



(12) **DEMANDE DE BREVET CANADIEN  
CANADIAN PATENT APPLICATION**

(13) **A1**

(86) Date de dépôt PCT/PCT Filing Date: 2016/12/30  
(87) Date publication PCT/PCT Publication Date: 2017/07/06  
(85) Entrée phase nationale/National Entry: 2019/06/27  
(86) N° demande PCT/PCT Application No.: US 2016/069593  
(87) N° publication PCT/PCT Publication No.: 2017/117575  
(30) Priorité/Priority: 2015/12/30 (US62/273,296)

(51) Cl.Int./Int.Cl. *A61K 31/465* (2006.01),  
*A24B 15/00* (2006.01), *A24B 15/16* (2006.01),  
*A24D 1/18* (2006.01), *A24F 47/00* (2006.01),  
*A61P 25/34* (2006.01), *A61M 11/00* (2006.01)  
(71) Demandeur/Applicant:  
NEXT GENERATION LABS, LLC, US  
(72) Inventeur/Inventor:  
ARNOLD, MICHAEL, US  
(74) Agent: CHATTERJEE, ALAKANANDA

(54) Titre : PRODUITS DE SUBSTITUTION DE LA NICOTINE COMPRENANT UNE NICOTINE DE SYNTHESE  
(54) Title: NICOTINE REPLACEMENT THERAPY PRODUCTS COMPRISING SYNTHETIC NICOTINE

(57) **Abrégé/Abstract:**

A composition suitable for use in nicotine replacement therapy products includes a nicotine product that includes a synthetic nicotine that is substantially free of one or more contaminants and/or impurities normally associated with tobacco-derived nicotine. For example, the synthetic nicotine is substantially free of one or more of nicotine-1'-N-oxide, nicotyrine, nornicotyrine, 2',3-bipyridyl, cotinine, anabasine, and/or anatabine. The composition further comprises one or more pharmaceutically acceptable excipients, additives and/or carriers. The nicotine replacement therapy products may include any number of such products, including transdermal nicotine delivery patches, nicotine gums, synthetic chewing tobacco, synthetic snuff, and synthetic strips (e.g., dissolvable synthetic tobacco). Additionally, a method of treating nicotine addiction includes administering a nicotine replacement composition, e.g., via a nicotine replacement therapy product, to a user.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau(43) International Publication Date  
6 July 2017 (06.07.2017)(10) International Publication Number  
**WO 2017/117575 A1**

## (51) International Patent Classification:

*A24B 15/16* (2006.01)      *A24D 1/18* (2006.01)  
*A24B 15/00* (2006.01)      *A24F 47/00* (2006.01)

## (21) International Application Number:

PCT/US2016/069593

## (22) International Filing Date:

30 December 2016 (30.12.2016)

## (25) Filing Language:

English

## (26) Publication Language:

English

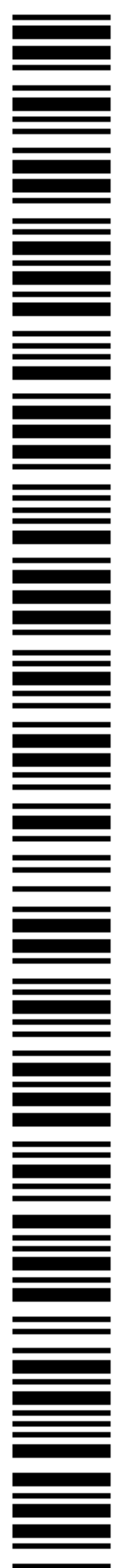
## (30) Priority Data:

62/273,296    30 December 2015 (30.12.2015)      US

(71) Applicant: **NEXT GENERATION LABS, LLC**  
[US/US]; 8505 Commerce Avenue, San Diego, California  
92121 (US).(72) Inventor: **ARNOLD, Michael**; c/o Next Generation Labs,  
LLC, 8505 Commerce Avenue, San Diego, California  
92121 (US).(74) Agent: **SCHNEIDER, Lauren E.**; Lewis Roca Rothgerber  
Christie LLP, P.O. Box 29001, Glendale, California  
91209-9001 (US).(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).**Published:**— *with international search report (Art. 21(3))*

(54) Title: NICOTINE REPLACEMENT THERAPY PRODUCTS COMPRISING SYNTHETIC NICOTINE

(57) Abstract: A composition suitable for use in nicotine replacement therapy products includes a nicotine product that includes a synthetic nicotine that is substantially free of one or more contaminants and/or impurities normally associated with tobacco-derived nicotine. For example, the synthetic nicotine is substantially free of one or more of nicotine-1'-N-oxide, nicotine, nornicotine, 2',3-bipyridyl, cotinine, anabasine, and/or anatabine. The composition further comprises one or more pharmaceutically acceptable excipients, additives and/or carriers. The nicotine replacement therapy products may include any number of such products, including transdermal nicotine delivery patches, nicotine gums, synthetic chewing tobacco, synthetic snuff, and synthetic strips (e.g., dissolvable synthetic tobacco). Additionally, a method of treating nicotine addiction includes administering a nicotine replacement composition, e.g., via a nicotine replacement therapy product, to a user.

