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23342 7590 10/13/2017
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EXAMINER

RAGHU, GANAPATHIRAM

ART UNIT

PAPER NUMBER

1652

DATE MAILED: 10/13/2017

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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15/445,254

02/28/2017

Brian Michael Green

098816-1039426
(ASP-006)

1846

TITLE OF INVENTION: METHODS FOR MAKING L-GLUFOSINATE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0	\$0	\$480	01/16/2018

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KILPATRICK TOWNSEND & STOCKTON LLP

By: /Debbie K. Cooke/
Debbie K. Cooke

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Brian Michael Green et al.

Application No.: 15/445,254

Filed: February 28, 2017

For: METHODS FOR MAKING L-
GLUFOSINATE

Customer No.: 23342

Confirmation No.: 1846

Examiner: Ganapathiram Raghu

Technology Center/Art Unit: 1652

AMENDMENT AND RESPONSE TO NON-FINAL OFFICE ACTION

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

In response to the Office Action mailed June 21, 2017, please enter the following amendments and consider the following remarks. This response is being timely filed within three months of the mailing date of the non-final Office Action, i.e., on or before September 21, 2017.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 4 of this paper.

Applicant Summary of Interview with the Examiner begins on page 8 of this paper.

Remarks begin on page 9 of this paper.

experimentation needed to practice the invention is undue or unreasonable. *Minerals Separation Ltd. v. Hyde*, 242 U.S. 261, 270 (1916); *see also* MPEP 2164.01.

The present claims are drawn to a method for making L-glufosinate. The method involves reacting D-glufosinate with a DAAO enzyme to form PPO followed by aminating PPO with a transaminase to form L-glufosinate. The Examiner indicates that “[t]he scope of the claims are not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides and encoding polynucleotides broadly encompassed by the claims.

In the *Invitrogen* case, discussed above for written description, the Federal Circuit also addressed the enablement of the sample claim set forth above. As noted, the claim in *Invitrogen* was broadly drawn to any DNA polymerase having substantially reduced RNase H activity, wherein said polypeptide is encoded by a modified reverse transcriptase nucleotide sequence that encodes a modified amino acid sequence resulting in said polypeptide having substantially reduced RNase H activity. No sequence was present in the claim. The Federal Circuit found that the claims were enabled as the specification taught a method of making the enzyme. The Federal Circuit noted that the enablement requirement is met if the specification discloses any method for making the invention.

As noted above, the enzymes required by the claims are well known in the art and can be tested for use in the method of the claims. Further, where the claims require a mutant enzyme, such enzyme is defined by specific mutations. Accordingly, the claims are enabled by the specification and Applicant requests withdrawal of the rejection.

35 U.S.C. § 103

Claims 1-4 and 7-11 were rejected under 35 U.S.C. § 103 as obvious over U.S. Patent No. 7,939,709 to Hawkes et al. (“Hawkes”) as evidenced by U.S. Patent No. 5,877,013 to Liao et al. (“Liao”) and further in view of Schulz *et al.*, *Appl. Environ. Microbiol.*, 56(1): 1-6 (1990) (“Schulz”) as evidenced by UniProtKB/Swiss-prot:P22256.1. Applicant respectfully traverses this rejection.

The present claims are directed to an *ex vivo* method of making L-glufosinate comprising (1) reacting D-glufosinate with a D-amino acid oxidase (DAAO) enzyme to form PPO (2-oxo-4-(hydroxy(methyl)phosphinoyl)butyric acid) while aerating and (2) aminating the PPO to L-

glufosinate by a transaminase (TA) enzyme, using an amine group from one or more amine donors. In the claimed method, at least 70% of the D-glufosinate is converted to L-glufosinate. The presently claimed method is novel and non-obvious. In fact, while others have discussed methods for the production of L-glufosinate for many years, no one had put together the method set forth in the present claims. Because of the reversible nature of the reactions, there was no way to predict whether one could successfully produce a product containing substantially L-glufosinate. Until the DAAO and transaminase enzymes had been used in the same process, there was no way to know whether there may have been an inhibitory effect of one or both of the enzymes when used together. In addition, the hydrogen peroxide produced by the DAAO during the course of the reaction could have damaged or inactivated one or more of the gabT enzyme, the PPO product of DAAO, or any of the other reactants or products in the reaction. Only with the present application do those of skill in the art know how to make L-glufosinate *ex vivo*, where at least 70% of the D-glufosinate is converted to L-glufosinate. As described below, such a method was neither disclosed nor suggested in the prior art and the present method produces unexpected results relative to the prior art methods.

