLife"), a leading importer, manufacturer, and developer of dietary supplements, in various matters, including certain intellectual property-related matters.

ThermoLife has recently learned that Hi-Tech/APS is infringing, at a minimum, the following United States patents issued to ThermoLife¹:

- (i) No. 8,455,531;
- (ii) No. 8,466,187;
- (iii) No. 8,183,288;
- (iv) No. 8,178,572.

ThermoLife's understanding is that Hi-Tech/APS is well aware of these patents, but if it is not, we direct you to <http://no3-t.com/> for more detailed information about these and other patents held by ThermoLife, including specific patent numbers.

ThermoLife demands that Hi-Tech/APS immediately cease such infringing activity, desist from such infringing activity in the future, and comply with ThermoLife's other requirements set forth in this letter.

ThermoLife takes its patents very seriously, and it will take any and all necessary steps to prevent infringement of any of them by you as well as your retailers and distributors. That said,

¹ ThermoLife has already sued Hi-Tech for infringement of U.S. Patent No. 7,777,074, but that case is currently stayed pending re-examination with respect to that patent.

Mr. Jared Wheat
March 17, 2015
Page 2

it is ThermoLife's preference to resolve this matter amicably, if possible.

It is ThermoLife's understanding that you have continued to market and sell "Jack'd Up," "Phosphagen," "Creatine Nitrate," "Mesomorph," and "Mesomorph 2.0"-branded products. ThermoLife has prepared the attached Initial Infringement Review detailing certain of the patent claims infringed by these products. This Analysis is provided to you without limitation and without prejudice.

By close of business March 24, 2015, please provide to ThermoLife (care of the undersigned) the following:

- 1) written confirmation that Hi-Tech/APS has (a) stopped offering for sale, selling, distributing, and/or marketing "Jack'd Up," "Phosphagen," "Creatine Nitrate," "Mesomorph," and "Mesomorph 2.0"-branded products, and (b) ceased all infringement of ThermoLife's patents;
- 2) written confirmation that Hi-Tech/APS has removed references to "Jack'd Up," "Phosphagen," "Creatine Nitrate," "Mesomorph," and "Mesomorph 2.0"-branded products from any and all websites, electronic media, and print media under your control (and, to that end, have ensured removal of same from the websites, electronic media, and print media of any distributors, retailers, etc.);
- 3) a written statement detailing the entirety of Hi-Tech/APS' commercial endeavors with "Jack'd Up," "Phosphagen," "Creatine Nitrate," "Mesomorph," and "Mesomorph 2.0"-branded products, including the quantities (i) Hi-Tech/APS made or purchased, (ii) Hi-Tech/APS imported into the United States, (iii) Hi-Tech/APS offered to sell or sold in the United States, and (iv) remaining in inventory; and
- 4) written confirmation that Hi-Tech/APS will hold all remaining disputed/infringing inventory pending resolution of this matter and preserve all documents and information (electronic or hardcopy) relating to your development of the "Jack'd Up," "Phosphagen," "Creatine Nitrate," "Mesomorph," and "Mesomorph 2.0"-branded products, ThermoLife, or ThermoLife patents.

Once we have received that information, ThermoLife would welcome the opportunity to discuss an amicable resolution of this matter. Thus, after providing ThermoLife this information, please contact me, or have your counsel contact me, directly so that we may begin those discussions.

However, if we do not receive the foregoing within the specified time, ThermoLife will not hesitate to vigorously enforce its intellectual property rights. Not only will ThermoLife pursue Hi-Tech/APS directly, but Hi-Tech/APS' infringements will leave ThermoLife no choice but to join in

Mr. Jared Wheat
March 17, 2015
Page 3

a lawsuit many of the distributors and retailers of "Jack'd Up," "Phosphagen," "Creatine Nitrate," "Mesomorph," and "Mesomorph 2.0"-branded products and to take legal action against them, as appropriate. Thus, your infringements and advertising puts those third parties at risk of legal action too.

We are sending a copy of this letter to some of Hi-Tech/APS' retailers and distributors we have identified thus far, to alert them to the fact that their continued selling of "Jack'd Up," "Phosphagen," "Creatine Nitrate," "Mesomorph," and "Mesomorph 2.0"-branded products places them in jeopardy of legal action as well.