**WO 2017/117575 A1**





## 1 SUMMARY

**[0004]** According to embodiments of the present invention, a composition suitable for use in a nicotine replacement product includes a nicotine product comprising a synthetic nicotine substantially free of one or more of nicotine-1'-N-oxide, 5 nicotyrine, nornicotyrine, cotinine, 2',3-bipyridyl, anabasine, N-methyl anatabine, N-methyl anabasine, anabasine, and/or anatabine. The composition further includes one or more pharmaceutically acceptable excipients, additives and/or carriers.

**[0005]** According to some embodiments, a nicotine replacement therapy product includes the nicotine replacement composition. In some embodiments, the nicotine 10 replacement therapy product may further include an atomizer for atomizing the composition. According to some embodiments, the nicotine replacement therapy product may further include a matrix comprising a resin, a polymer or a gum base in which the nicotine replacement composition is embedded or impregnated, and a support on which the matrix and the composition are supported. In some 15 embodiments, the nicotine replacement therapy product further includes a reservoir housing the composition, a support, and a permeable membrane. According to some embodiments, the nicotine replacement therapy product may further include a resin, a polymer or a gum base. The nicotine replacement therapy product may include the nicotine replacement composition impregnated or embedded in polymer 20 particles or fibers. The polymer particles or fibers may be soluble in water and/or saliva.

**[0006]** According to some embodiments, a method of treating nicotine addiction includes administering the nicotine replacement composition to a user. The 25 administering the nicotine replacement composition may include administering a first nicotine replacement composition having a first concentration of the nicotine product, and then administering a second nicotine replacement composition having a second concentration of the nicotine product, where the second concentration is lower than the first concentration. In some embodiments, the administering may include 30 administering a first nicotine replacement composition having a first concentration of R-isomer in the nicotine product, and then administering a second nicotine replacement composition having a second concentration of R-isomer in the nicotine product, where the second concentration of R-isomer is greater than the first concentration of R-isomer.

## 35 DETAILED DESCRIPTION

**[0007]** According to embodiments of the present invention, a composition suitable for nicotine replacement therapy products (also referred to herein as "nicotine replacement compositions" or "NRT compositions") includes a nicotine product that



1 includes a synthetic nicotine that is substantially free of certain contaminants or  
impurities normally found in tobacco-derived nicotine, such as for example nicotine-  
N'-oxide (e.g., nicotine-1'-N-oxide), nicotine (e.g.,  $\beta$ -Nicotine), cotinine,  
nornicotine, 2',3-bipyridyl, anabasine, N-methyl anatabine, N-methyl anabasine,  
5 anabasine, and/or anatabine. As used herein, the term "substantially" is used as a  
term of approximation, and not as a term of degree, and is intended to account for  
the possibility of incidental impurities in the listed component. For example, the term  
"substantially free of" the listed compounds refers to a composition that does not  
include added amounts of the listed compounds, and refers to the inclusion of any  
10 such components in the composition only as incidental impurities in negligible  
amounts that do not contribute to the function or properties of the composition. In  
contrast, a composition that is "free of" or "completely free of" the listed compounds  
contains no measurable amount of the listed components.

**[0008]** In some embodiments, for example, the nicotine replacement composition  
15 may include a synthetic nicotine that is free or substantially free of any one or more  
of nicotine-N'-oxide (e.g., nicotine-1'-N-oxide), nicotine (e.g.,  $\beta$ -Nicotine),  
cotinine, nornicotine, 2',3-bipyridyl, anabasine, N-methyl anatabine, N-methyl  
anabasine, anabasine, and/or anatabine. In some embodiments, the nicotine  
replacement composition may include a synthetic nicotine that is free or substantially  
20 free of any combination of two or more of nicotine-N'-oxide (e.g., nicotine-1'-N-  
oxide), nicotine (e.g.,  $\beta$ -Nicotine), cotinine, nornicotine, 2',3-bipyridyl,  
anabasine, N-methyl anatabine, N-methyl anabasine, anabasine, and/or anatabine.  
In some embodiments, the nicotine replacement composition may include a synthetic  
nicotine that is free or substantially free of all of nicotine-N'-oxide (e.g., nicotine-1'-N-  
25 oxide), nicotine (e.g.,  $\beta$ -Nicotine), cotinine, nornicotine, 2',3-bipyridyl,  
anabasine, N-methyl anatabine, N-methyl anabasine, anabasine, and/or anatabine.