1. *Hawkes, Liao, and Schulz fail to disclose or suggest each and every limitation of the present claims.*

To support an obviousness rejection, “[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art.” *See* M.P.E.P. § 2143.03, quoting *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970). Thus, *all* claim limitations must be accounted for to establish a *prima facie* case of obviousness.

Amended claim 1 recites a method for making L-glufosinate, comprising reacting D-glufosinate with a D-amino acid oxidase (DAAO) enzyme to form PPO (2-oxo-4-(hydroxy(methyl)phosphinoyl)butyric acid) while aerating; and aminating the PPO to L-glufosinate by a transaminase (TA) enzyme, using an amine group from one or more amine donors, wherein at least 70% of the D-glufosinate is converted to L-glufosinate and wherein the method is performed *ex vivo*. Hawkes, Liao, and Schulz, in combination, fail to disclose or suggest the method for making L-glufosinate as recited in the present claims.

Hawkes is drawn to methods for making male and female sterile plants. Plants were transformed with a DAAO enzyme operably linked to a tissue specific promoter. Upon

application of D-glufosinate, the DAAO enzyme oxidizes D-glufosinate to 2-oxo-4-(methylphosphinyl)-butanoic acid. The reaction relies upon endogenous transaminase for conversion to L-glufosinate. The purpose of Hawkes was to find a method for the production of sterile plants. *The reaction described takes place inside an organelle of the plant.* Such *in vivo* conditions are very different than the *ex vivo* production of L-glufosinate (for the reasons outlined above), as described in the present application and as recited in the present claims. Hawkes was not concerned with making a substantial amount of L-glufosinate and in fact would not have because the conversion of a small amount of D-glufosinate to L-glufosinate would have killed the cell. Therefore, Hawkes fails to disclose or suggest the methods recited in the present claims.

As the Examiner noted in the interview, Hawkes did perform half of the claimed invention *ex vivo*. These DAAO reactions alone were performed to determine the reaction rate of various mutant DAAO enzymes; typically, reaction rates are determined when the substrate is not limiting and so Hawkes would not have been concerned about reaching the 70% conversion in the present invention. In addition, as discussed below, Hawkes did these reactions in sealed, un aerated vessels, not in the aerated environment of the present invention.

However, even though Hawkes did study the DAAO enzyme in an *ex vivo* environment, there was no teaching to combine this reaction with a transaminase *ex vivo* to make L-glufosinate. Nothing in Hawkes teaches or suggests that the combination of the enzymes would be useful for the production of commercial levels of L-glufosinate. In fact, although the desired enantiomer is different, Hawkes was presented with the problem of generating *ex vivo* samples of an enantiomerically enriched version of glufosinate (in Hawkes' case, D-glufosinate) and proposed 8 solutions. *See* Hawkes, column 10, line 14 through column 11, line 7. None of these solutions involves a combination of an amino acid oxidase and a transaminase. One of these proposed solutions even describes using an L-amino acid oxidase, but none suggest combining an amino acid oxidase with a transaminase. Therefore, Hawkes fails to disclose or suggest the use of a DAAO and a transaminase to make enantiomerically enriched versions of glufosinate *ex vivo*. Accordingly, the reference does not teach or suggest the presently claimed invention. The present invention demonstrates that surprisingly 70% and greater amounts of L-glufosinate can be generated using the methods set forth in the present claims.