Please do not hesitate to contact me, or to have your counsel contact me, if you have any questions or would like to discuss this matter further.

This letter is written without prejudice to any of ThermoLife's other rights or claims under applicable federal or state law, all of which are hereby expressly reserved.

Sincerely,

A handwritten signature in blue ink, appearing to read "David N. Farsiou".

David N. Farsiou
Partner

EXHIBIT N

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10 Attorneys for Plaintiff ThermoLife International LLC

11 UNITED STATES DISTRICT COURT
12 FOR THE DISTRICT OF ARIZONA

13 ThermoLife International, LLC, an
14 Arizona limited liability company,

No.

15 Plaintiff,

COMPLAINT

16 v.

17 Hi-Tech Pharmaceuticals, Inc. a Georgia
18 corporation,

(Jury Trial Demanded)

19 Defendant.

20 Plaintiff ThermoLife International LLC, for its complaint against defendant Hi-
21 Tech Pharmaceuticals Inc. (“Hi-Tech”) alleges upon personal knowledge with respect to
22 itself and its own acts, and upon information and belief with respect to all other matters, as
23 follows:

NATURE OF ACTION

24 1. Plaintiff ThermoLife International LLC (“ThermoLife”) brings claims for
25 patent infringement, inducement of patent infringement, and contributory patent
26 infringement against its competitor Hi-Tech.

2. Hi-Tech is openly violating ThermoLife’s U.S. Patent No. 7,777,074 (“the
‘074 Patent”), which protects and covers amino acid compounds consisting a nitrate of an

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1 amino acid, including Creatine Nitrate. *See* Exhibit A. As stated in the ‘074 Patent,
2 Creatine Nitrate effectively increases vasodilatation in humans, and is, therefore, a
3 desirable additive to dietary supplements for athletes and others.

4 3. Hi-Tech is also openly violating ThermoLife’s U.S. Patent No. 8,178,572
5 (“the ‘572 Patent”), which protects and covers “a method for increasing the vasodilative
6 characteristics of amino acids in a human or animal, the method comprising
7 administering to the human or animal a pharmaceutically effective amount of an amino
8 acid compound consisting essentially of a nitrate or nitrate of an amino acid selected from
9 the group consisting of Arginine, Armatine, Beta Alanine, Citrulline, Creatine,
10 Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, Ornithine, and Valine.” *See*
11 Exhibit B.

12 4. Hi-Tech previously obtained its supply of ThermoLife’s patented Creatine
13 Nitrate through ThermoLife’s authorized supplier, Prinova (formerly Premium
14 Ingredients International). Since April 2011, Hi-Tech has not purchased Creatine Nitrate
15 from Prinova; nonetheless, Hi-Tech continues to manufacture and distribute dietary
16 supplements that include ThermoLife’s patented Creatine Nitrate.

17 5. In this case, Hi-Tech has violated ThermoLife’s ‘074 Patent and ‘572 Patent
18 by manufacturing and selling at least the following products: BodyFuse’s Torque
19 Reloaded, BodyFuse’s Cre-8, NLN’s N-Power, NZ Nutraceuticals’ Invincible, Unleashed
20 Muscle’s Creatine Nitrate, Unleashed Muscle’s Uprising. Each of these products rely on
21 Creatine Nitrate to increase the vasodilative characteristics of amino acids in a human. In
22 addition to the identified products, ThermoLife believes that Hi-Tech has manufactured
23 and sold other products that infringe ThermoLife’s ‘074 Patent and ‘572 Patent.

24 6. ThermoLife brings this action to enjoin Hi-Tech from continuing to violate
25 the ‘074 Patent and ‘572 Patent and to recover a reasonable royalty and treble damages for
26

1 its lost sales resulting from defendant’s willful infringement. In addition, Hi-Tech should
2 be made to disgorge its illegal profits made by violating ThermoLife’s valid patents.