**[0009]** According to aspects of embodiments of the present invention, a  
composition suitable for nicotine replacement therapy products (also referred to  
herein as "nicotine replacement compositions" or "NRT compositions") comprises a  
30 nicotine product comprising a synthetic nicotine that is free or substantially free of  
nicotine (e.g.,  $\beta$ -Nicotine), cotinine, nornicotine, 2',3-bipyridyl, anabasine, N-  
methyl anatabine, N-methyl anabasine, anabasine, and/or anatabine. In some  
embodiments, for example, the nicotine replacement composition may include a  
synthetic nicotine that is free or substantially free of any one or more of nicotine  
35 (e.g.,  $\beta$ -Nicotine), cotinine, nornicotine, 2',3-bipyridyl, anabasine, N-methyl  
anatabine, N-methyl anabasine, anabasine, and/or anatabine. In some  
embodiments, the nicotine replacement composition may include a synthetic nicotine  
that is free or substantially free of any combination of two or more of nicotine (e.g.,

1  $\beta$ -Nicotyrine), cotinine, nornicotyrine, 2',3-bipyridyl, anabasine, N-methyl anatabine,  
N-methyl anabasine, anabasine, and/or anatabine. In some embodiments, the  
nicotine replacement composition may include a synthetic nicotine that is free or  
substantially free of all of nicotyrine (e.g.,  $\beta$ -Nicotyrine), cotinine, nornicotyrine, 2',3-  
5 bipyridyl, anabasine, N-methyl anatabine, N-methyl anabasine, anabasine, and/or  
anatabine.

**[0010]** For example, in some embodiments, a nicotine replacement composition  
or NRT composition comprises a nicotine product comprising a synthetic nicotine  
that is free or substantially free of nicotyrine (e.g.,  $\beta$ -Nicotyrine), cotinine, anabasine,  
10 N-methyl anatabine, N-methyl anabasine, anabasine, and/or anatabine. In some  
embodiments, for example, the nicotine replacement composition may include a  
synthetic nicotine that is free or substantially free of any one or more of nicotyrine  
(e.g.,  $\beta$ -Nicotyrine), cotinine, anabasine, N-methyl anatabine, N-methyl anabasine,  
anabasine, and/or anatabine. In some embodiments, the nicotine replacement  
15 composition may include a synthetic nicotine that is free or substantially free of any  
combination of two or more of nicotyrine (e.g.,  $\beta$ -Nicotyrine), cotinine, anabasine, N-  
methyl anatabine, N-methyl anabasine, anabasine, and/or anatabine. In some  
embodiments, the nicotine replacement composition may include a synthetic nicotine  
that is free or substantially free of all of nicotyrine (e.g.,  $\beta$ -Nicotyrine), cotinine,  
20 anabasine, N-methyl anatabine, N-methyl anabasine, anabasine, and/or anatabine.

**[0011]** In some embodiments, for example, a nicotine replacement composition or  
NRT composition comprises a nicotine product comprising a synthetic nicotine that is  
free or substantially free of anabasine, N-methyl anatabine, N-methyl anabasine,  
cotinine and/or anatabine. In some embodiments, for example, the nicotine  
25 replacement composition may include a synthetic nicotine that is free or substantially  
free of one or more of anabasine, N-methyl anatabine, N-methyl anabasine, cotinine,  
and/or anatabine. In some embodiments, the nicotine replacement composition may  
include a synthetic nicotine that is free or substantially free of two or more of  
anabasine, N-methyl anatabine, N-methyl anabasine, cotinine and/or anatabine. For  
30 example, in some embodiments, the nicotine replacement composition may include  
a synthetic nicotine that is free or substantially free of two or more of anabasine, N-  
methyl anatabine, N-methyl anabasine, cotinine and/or anatabine.

**[0012]** Those of ordinary skill in the art would understand known methods of  
determining the presence of the compounds and impurities discussed herein.  
35 However, one nonlimiting example of a suitable technique for determining whether  
these impurities are present in a particular composition includes USP-HPLC, i.e.,  
high performance liquid chromatography according to USP standards, which tests for  
the main impurities in tobacco-derived or natural nicotine (including, e.g., cotinine



1 and anatabine). Those of ordinary skill in the art would be readily capable of performing such a technique, and would recognize a yield of a detectable amount of any of the impurities or contaminants found in tobacco-derived nicotine confirms the composition as natural or tobacco-derived nicotine.