Liao and Schulz fail to cure the deficiencies of Hawkes. Specifically, Liao relates to an isolated nucleic acid encoding a DAAO of the genus *Rhodospiridium*. The nucleotide sequence of the novel enzyme is provided. There is no mention in the patent of the production of L-glufosinate. Schulz is drawn to the isolation and characterization of a phosphinothricin-specific transaminase from *E. coli*. The publication describes the production of L-glufosinate from 2-oxo-4-[(hydroxy)(methyl) phosphinoyl] butyric acid (PPO) by transamination. As set forth in the Materials and Methods section of the paper (see page 1, first column of Schulz), PPO was synthesized for use in the reaction. While the secondary references cited by the Examiner, Liao and Schulz, describe enzymes which can be used in the presently claimed method, neither reference puts the steps together for the production of L-glufosinate as required in the present claims.

The Examiner cites M.P.E.P. § 2144.05 to support the position that optimization of a process is not patentable unless differences in concentration or temperature are critical. It is noted that “[w]here the general conditions of a claims are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *See* Office Action, pages 27-28. However, as detailed above, the claimed process is neither suggested nor disclosed in the prior art. No one, including Hawkes, Liao, and/or Schulz, disclosed or suggested the claimed method for the *ex vivo* production of L-glufosinate. Because the claimed conditions are not disclosed in the prior art, this section of the M.P.E.P. does not apply.

2. *The claimed methods exhibit unexpected and superior results relative to Hawkes, Liao, and Schulz.*

In addition, Applicant respectfully submits that the presently claimed method produces L-glufosinate with an efficiency that is unexpected and superior to production methods in the prior art. As described above, the method described in Hawkes differs considerably from the presently claimed method. For example, Hawkes only describes performing the DAAO step *ex planta* and not the combination of steps with DAAO and transaminase as described in the present claims. In addition, the DAAO step in Hawkes is not performed under continuous aeration conditions. The amended claims, however, require that the reaction takes place *ex vivo* and *while aerating*. Such distinctions are far from trivial. As described above, the present method was not suggested in the art and thus there was no way to know, until the present invention, whether the method would in

fact work to produce compositions containing substantially pure L-glufosinate, wherein at least 70% of the D-glufosinate is converted to L-glufosinate. In fact, Examples 7 and 8 of the present application demonstrate that in order for the DAAO reaction to occur at useful rates, aeration must be added to larger scale vessels. Specifically, the DAAO reaction reached equilibrium within 8 hours when the method was performed while aerating. *See* Example 7 of the present application. However, in the absence of aeration, the DAAO reaction rate was almost 5 times as long, taking over 60 hours to reach equilibrium. *See* Example 8 of the present application. Such an effect is unexpected and superior, and is neither disclosed nor suggested in Hawkes, Liao, and/or Schulz.

3. *The claimed methods meet a need in the art.*

Farmers are facing increasing pressure due to weeds that are resistant to commonly used herbicides. The Schulz reference was published in 1990, the Liao reference was published in 1999, and the first publication in the Hawkes family of patents (WO 2003/072792) was published on March 18, 2004. During this time, numerous approaches, including resurrecting older chemistries such as dicamba and 2,4-D, have been attempted, but these solutions remain suboptimal. In fact, alternative approaches to L-glufosinate production have even been proposed (such as CN 106978368A and CN 106916857A) without conceiving the current invention. The crop protection industry, despite 1) desiring to meet farmers' needs for alternative herbicide solutions, 2) having large numbers of individuals skilled in the art employed to meet those needs, and 3) being in possession of the Schulz, Liao, and Hawkes data for more than 13 years, had not arrived at the method of the current invention until the present invention. The present invention, which allows for greater than 70% conversion of D-glufosinate to L-glufosinate, will enable a cost effective alternative for farmers in controlling resistant and otherwise recalcitrant weeds.

Accordingly, for all of these reasons, Applicant respectfully requests withdrawal of the rejection of claims 1-4 and 7-11.

NEW CLAIMS

New claims 21-30 are drawn to a method of making L-glufosinate. The claims use the novel DAAO enzymes set forth in the application. Accordingly, it is believed that the claims are novel and should be found allowable.