3 **PARTIES, JURISDICTION AND VENUE**

4 7. Plaintiff ThermoLife is an Arizona limited liability company. ThermoLife’s
5 principal place of business is 3914 East Chandler Boulevard, Phoenix, Arizona 85048.

6 8. Hi-Tech is a Georgia corporation, with its principle place of business located
7 at 6015-B Unity Drive, Norcross, Georgia 30071.

8 9. Hi-Tech ships and sells products nationwide, including in Arizona.

9 10. Hi-Tech advertises its products nationwide, including in Arizona.

10 11. The Court has jurisdiction over Plaintiff’s federal claims under 28 U.S.C.
11 §§1331 and 1338 because this action, at least in part, is for patent infringement and arises
12 under the patent laws of the United States, Title 35, Section 271 *et seq.* of the United
13 States Code.

14 12. This Court also has jurisdiction over this matter pursuant to 28 U.S.C. §1332
15 because ThermoLife and Hi-Tech are diverse in citizenship and the amount in
16 controversy exceeds \$75,000, exclusive of interests and costs.

17 13. Venue is proper in this District under 28 U.S.C. §1391(b)-(c), because a
18 substantial part of the events or omissions giving rise to ThermoLife’s claims occurred in
19 this District. Venue with respect to Hi-Tech is also proper in this district because Hi-Tech
20 is subject to personal jurisdiction in this district.

21 **FACTUAL ALLEGATIONS**

22 **A. ThermoLife**

23 14. Ron Kramer (“Kramer”) founded ThermoLife in 1998. Prior to founding
24 ThermoLife, Kramer was a gym owner who had competed in bodybuilding and later
25 promoted professional bodybuilding competitions for the International Federation of
26 Bodybuilders.

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1 15. Between 1994 and 1997, Kramer opened and operated a Gold's Gym in Santa
2 Cruz, California.

3 16. During his time as a bodybuilder, promoter, and gym owner, Kramer
4 discovered that many dietary supplements failed to meet any quality control standards.
5 Often supplements are spiked with hidden ingredients and labeled incorrectly. Many were
6 ineffective.

7 17. At the time ThermoLife was established, few supplements were clinically
8 researched or field tested. Even today, relatively few supplements have been proven to
9 work as advertised.

10 18. In 1998, Kramer founded ThermoLife in order to provide the public with
11 quality proven supplements. ThermoLife is committed to selling only the purest, most
12 effective and innovative products.

13 19. By relying on supposedly proprietary formulas, supplement companies often
14 hide the ingredients in their products from consumers. Unlike other supplement
15 companies, ThermoLife develops unique and novel products and formulas that it fully
16 discloses to the public. In this way, ThermoLife allows consumers to know exactly what
17 products and raw materials they consume.

18 20. ThermoLife has been awarded patents on twenty individual compounds.
19 These patents protect ThermoLife's innovative and proven products from being copied by
20 ThermoLife's competitors.

21 21. By fully disclosing its formulas and relying on scientifically proven and
22 protected formulas and ingredients, ThermoLife has taken a lead role in ending the
23 deceptive business practices that have plagued the supplement industry.

24 22. One of the patents owned by ThermoLife is U.S. Patent 7,777,074. On
25 August 17, 2010, the '074 Patent was duly and legally issued to Kramer, *et al.*
26 ThermoLife is the assignee of all rights in and title to the '074 Patent. A true and correct

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1 copy of the '074 Patent is attached as Exhibit A, and incorporated herein by this
2 reference.

3 23. ThermoLife also owns U.S. Patent No. 8,178,572. The '572 Patent was
4 issued on May 22, 2012. ThermoLife is the assignee of all rights in and title to the '572
5 Patent. A true and correct copy of the '572 Patent is attached as Exhibit B, and
6 incorporated herein by this reference.

7 24. ThermoLife's supplements are sold nationwide on the internet and in vitamin
8 and dietary supplement stores such as The Vitamin Shoppe.

9 **B. Hi-Tech's Infringement**

10 25. Hi-Tech manufactures and sells its own line of products under the label "Hi-
11 Tech Pharmaceuticals."

12 26. In addition to manufacturing and selling its own line of products, Hi-Tech
13 formulates, manufactures and sells products for other dietary supplement companies.