5 **[0013]** The synthetic nicotine according to embodiments of the present invention is distinct and distinguishable from its tobacco-derived or natural counterpart. The impurities discussed above are one way in which the synthetic nicotine according to embodiments of the present invention may be chemically and physically distinguished from tobacco-derived or natural nicotine. However, additional methods  
10 for distinguishing synthetic vs. natural nicotine may also be used. For example, because natural nicotine is derived from, or extracted from a living tobacco plant, the nicotine obtained from that source will inherently include a measurable amount of radioactive isotopes, e.g.,  $^{14}\text{C}$ ,  $^{13}\text{C}$  and D. See Randolph A. Culp et al., "Identification of Isotopically Manipulated Cinnamic Aldehyde and Benzaldehyde," *J. Agric. Food Chem.*, 1990, 38, 1249-1255; and Randolph A. Culp et al.,  
15 "Determination of Synthetic Components in Flavors by Deuterium/Hydrogen Isotopic Ratios," referred to collectively herein as "the Culp references," the entire contents of both of which are incorporated herein by reference. As noted in the Culp references, a natural (or plant-derived) source of a compound can be determined through isotopic analysis to determine the level of  $^{14}\text{C}$  as well as the isotopic abundance of  
20  $^{13}\text{C}$  and D (typically reported as  $\delta^{13}\text{C}$  and  $\delta\text{D}$ , respectively). The  $\delta^{13}\text{C}$  and  $\delta\text{D}$  indications refer to the isotopic abundance, i.e., the ratio of the heavier isotope (e.g.,  $^{13}\text{C}$  or D) to the lighter isotope (e.g.,  $^{12}\text{C}$  or H). As discussed in the Culp references, these ratios are measurably different in corresponding synthetic vs. naturally-derived  
25 or plant-derived compounds. As such, in some embodiments of the present invention, the synthetic nicotine has an isotopic abundance (e.g., a  $\delta^{13}\text{C}$  and  $\delta\text{D}$  value) and/or  $^{14}\text{C}$  level that is different from that of the natural or tobacco-derived counterpart compound. For example, in some embodiments, the synthetic nicotine has an isotopic abundance (e.g., a  $\delta^{13}\text{C}$  and  $\delta\text{D}$  value) and/or  $^{14}\text{C}$  level that is lower  
30 than that of the natural or tobacco-derived counterpart compound. For example, in some embodiments, the synthetic nicotine may have a  $^{14}\text{C}$  level of up to about 10 dpm/gC (disintegrations per minute / grams C). In some embodiments, for example the synthetic nicotine may have  $^{14}\text{C}$  level of about 0.1 to about 9 dpm/gC, or in some embodiments about 2 to about 8 dpm/gC, or about 3 to about 8 dpm/gC. For  
35 example, in some embodiments, the synthetic nicotine may have a  $^{14}\text{C}$  level of about 3.5 to about 7 dpm/gC, or about 4 to about 6 dpm/gC. In contrast, the 2015 and present day  $^{14}\text{C}$  reference standard is 14.0 dpm/gC. Accordingly, the synthetic nicotine according to embodiments of the present invention has a significantly



1 different  $^{14}\text{C}$  level than that of natural nicotine (i.e., based on the 2015 and present  
day reference standard for  $^{14}\text{C}$  activity). For example, in some embodiments, the  
synthetic nicotine has a  $^{14}\text{C}$  level that is up to about 72% that of natural nicotine, or  
about 0.5% to about 65% that of natural nicotine. In some embodiments, for  
5 example, the synthetic nicotine has a  $^{14}\text{C}$  level that is about 14% to about 58% that  
of natural nicotine, or about 20% to about 58% that of natural nicotine. For example,  
in some embodiments, the synthetic nicotine has a  $^{14}\text{C}$  level that is about 25% to  
about 50% that of natural nicotine, or about 28% to about 43% that of natural  
nicotine.

10 **[0014]** As referenced above, the unstable radio-isotope of carbon,  $^{14}\text{C}$ , has  
different radioactivity based on its age, e.g., the older it is, the less radioactive it  
becomes. Comparison of the radioactivity of natural or tobacco-derived nicotine  
(e.g., the United States Pharmacopeia (USP) standard) to that of a synthetic sample  
provides an avenue for identifying the source of the nicotine. For example, if the  
15 nicotine is petroleum based, then the radioactivity will be significantly lower than if  
the nicotine is natural or tobacco-derived. However, some synthetic nicotine may be  
produced from chemicals that originate from living plants, e.g., sugar cane or corn.  
To tell the difference between tobacco-derived nicotine and such sugar- or corn-  
derived nicotine, the amounts of the stable isotope of carbon are determined. Since  
20 sugar cane and corn are in a different class of plant than tobacco, they metabolize  
the heavy isotopes of carbon ( $\text{C}^{13}$ ) and water ( $\text{D}_2\text{O}$ ) at different magnitudes than the  
tobacco plant. As such, if the comparative measurement data for these stable  
isotopes is different, then it can be determined that the nicotine is not from tobacco;  
and if the comparative measurement data is similar, then it can be determined that  
25 the nicotine is from tobacco. For example, natural nicotine has a  $\delta^{13}\text{C}$  ( $^{13}\text{C}/^{12}\text{C}$ )  
around -30 to -32 parts per mil relative to the international standard PDB ( $\pm\sigma$ ). In  
contrast, according to embodiments of the present invention, the synthetic nicotine  
may have a  $\delta^{13}\text{C}$  of about -20 to about -29 parts per mil relative to the international  
standard PDB ( $\pm\sigma$ ), or about -23 to about -29 parts per mil relative to the  
30 international standard PDB ( $\pm\sigma$ ). In some embodiments, for example, the synthetic  
nicotine may have a  $\delta^{13}\text{C}$  of about -25 to about -28.5 parts per mil relative to the  
international standard PDB ( $\pm\sigma$ ), or about -26 to about -28.5 parts per mil relative to  
the international standard PDB ( $\pm\sigma$ ). As such, the synthetic nicotine according to  
embodiments of the present invention may have a  $\delta^{13}\text{C}$  that is about 66% to about  
35 97% that of natural nicotine, or about 76% to about 97% that of nicotine. For  
example, in some embodiments, the synthetic nicotine according to embodiments of  
the present invention may have a  $\delta^{13}\text{C}$  that is about 83% to about 95% that of natural  
nicotine, or about 87% to about 95% that of nicotine.