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15/445,254	02/28/2017	Brian Michael Green	098816-1039426 (ASP-006)	1846
23342	7590	06/21/2017	EXAMINER	
KILPATRICK TOWNSEND & STOCKTON LLP			RAGHU, GANAPATHIRAM	
Mailstop: 22 - IP Docketing			ART UNIT	
1100 Peachtree Street			PAPER NUMBER	
Suite 2800			1652	
Atlanta, GA 30309			NOTIFICATION DATE	
			DELIVERY MODE	
			06/21/2017	
			ELECTRONIC	

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with the scope of the claims broadly including polypeptides with an enormous number of modifications. The scope of the claim must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1975)). Without sufficient guidance, determination of polypeptides having the desired biological characteristics in the claimed method is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

Although the claims are examined in the light of the specification, specification cannot be read into the claims, i.e., the limitations of the specification cannot be read into the claims (see MPEP 2111 R-5).

415 F.3d at 1316, 75 USPQ2d at 1329. See also *In re Hyatt*, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). Applicant always has the opportunity to amend the claims during prosecution, and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-51 (CCPA 1969) (Claim 9 was directed to a process of analyzing data generated by mass spectrographic analysis of a gas. The process comprised selecting the data to be analyzed by subjecting the data to a mathematical manipulation. The examiner made rejections under 35 U.S.C. 101 and 102. In the 35 U.S.C. 102 rejection, the examiner explained that the claim was anticipated by a mental process augmented by pencil and paper markings. The court agreed that the claim was not limited to using a machine to carry out the process since the claim did not explicitly set forth the machine. The court explained that "reading a claim in light of the specification, to thereby interpret limitations explicitly recited in the claim, is a quite different thing from reading limitations of the specification into a claim," to thereby narrow the scope of the claim by implicitly adding disclosed limitations which have no express basis in the claim." The court found that applicant was advocating the latter, i.e., the impermissible importation of subject matter from the specification into the claim.). See also *In re Morris*, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997) (The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."). The broadest reasonable interpretation of the claims must also be consistent with the interpretation that those skilled in the art would reach.

Claim Rejections: 35 USC § 103 (AIA)

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102 of this title, if the differences between the claimed invention and

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the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection **will not be considered** a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

Claims 1-4 and 7-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hawkes et al., (US 7,939,709 B2, in IDS), as evidenced by Liao et al., (US 5,877,013; see provided sequence alignment) and further in view of Schulz et al., (Appl. Environ. Microbiol., 1990, Vol. 56 (1): 1-6, in IDS), as evidenced by UniProtKB/Swiss-prot:P22256.1 (10 pages downloaded from <https://www.ncbi.nlm.nih.gov/protein/P22256> on 06/12/17).

Claims 1-4 and 7-11 are directed to a method for making L-glufosinate (L-pohosphinothricin), comprising: reacting D-glufosinate (D-pohosphinothricin) with a D-amino acid oxidase (DAAO) enzyme to form PPO (2-oxo-4-(hydroxyl(methyl)phosphinoyl)butyric acid); and aminating the PPO to L-glufosinate (L-pohosphinothricin) by a transaminase (TA) enzyme ..., wherein said method

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encompasses/comprises any D-amino acid oxidase (DAAO) enzyme ... and any transaminase (TA) enzyme) including variants, mutants and homologs (**no structural limitations**; examiner takes the position that “comprising” is an “open language” and only the corresponding recited amino acid residues in the claimed DAAO are defined in the claimed structure and the remainder of the molecule(s)/mutated DAAO is undefined; thus, claims as written encompasses **unlimited/undefined structures**; also see 112 (b) rejection above for claims interpretation).