14 27. Hi-Tech's website advertises its formulation and manufacturing services,
15 stating, "Hi-Tech Nutraceuticals is one of the world's leading suppliers of nutritional and
16 dietary supplements because it consistently provides high-quality, bulk raw materials and
17 time proven, effective ingredients to its rapidly expanding customer base. Hi-Tech can
18 supply any custom herbal extracts and specialty ingredients on a timely basis and at
19 extremely competitive prices."

20 28. Hi-Tech's website also provides a list of the raw materials that Hi-Tech has
21 available to include in any dietary supplement. Hi-Tech's website lists Creatine Nitrate
22 among its available raw materials. (Hi-Tech Website Printout, attached as Exhibit C.)

23 29. Hi-Tech began purchasing Creatine Nitrate from ThermoLife's authorized
24 distributor in August 2010. Hi-Tech made its last purchase of Creatine Nitrate on April 7,
25 2011. The Creatine Nitrate that Premium Ingredients sold to Hi-Tech on April 7, 2011, is
26 identified by lot number 101209.

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1 30. It is a regulatory requirement that the dietary supplement manufacturer
2 perform adequate identification tests on each lot of raw materials received, prior to
3 release of a dietary supplement. In order to meet this requirement, Creatine Nitrate is sold
4 with a Certificate of Analysis (“COA”). The Certificate of Analysis for lot number
5 101209, which Hi-Tech purchased on April 7, 2011, states that the Creatine Nitrate had
6 an expiration date of December 3, 3012. (COA attached as Exhibit D.)

7 31. Since the Creatine Nitrate that Hi-Tech purchased from Premium Ingredients
8 has an expiration date of December 3, 2012, any end product that includes this Creatine
9 Nitrate should expire on or before December 3, 2012. While there are potentially
10 incubation processes that could extend the expiration date of Creatine Nitrate, no known
11 incubation process could increase the expiration date by more than two years.

12 32. In late May 2012, ThermoLife discovered that the following dietary
13 supplements were being sold with labels that listed Creatine Nitrate as an ingredient:
14 BodyFuse’s Torque Reloaded, BodyFuse’s Cre-8, NLN’s N-Power, NZ Nutraceuticals’
15 Invincible, Unleashed Muscle’s Creatine Nitrate, and Unleashed Muscle’s Uprising
16 (hereinafter “the Infringing Products”). When ThermoLife purchased some of these
17 products, it learned at least some of these products purported to expire as late as July
18 2016.

19 33. Each of the Infringing Products are distributed by companies that are owned
20 or operated by Joe Eckstrom, Chief Executive Officer of Nutrition Zone Worldwide, Inc.

21 34. ThermoLife contacted Mr. Eckstrom in early June 2012, regarding these
22 products.

23 35. Mr. Eckstrom confirmed to ThermoLife that the Creatine Nitrate included in
24 the Infringing Products was purchased from Hi-Tech.

25 36. Because these products list an expiration date on or after December 3, 2012,
26 Hi-Tech could not have purchased the Creatine Nitrate included in these products from

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1 ThermoLife’s authorized distributor. Even if Hi-Tech incubated the Creatine Nitrate
2 included in these products, none of the products should have an expiration date after
3 December 3, 2014.

4 37. As a member of the nutritional supplement and bodybuilding industries, Hi-
5 Tech appreciates the scope of the ‘572 and ‘074 Patents, as well as the other patents
6 assigned to ThermoLife.

7 38. As a result of its prior purchases of Creatine Nitrate, since at least April 7,
8 2010, Hi-Tech has had notice of the ‘074 Patent.

9 39. Notwithstanding Hi-Tech’s appreciation of the value and scope of the ‘074
10 Patent, Hi-Tech has obtained Creatine Nitrate from an unauthorized source and sold,
11 manufactured, imported and/or used infringing Creatine Nitrate compositions.

12 40. The Infringing Products have at least one compositional feature corresponding
13 to an Amino Acid Compound consisting essentially of a nitrate or nitrite of an Amino
14 Acid elected from the group consisting of Arginine Beta Alanine, Agmatine, Citrulline,
15 Creatine, Glutamine, L-Histidine, Isoleucine, Leucine, Norvaline, or Ornithine. Here, the
16 Infringing Products includes Creatine Nitrate.