1 **[0015]** Additionally, natural nicotine has a  $\delta D$  (D/H) around -170 to -171 parts per  
mil relative to the international standard V-SMOW ( $\pm\sigma$ ). In contrast, according to  
embodiments of the present invention, the synthetic nicotine may have a  $\delta D$  of about  
-140 to about -160 parts per mil relative to the international standard V-SMOW ( $\pm\sigma$ ),  
5 or about -145 to about -160 parts per mil relative to the international V-SMOW  
( $\pm\sigma$ ). In some embodiments, for example, the synthetic nicotine may have a  $\delta D$  of  
about -150 to about -160 parts per mil relative to the international standard V-  
SMOW ( $\pm\sigma$ ), or about -152 to about -158 parts per mil relative to the international  
standard V-SMOW ( $\pm\sigma$ ). As such, the synthetic nicotine according to embodiments  
10 of the present invention may have a  $\delta D$  that is about 82% to about 95% that of  
natural nicotine, or about 85% to about 95% that of nicotine. For example, in some  
embodiments, the synthetic nicotine according to embodiments of the present  
invention may have a  $\delta D$  that is about 88% to about 95% that of natural nicotine, or  
about 89% to about 93% that of natural nicotine.

15 **[0016]** As discussed above, the nicotine replacement compositions or NRT  
compositions according to embodiments of the present invention include a nicotine  
product. The nicotine replacement composition may be a solid or liquid mixture and  
may be incorporated into a nicotine replacement product, such as, for example, a  
smoking cessation patch or gum. In some embodiments, for example, the nicotine  
20 replacement composition may comprise about 0.001 wt% to about 25 wt%, for  
example about 0.01 wt% to about 10 wt%, or about 0.1 wt% to about 1 wt% of the  
nicotine product based on the total weight of the nicotine replacement composition.

**[0017]** However, the total amount of the nicotine product in a nicotine  
replacement composition will vary depending on the application, e.g., depending on  
25 the type of nicotine replacement product for which the nicotine replacement  
composition is intended. For example, a smoking cessation patch may incorporate a  
nicotine replacement composition having a different concentration of the nicotine  
product than the nicotine replacement composition of a smoking cessation gum.  
Additionally, a nicotine replacement product may have nicotine replacement  
30 compositions having varying concentrations of the nicotine product, for example, a  
set of products having progressively lesser amounts of the nicotine product in order  
to gradually wean a user off of nicotine as a means for treating or addressing that  
user's nicotine addiction. In some embodiments, for example, a user may begin  
using a first nicotine replacement product (e.g., a gum or patch) incorporating a first  
35 nicotine replacement composition having a first concentration of the nicotine product,  
and then move to using a second nicotine replacement product (e.g., a gum or  
patch) incorporating a second nicotine replacement composition having a second  
concentration of the nicotine product that is lower than the first concentration of



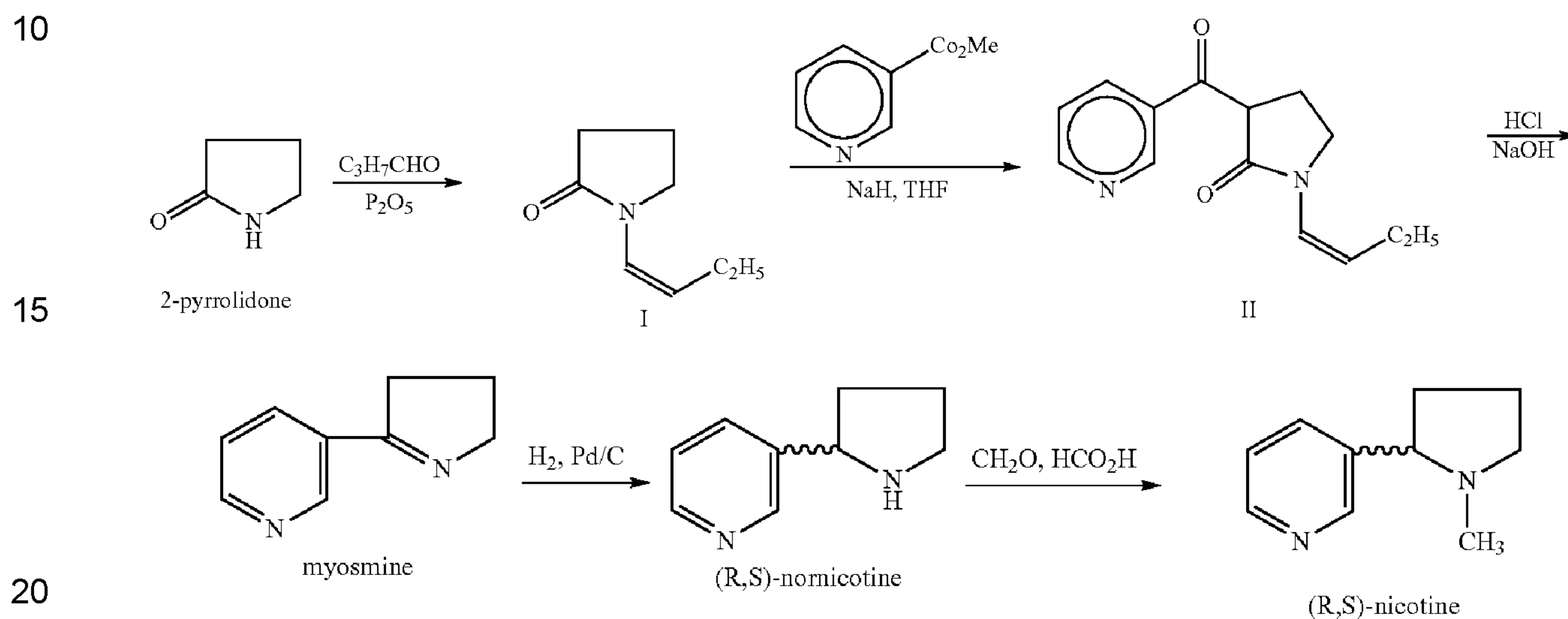
1 nicotine. Any number of additional nicotine replacement compositions having lower  
or higher concentrations of the nicotine product could also be used in such a  
regimen. Accordingly, it is understood that the nicotine concentrations described  
here are simply examples of suitable concentrations, and that embodiments of the  
5 present invention are not limited to these values. With that in mind, in some  
embodiments, a nicotine replacement product may include a nicotine replacement  
composition providing a dosage of nicotine of about 0.1 to about 10 mg/dose, for  
example, about 0.5 to about 8 mg/dose, or about 1.5 to about 6 mg/dose. In some  
embodiments, for example, a nicotine replacement product may include a nicotine  
10 replacement composition providing a dosage of nicotine of about 3 to about 6  
mg/dose.