Regarding claims 1-4 and 8-11, analogous art Hawkes et al., (US 7,939,709 B2, in IDS), as evidenced by Liao et al., (US 5,877,013; see provided sequence alignment) teach a method for making PPO comprising: reacting D-glufosinate (D-phosphinothricin) with a D-amino acid oxidase (DAAO) enzyme isolated from *Rhodospiridium* sp., including specific variants of said DAAO enzyme to form PPO (2-oxo-4-(hydroxyl(methyl)phosphinoyl)butyric acid) and also “glutamate” as the amino donor in said catalytic reactions. Applicants’ are directed to the following sections in Hawkes et al., (US 7,939,709 B2): Abstract; col. 6, lines 38-44; col. 7, lines 60-67 to col. 8, lines 1-46; Example 1, col. 20, lines 50-67 to col. 21, lines 1-34; col. 36, lines 41-67 to col. 37, lines 1-36; col. 42, lines 54-60. Some of the relevant sections from Hawkes et al., (US 7,939,709 B2, in IDS) are reproduced below:

Col. 6

(3) D-amino acid oxidases capable of catalysing the oxidation:
 40 D-amino acid+O₂+H₂O→NH₃+H₂O₂+2-oxo acid
 and in certain embodiments particularly the reaction
 D-phosphinothricin+O₂+H₂O→NH₃+H₂O₂+2-oxo-4-
 methylphosphinobutyrate

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Col. 7

The D-amino acid oxidase (DAMOX) enzyme may be selected from amongst those produced by *Rhodospiridium* sp. (*Rhodotorula* sp.), *Trigonopsis* sp, pig, *Fusarium* sp, *Candida* sp, *Schizosaccharomyces* sp and *Verticillium* sp, and may be selected from proteins having sequences corresponding to Swissprot accession numbers P80324, Q99042, P00371, P24552 or SPITREMBL numbers Q9HGY3 and Q9Y7N4. The DNA sequences which encode the D amino acid oxidase

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may be selected from sequences comprised within EMBL accessions A56901, RGU60066, Z50019, S5DA04, D00809, AB042032, RCDAAOX, A81420 and SPCC1450. D-amino acid oxidases are ubiquitous flavoenzymes.

Where the non-phytotoxic substance is D phosphinothricin or D-bialaphos or D-aspartate or D-glutamate then particularly preferred D-amino acid oxidases are obtained from *Rhodotorula gracilis* mutants or is a D-aspartate oxidase. Such mutants, whatever the non-phytotoxic substance, may comprise single and double amino acid substitutions at positions 213 and 238 when compared with the wild type sequence. Preferably at position 213 the wild type methionine is replaced by Arg, Lys, Ser, Cys, Asn or Ala, and the wild type Tyr at position 238 is replaced by His, Ser, Gys, Asn or Ala.

However, the enzyme may comprise substitutions in addition to, or at other than, the positions mentioned in the preceding paragraph. In particular, the Phe at position 58 in the wild type sequence may be replaced by a residue selected from the group consisting of His, Ser, Lys, Ala, Arg, and Asp, and preferably is either His, Ser or Ala. In addition, or alternatively, the Met at position 213 in the wild type sequence may be replaced by a residue selected from the group consisting of His, Ser, Lys, Ala, Arg, and Asp, and preferably is either Ser or Ala. In addition, or alternatively, the Tyr at position 223 in the wild type sequence may be replaced by a residue selected from the group consisting of His, Ser, Ala, Arg, and Asp. In addition, or alternatively, the Tyr at position 238 in the wild type sequence may be replaced by a residue selected from the group consisting of His, Ser, Lys, Ala, Arg, and Asp.

A particularly preferred mutant form of the enzyme comprises at least two of the above mentioned mutations. A first embodiment of such a double mutant has His at position 58 (rather than Phe in the wild type sequence), and Ser at position 213 (rather than Met). A second embodiment of such a double mutant has Ser at position 58 (rather than the wild-type Phe) and Arg at position 213 (rather than the wild-type Met).