17 41. The Infringing Products also rely on Creatine Nitrate in order to increase the
18 vasodilative characteristics of amino acids in a human.

19 **COUNT I – PATENT INFRINGEMENT**

20 42. ThermoLife repeats and realleges each and every allegation contained in
21 Paragraphs 1 through 41 of this Complaint, as if fully set forth herein.

22 43. This cause of action arises under the Laws of the United States, Title 35,
23 United States Code, in particular under 35 U.S.C. § 271(a).

24 44. The ‘074 and ‘572 Patents are valid and enforceable.

25 45. Hi-Tech, acting through and by its respective officers and owners, has,
26 without authority, consent, right or license, and in direct infringement of the ‘074 Patent

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1 and '572 Patent, imported, made, used, and/or sold the Infringing Products. In addition to
2 the Infringing Products, ThermoLife believes that Hi-Tech has manufactured and sold
3 other products that infringe ThermoLife's '074 Patent and '572 Patent.

4 46. Hi-Tech's infringing conduct is willful, intentional, unlawful and, upon
5 information and belief, will continue unless enjoined by this Court.

6 47. ThermoLife has no adequate remedy at law for the harm caused by
7 defendant's acts.

8 48. By reason of Hi-Tech's acts complained of herein, ThermoLife has suffered
9 monetary damages in an amount that has not yet been determined, but upon information
10 and belief, is substantially in excess of the sum or value of \$75,000, exclusive of interest
11 and costs.

12 49. Due to the intentional nature of Hi-Tech's acts, this is an exceptional case in
13 which ThermoLife is entitled to treble damages, attorneys' fees and costs pursuant to 35
14 U.S.C. §§ 284 and 285.

15 50. Pursuant to 35 U.S.C. § 284, ThermoLife is entitled to: an accounting by Hi-
16 Tech of funds comprising all revenues received through the commercial exploitation of
17 the Infringing Products; the imposition of a constructive trust for the benefit of
18 ThermoLife for all such funds in the custody or control of Hi-Tech; and to such other
19 damages to which ThermoLife may be determined to be entitled.

20 **COUNT II – INDUCEMENT OF PATENT INFRINGEMENT**

21 51. ThermoLife repeats and realleges each and every allegation contained in
22 Paragraphs 1 through 50 of this Complaint, as if fully set forth herein.

23 52. This cause of action arises under the Patent Laws of the United States, Title
24 35, United States Code, in particular under 35 U.S.C. § 271(b).

25 53. The '074 and '572 Patents are valid and enforceable.

26

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1 54. To extent any of Hi-Tech’s actions do not constitute direct infringement of the
2 ‘074 and ‘572 Patents, Hi-Tech has induced each of the companies that sell the Infringing
3 Products to directly infringe the ‘074 and ‘572 Patents.

4 55. Hi-Tech’s infringing conduct is willful, intentional, unlawful and, upon
5 information and belief, will continue unless enjoined by this Court.

6 56. ThermoLife has no adequate remedy at law for the harm caused by Hi-Tech’s
7 acts.

8 57. By reason of Hi-Tech’s acts complained of herein, ThermoLife has suffered
9 monetary damages in an amount that has not yet been determined, but upon information
10 and belief, is substantially in excess of the sum or value of \$75,000, exclusive of interest
11 and costs.

12 58. Due to the intentional nature of Hi-Tech’s acts, this is an exceptional case in
13 which ThermoLife is entitled to treble damages, attorneys’ fees and costs pursuant to 35
14 U.S.C. §§ 284 and 285.

15 **COUNT III – CONTRIBUTORY PATENT INFRINGEMENT**

16 59. ThermoLife repeats and realleges each and every allegation contained in
17 Paragraphs 1 through 58 of this Complaint, as if fully set forth herein.

18 60. This cause of action arises under the Patent Laws of the United States, Title
19 35, United States Code, in particular under 35 U.S.C. § 271(c).

20 61. The ‘074 and ‘572 Patents are valid and enforceable.