**[0018]** At least a portion of the nicotine product present in the nicotine  
replacement composition is synthetic. As used herein, the term "synthetic" means  
that the identified compound (e.g., nicotine) is prepared through a chemical process  
15 that does not include deriving/extracting the nicotine from a naturally occurring  
source, such as tobacco leaves. The terms "tobacco derived," "natural" and "non-  
synthetic" are used interchangeably herein, and refer to the identified compound or  
composition that is derived from or extracted from a natural source (such as, for  
example, tobacco). For example, as used herein, "tobacco derived nicotine,"  
20 "natural nicotine" and "non-synthetic nicotine" refer to nicotine derived from or  
extracted from tobacco leaves, and does not encompass nicotine produced from  
independent chemical synthesis. In aspects of embodiments of the present  
invention, the relative portion of the nicotine product that is synthetic is not  
particularly limited, and may be any suitable amount. For example, as a portion of  
25 the total amount of the nicotine product present in the nicotine replacement  
composition, the synthetic nicotine may be present in an amount of about 0.1 wt% or  
greater, for example about 0.5 wt% or greater, about 1.0 wt% or greater, about 20  
wt% or greater, about 30 wt% or greater, about 40 wt% or greater, about 50 wt% or  
greater, about 60 wt% or greater, about 70 wt% or greater, about 80 wt% or greater,  
30 about 90 wt% or greater, about 95 wt % or greater, about 98% or greater, about 99%  
or greater, about 99.5% or greater, or in a positive amount (i.e., greater than 0%) up  
to about 100 wt%. When less than 100 wt% of the nicotine product in the nicotine  
replacement composition is synthetic, the remaining portion of the nicotine product  
may be tobacco-derived nicotine.

35 **[0019]** According to some embodiments, the synthetic nicotine in the nicotine  
replacement composition may be prepared by any suitable process, nonlimiting  
examples of which include the processes disclosed in U.S. Patent Nos. 8,367,837,  
8,378,110 and 8,389,733 and European Patent No. EP 2487172, the entire contents



1 of all of which are incorporated herein by reference. For example, in some  
 5 embodiments, as described generally in U.S. Patent Nos. 8,367,837, 8,378,110 and  
 8,389,733 and European Patent No. EP 2487172 to Divi, et al., 1-(but-1-  
 enyl)pyrrolidin-2-one may be condensed with nicotinic acid ester to give 1-(but-1-  
 5 enyl)-3-nicotinoylpyrrolidin-2-one, which may then be treated with an acid and base  
 to give myosamine, which, in turn, is converted to (R,S)-nicotine by reduction and  
 subsequent N-methylation. An example of this reaction scheme is shown below,  
 reproduced from U.S. Patent Nos. 8,367,837, 8,378,110 and 8,389,733 and  
 European Patent No. EP 2487172 to Divi, et al.