Col. 19

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The present invention also provides a method of producing enantiomerically pure D-Phosphinothricin (D-PPT), comprising the steps of:

- (a) Providing cells which contain an enzyme capable of selectively N-acylating PPT;
- (b) Growing said cells in a medium which contains D-L PTT to produce conditioned medium;
- (c) Separating the cells from the conditioned medium of (b);
- (d) Optionally extracting the conditioned medium with a non-aqueous, non miscible solvent, at various pHs, so that the PPT containing fraction is separated from the fraction that contains molecules more water soluble than is PPT;
- (e) Optionally admixing with the conditioned or PPT-containing extracted media of step (d) a cation exchange resin in its protonated form, in an amount, and at pH, sufficient to absorb a substantial proportion of the cations—other than PPT, from the medium;
- (f) Admixing with the conditioned medium, extracted medium or medium to result from step (e) a cation exchange resin in its protonated form, in an amount, and at a pH, sufficient to bind the bulk of the PPT in the medium;
- (g) Harvesting the cation ion exchange resin from step (f) to which the PPT is bound and selectively eluting PPT from it using an eluting medium having a sufficient pH and ionic strength, with the proviso that the pH of the said eluting medium is not so low as to cause racemisation of the thus eluted PPT.

However, Hawkes et al., (US 7,939,709 B2, in IDS) are silent regarding aminating the formed PPO to L-glufosinate (L-phosphinothricin) with a transaminase (TA) enzyme in the claimed method of the instant invention.

Regarding claims 1 and 7, Schulz et al., (Appl. Environ. Microbiol., 1990, Vol. 56 (1): 1-6, in IDS), as evidenced by UniProtKB/Swiss-prot:P22256.1 (10 pages downloaded from <https://www.ncbi.nlm.nih.gov/protein/P22256> on 06/12/17) teach a method for **aminating the formed PPO to L-glufosinate** (L-phosphinothricin) with a transaminase (TA) enzyme) isolated from *E.coli*. Applicants are directed to the following sections in Schulz et al., (Appl. Environ. Microbiol., 1990, Vol. 56 (1): 1-6, in IDS):

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Abstract; Introduction, col. 1, paragraphs 1-3, page 1; TABLE 2, page 3; FIG. 2, page 3; TABLE 4, page 5; and entire document.

It would have been obvious to a person of ordinary skill in the art to modify the teachings of Hawkes et al., that teaches a method for making PPO comprising: reacting D-glufosinate (D-pohosphinothricin) with a D-amino acid oxidase (DAAO) enzyme isolated from *Rhodospiridium* sp., including specific variants of said DAAO enzyme to form PPO (2-oxo-4-(hydroxyl(methyl)phosphinoyl)butyric acid) and also "glutamate" as the amino donor in said catalytic reactions, by incorporating the method of aminating the formed PPO to L-glufosinate (L-pohosphinothricin) with a transaminase (TA) enzyme as taught by the reference of Schulz et al. Motivation to do so is provided by references of Hawkes et al and Schulz et al., that clearly define the role of DAAO and TA enzymes for efficient production of L-glufosinate (L-pohosphinothricin), an herbicide with various industrial applications and commercially important. The expectation of success is high, because the combined teachings of Hawkes et al., Liao et al., Schulz et al., provide the structural and functional elements of the instant invention (Teaching, Suggestion and Motivation).

Examiner also finds support in: MPEP 2144.05 [R-5]: Optimization Within Prior Art Conditions or Through Routine Experimentation Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine

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experimentation". As to optimization results, a patent will not be granted based upon the optimization of result effective variables when the optimization is obtained through routine experimentation unless there is a showing of unexpected results which properly rebuts the *prima facie* case of obviousness. See *In re Boesch*, 617 F.2d 272,276,205 USPQ 215,219 (CCPA 1980). See also *In re Woodruff*, 919 F.2d 1575, 1578, 16 USPQ2d 1934, 1936-37 (Fed. Cir. 1990), and *In re Aller*, 220 F.2d 454,456,105 USPQ 233,235 (CCPA 1955).

Therefore, claims 1-4 and 7-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hawkes et al., (US 7,939,709 B2, in IDS), as evidenced by Liao et al., (US 5,877,013; see provided sequence alignment) and further in view of Schulz et al., (Appl. Environ. Microbiol., 1990, Vol. 56 (1): 1-6, in IDS), as evidenced by UniProtKB/Swiss-prot:P22256.1 (10 pages downloaded from <https://www.ncbi.nlm.nih.gov/protein/P22256> on 06/12/17).