21 62. To extent any of Hi-Tech’s actions do not constitute direct infringement of the
22 ‘074 and ‘572 Patents, Hi-Tech is liable for contributory infringement, pursuant to 35
23 U.S.C. § 271(c), in that Hi-Tech has imported, made, and/or sold within the United States
24 a component of a patented combination or composition, consisting of a material part of
25 the invention, knowing the same to be especially made or adapted for use in the
26

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1 infringement of the '074 and '572 Patents and not a staple article or commodity of
2 commerce suitable for substantial non-infringing use.

3 63. Hi-Tech's infringing conduct is willful, intentional, unlawful and, upon
4 information and belief, will continue unless enjoined by this Court.

5 64. ThermoLife has no adequate remedy at law for the harm caused by Hi-Tech's
6 acts.

7 65. By reason of Hi-Tech's acts complained of herein, ThermoLife has suffered
8 monetary damages in an amount that has not yet been determined, but upon information
9 and belief, is substantially in excess of the sum or value of \$75,000, exclusive of interest
10 and costs.

11 66. Due to the intentional nature of Hi-Tech's acts, this is an exceptional case in
12 which ThermoLife is entitled to treble damages, attorneys' fees and costs pursuant to 35
13 U.S.C. §§ 284 and 285.

14 **JURY TRIAL DEMAND**

15 1. Plaintiff requests a trial by jury on all aspects of the Complaint.

16 **PRAYER FOR RELIEF**

17 WHEREFORE, Plaintiff ThermoLife International, LLC prays for relief and
18 judgment against Defendant Hi-Tech as follows:

19 A. For a judicial determination and declaration that the '074 Patent is valid and
20 enforceable;

21 B. For a judicial determination and declaration that the '572 Patent is valid and
22 enforceable;

23 C. That a preliminary and permanent injunction issue against Hi-Tech, its agents,
24 officers, directors, employees, attorneys, successors and assigns, all parent and subsidiary
25 entities, and all those acting for or on the behalf of Hi-Tech, or in active concert,
26

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1 participation, or combination with them, including customers and distributors, prohibiting
2 Hi-Tech from:

- 3 i. continuing acts of infringement of ThermoLife's '074 and '572 Patents;
- 4 ii. making, using, selling and/or importing Infringing Products, to include any
5 colorable imitation thereof; and
- 6 iii. otherwise infringing upon ThermoLife's patents.

7 D. That an Order issue from this Court requiring Hi-Tech, its officers, agents,
8 servants and employees, to deliver up to this Court for destruction all articles and
9 materials infringing upon the rights of ThermoLife and all formulations and other matter
10 or materials for reproducing such Infringing Products;

11 E. That defendant be required to file with the Court within thirty (30) days after
12 entry of an injunctive order or final judgment a written statement under oath setting forth
13 the manner in which defendant has complied with the order or final judgment;

14 F. Awarding ThermoLife its damages sustained due to Hi-Tech's infringement
15 of the '074 and '572 Patents;

16 G. In the alternative, ordering Hi-Tech to pay ThermoLife all profits, gains, and
17 advantages defendant has received or obtained from their unlawful conduct, in an amount
18 to be determined at trial;

19 H. In the alternative, that a reasonable royalty for defendant's infringement be
20 awarded to ThermoLife pursuant to 35 U.S.C. § 284;

21 I. That, due to defendant's willful infringement of ThermoLife's patent rights,
22 defendant be ordered to pay ThermoLife treble damages pursuant to 35 U.S.C. §284;

23 J. An award of the costs of this action, including pre- and post-judgment
24 interest, pursuant to 35 U.S.C. § 284;

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1 K. That, due to defendant's willful and flagrant disregard of ThermoLife's patent
2 rights, defendant be ordered to pay ThermoLife its reasonable attorneys' fees and experts'
3 fees pursuant to 35 U.S.C. § 285; and

4 L. For such other and further relief as this Court deems necessary, just and
5 proper under the circumstances.

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7 DATED this 6th day of July, 2012.

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9 KERCSMAR & FELTUS PLLC

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11 By s/ Gregory B. Collins

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