**[0020]** In some embodiments, the synthetic nicotine in the nicotine replacement composition may be prepared by the synthetic route outlined in Scheme 1:

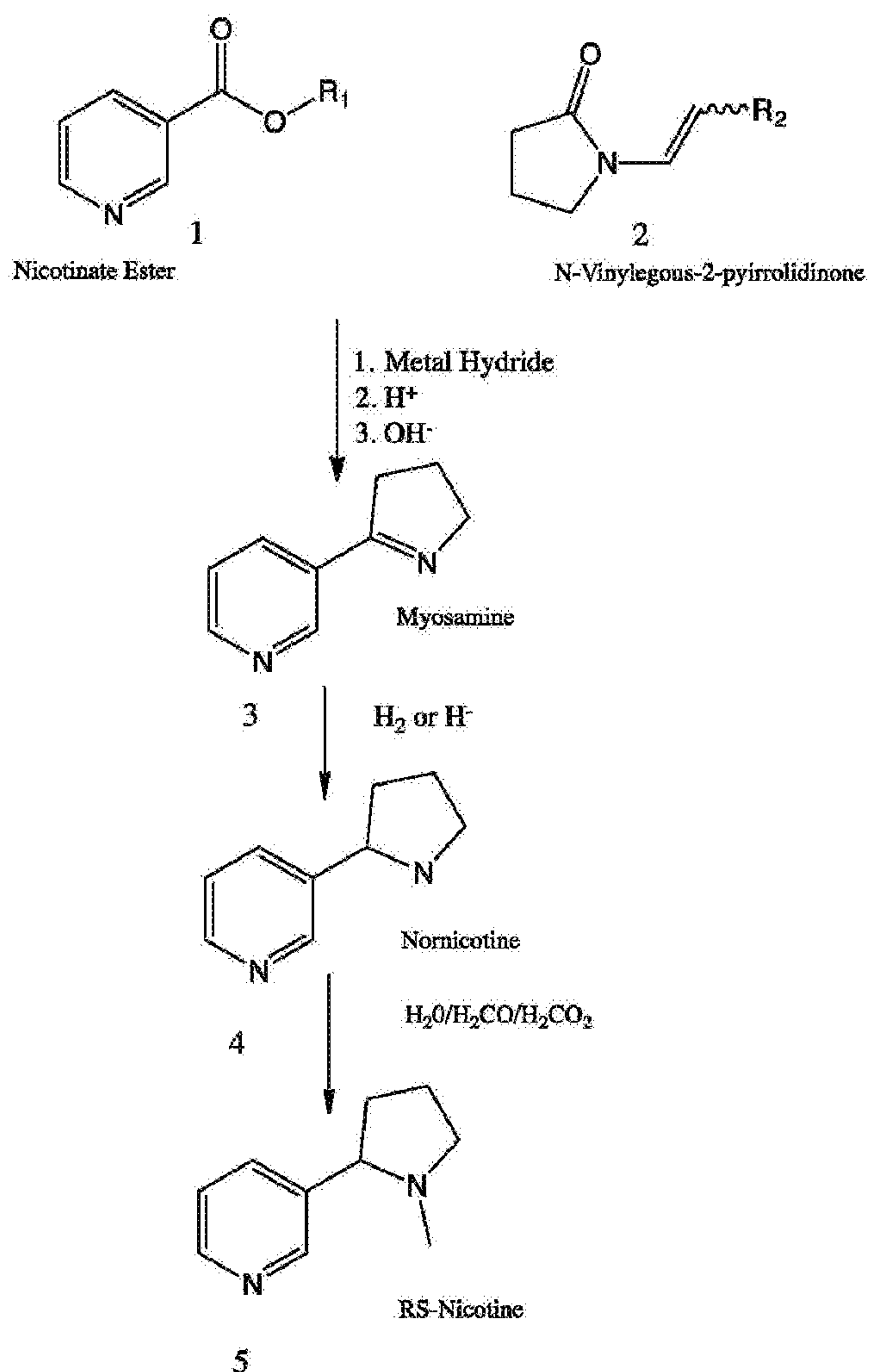
1

5

10

15

20



SCHEME 1

25

**[0021]** In the synthetic route depicted in Scheme 1, a carbon-carbon bond forming condensation is first performed under anhydrous conditions. In this condensation, an appropriate nicotinate ester (1) is condensed with a suitable N-vinyllogous-2-pyrrolidinone (2) under mild conditions, utilizing a suitable dry solvent in combination with a suitable strong base, for example a metal hydride. This condensation gives good yield of the condensation adduct (as its metal salt).

30

**[0022]** In some embodiments, the condensation reaction mixture utilizes alkyl esters of nicotinic acid in combination with N-vinyl-2-pyrrolidinone, and a metal hydride base in a suitable dry solvent. In some embodiments, the nicotinate alkyl ester comprises short chain alkyl groups (for example, R<sub>1</sub> in compound (1) may be C<sub>1-3</sub>, or in some embodiments C<sub>2</sub>). In some embodiments, the N-vinyllogous-2-pyrrolidinone may comprise a vinyl substituent with a short chain alkyl group. In some embodiments, R<sub>2</sub> in compound (2) may be a short chain (e.g., C<sub>1-10</sub>) alkyl

35



1 (such as, e.g., methyl, isopropyl, etc.), or in some embodiments, R<sub>2</sub> is hydrogen (H).  
In some embodiments, the N-vinylogous-2-pyrrolidinone is n-vinyl-2-pyrrolidinone.

5 **[0023]** The amount (in relative moles) of metal hydride utilized in the  
condensation reaction mixture with respect to 1 part nicotinate ester is about 0.1 part  
to about 2.5 parts, for example about 1.2 parts to about 2.1 parts, or about 1.8 parts  
to about 2 parts. In some embodiments, the mole ratio of metal hydride to nicotinate  
ester is about 1 to 4, for example about 1: 2 to about 1.6: 2, or about 2:2. In some  
embodiments, the metal in the metal hydride may be lithium, potassium or sodium,  
for example potassium or sodium, or in some embodiments, sodium.