Allowable Subject Matter/Conclusion

None of the claims are allowable.

1) Claims 4, 5 and 7 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph.

2) Claims 1-5 and claims 7-11 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112, first paragraph, for written-description and enablement.

3) Claims 1-4 and 7-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hawkes et al., (US 7,939,709 B2, in IDS), as evidenced by Liao et al., (US 5,877,013; see provided sequence alignment) and further in view of Schulz et al., (Appl. Environ. Microbiol., 1990, Vol. 56 (1): 1-6, in IDS), as

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evidenced by UniProtKB/Swiss-prot:P22256.1 (10 pages downloaded from <https://www.ncbi.nlm.nih.gov/protein/P22256> on 06/12/17).

4) Claim 6 is objected as it depends from rejected base claim 1.

5) Claims 12-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached between 8 am-4: 30 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

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/Ganapathirama Raghu/
Primary Examiner
Art Unit 1652



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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
15/445,254	02/28/2017	1662	730	098816-1039426 (ASP-006)	20	3

CONFIRMATION NO. 1846

23342
KILPATRICK TOWNSEND & STOCKTON LLP
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WINSTON-SALEM, NC 27101

FILING RECEIPT



0000000089927378

Date Mailed: 03/15/2017

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

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Assignment For Published Patent Application

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Power of Attorney: The patent practitioners associated with Customer Number 23342

Domestic Priority data as claimed by applicant

This appln claims benefit of 62/413,240 10/26/2016 ABN
and claims benefit of 62/336,989 05/16/2016 ABN
and claims benefit of 62/302,421 03/02/2016 ABN

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

WHAT IS CLAIMED IS:

1. A method for making L-glufosinate, comprising:
reacting D-glufosinate with a D-amino acid oxidase (DAAO) enzyme to form PPO (2-oxo-4-(hydroxy(methyl)phosphinoyl)butyric acid); and
aminating the PPO to L-glufosinate by a transaminase (TA) enzyme, using an amine group from one or more amine donors,
wherein at least 70% of the D-glufosinate is converted to L-glufosinate.
2. The method of claim 1, wherein the amine donor is selected from the group consisting of glutamate, L-glutamate, alanine, sec-butylamine, phenylethylamine, glycine, lysine, valine, serine, glutamine, isopropylamine, ethanolamine, 2-aminobutyric acid, diaminopropionic acid, or any secondary amine or amino acid.
3. The method of claim 1, wherein the D-glufosinate is originally present in a racemic mixture of D- and L- glufosinate or salts thereof.
4. The method of claim 1, wherein the DAAO enzyme is a mutant DAAO comprising one or more mutations at positions 54, 56, 58, 213, and 238,
wherein the mutation at position 54 is selected from the group consisting of N54C, N54L, N54T, and N54V; the mutation at position 56 is T56M; and the mutation at position 58 is selected from the group consisting of F58A, F58G, F58H, F58K, F58N, F58Q, F58R, F58S, and F58T.
5. The method of claim 4, wherein the mutations comprise N54V, F58Q, and M213S.
6. The method of claim 1, wherein the TA enzyme is an enzyme encoded by SEQ ID NO: 1.
7. The method of claim 1, wherein the TA enzyme is a GabT transaminase having UniProt No. P22256.

8. The method of claim 1, wherein the reacting step and the aminating step are performed in a single container.
9. The method of claim 8, wherein all reagents are substantially added at the start of the reaction.
10. The method of claim 8, wherein the reagents for the reacting step and the reagents for the aminating step are added to the single container at different times.
11. The method of claim 1, wherein the reacting step and the aminating step are performed in separate containers.
12. A composition comprising D-glufosinate, PPO, and L-glufosinate.
13. The composition of claim 12, wherein the amount of L-glufosinate is 90% or greater based on the total amount of D-glufosinate, PPO, and L-glufosinate.
14. A formulation, comprising:
 - L-glufosinate ammonium in an amount from 10-30% by weight of the formulation;
 - one or more additional components selected from the group consisting of sodium alkyl ether sulfate in an amount from 10-40% by weight of the formulation; 1-methoxy-2-propanol in an amount from 0.5-2% by weight of the formulation; dipropylene glycol in an amount from 0-18% by weight of the formulation; and alkyl polysaccharide in an amount from 3-20% by weight of the formulation; and
 - water as the balance of the formulation.
15. The formulation of claim 14, wherein the formulation comprises:
 - L-glufosinate ammonium in an amount of 12.25% by weight of the formulation;
 - sodium alkyl ether sulfate in an amount of 31.6% by weight of the formulation;
 - 1-methoxy-2-propanol in an amount of 1% by weight of the formulation;
 - dipropylene glycol in an amount of 8.6% by weight of the formulation;
 - alkyl polysaccharide in an amount of 9.8% by weight of the formulation; and

water in an amount of 36.75% by weight of the formulation.

16. The formulation of claim 14, wherein the formulation comprises:
L-glufosinate ammonium in an amount of 24.5% by weight of the formulation;
sodium alkyl ether sulfate in an amount of 31.6% by weight of the formulation;
1-methoxy-2-propanol in an amount of 1% by weight of the formulation;
dipropylene glycol in an amount of 8.6% by weight of the formulation;
alkyl polysaccharide in an amount of 9.8% by weight of the formulation; and
water in an amount of 24.5% by weight of the formulation.
17. The formulation of claim 14, wherein the formulation comprises:
L-glufosinate ammonium in an amount of 12.25% by weight of the formulation;
sodium alkyl ether sulfate in an amount of 15.8% by weight of the formulation;
1-methoxy-2-propanol in an amount of 0.5% by weight of the formulation;
dipropylene glycol in an amount of 4.3% by weight of the formulation;
alkyl polysaccharide in an amount of 4.9% by weight of the formulation; and
water in an amount of 62.25% by weight of the formulation.
18. The formulation of claim 14, wherein the formulation comprises:
L-glufosinate ammonium in an amount of 12.25% by weight of the formulation;
sodium alkyl ether sulfate in an amount of 22.1% by weight of the formulation;
1-methoxy-2-propanol in an amount of 1% by weight of the formulation;
alkyl polysaccharide in an amount of 6.2% by weight of the formulation; and
water in an amount of 58.45% by weight of the formulation.
19. The formulation of claim 14, wherein the formulation comprises:
L-glufosinate ammonium in an amount of 24.5% by weight of the formulation;
sodium alkyl ether sulfate in an amount of 22.1% by weight of the formulation;
1-methoxy-2-propanol in an amount of 1% by weight of the formulation;
alkyl polysaccharide in an amount of 6.2% by weight of the formulation; and
water in an amount of 46.2% by weight of the formulation.

20. The formulation of claim 14, wherein the formulation comprises:
L-glufosinate ammonium in an amount of 12.25% by weight of the formulation;
sodium alkyl ether sulfate in an amount of 11.05% by weight of the formulation;
1-methoxy-2-propanol in an amount of 0.5% by weight of the formulation;
alkyl polysaccharide in an amount of 3.1% by weight of the formulation; and
water in an amount of 73.1% by weight of the formulation.

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	098816-1039426 (ASP-006)
		Application Number	
Title of Invention	METHODS FOR MAKING L-GLUFOSINATE		
The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76. This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.			

Secrecy Order 37 CFR 5.2:

☐	Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)
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Inventor Information:

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Petitioner Ex. 1016

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	098816-1039426 (ASP-006)
		Application Number	
Title of Invention	METHODS FOR MAKING L-GLUFOSINATE		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Abandoned	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Claims benefit of provisional	62413240	2016-10-26
Prior Application Status	Abandoned	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Claims benefit of provisional	62336989	2016-05-16
Prior Application Status	Abandoned	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Claims benefit of provisional	62302421	2016-03-02
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.			Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)ⁱ the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

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