10 **[0024]** The amount of N-vinylogous-2-pyrrolidinone with respect to the amount (in  
mole equivalents) of nicotinate ester utilized in the condensation reaction mixture  
may be about 0.1 parts to about 10 parts, for example about 0.5 parts to about 3  
parts, or about 1.0 part to about 1.2 parts.

15 **[0025]** The amount of solvent utilized in the condensation reaction mixture with  
respect to 1 part (in mole equivalents) nicotinate ester may be about 1 parts to about  
15 parts, for example about 3 parts to about 10 parts, about 4 parts to about 8 parts,  
or about 5 parts to about 7 parts. In some embodiments, the solvent may be  
anhydrous. Nonlimiting examples of suitable solvents include aromatic hydrocarbon  
or hydrocarbon solvents, dipolar aprotic solvents (such as, for example,  
20 dimethylformamide (DMF)), ethers (such as, for example, ethyl ether,  
tetrahydrofuran (THF) or tetrahydrofuran derivatives), polyethers (such as, for  
example, "glyme" or "diglyme"), and combinations thereof. Nonlimiting examples of  
suitable aromatic hydrocarbons or hydrocarbon solvents include alcohols, toluene,  
xylenes, benzene, and the like. In some embodiments, for example, the solvent is  
25 an alcohol, or an alcohol and ether combination. In some embodiments, the solvent  
may be THF, or a mixture of DMF and ether, and/or a mixture of DMF and a  
hydrocarbon or aromatic hydrocarbon. In some embodiments, the solvent may be  
toluene (or benzene). Alcohols such as ethanol, methanol, and/or propanol may be  
added to help catalyze the condensation, or the alcohol(s) may be used as the only  
30 solvent. If an alcohol is to be used as a solvent or co-solvent in the condensation,  
then the metals sodium, potassium or lithium may be employed in less than or equal  
to stoichiometric amounts with respect to the nicotinate ester. In some  
embodiments, the time of solvent addition is such that a mild effervescence is  
maintained, and an internal temperature of between 50°C and 80°C is maintained  
35 throughout the addition process. The time of addition varies with volume, but may  
take place within a matter of minutes to hours.

**[0026]** After addition of the solvent to the nicotinate ester and N-vinylogous-  
pyrrolidinone, the condensation reaction mixture becomes greenish. This greenish

1 condensation reaction mixture may be stirred, in some embodiments, under an inert  
atmosphere for an appropriate amount of time in order to complete the reaction. In  
some embodiments, the greenish condensation reaction mixture may be heated to  
an internal temperature of about 40°C to about 110°C, for example about 60°C to  
5 about 100°C, or about 80°C to about 95°C.

**[0027]** After reacting the nicotinate ester with the N-vinylogous-2-pyrrolidinone,  
the condensation reaction mixture may contain a reaction product mixture that  
includes some unreacted starting material (i.e., nicotinate ester, n-vinylogous-2-  
pyrrolidinone, sodium hydride) as well as the desired reaction products, i.e., the main  
10 condensation product which is the nicotinate-n-vinylogous-2-pyrrolidinone adduct  
(the condensation adduct, an organic bicyclic compound as the metal salt, e.g., 1-(1-  
alkenyl)-3-nicotinoylpyrrolidine-2-one, where the alkenyl may be ethenyl in some  
embodiments), the alcohol as the metal salt, and some alcohol that is displaced from  
the nicotinate ester as the alcohol.

15 **[0028]** After completion of the reaction that takes place as a result of the action of  
the condensation reaction mixture, the reaction product mixture may be either  
injected (or poured) directly into a solution of acid to form an acid reaction mixture.  
The acid solution may be a boiling acid solution, or a cold acid aqueous solution. In  
some embodiments, the acid is an aqueous hydrochloric acid solution. In some  
20 embodiments, the normality of the acid solution may be about 3 to about 12, for  
example about 4 to about 7, or about 5 to about 6.

**[0029]** According to some embodiments, the acid reaction mixture may be  
prepared by cooling the completed condensation reaction mixture to ambient  
temperature and then injecting the cooled condensation reaction mixture into a cold  
25 solution of acid. The amount of the acid may be about 0.25 parts to about 5 parts,  
for example about 0.5 parts to about 2 parts, or about 0.75 parts to about 1.5 parts  
with respect to one part of the condensation reaction mixture.

**[0030]** The reaction of the acid reaction mixture yields a biphasic mixture in which  
the protonated bicyclic pyridine-pyrrolidinone adduct (i.e., protonated condensation  
30 adduct) which is soluble in water and insoluble in the organic solvent is present in  
the aqueous phase (or layer), and any unreacted pyrrolidinone starting material is in  
the organic phase (or layer). When the reaction is allowed to settle without agitation,  
two distinct layers are formed, aqueous and organic (non-aqueous), and the product  
of the reaction is in the aqueous layer, which aqueous layer is then separated and  
35 subjected to further reaction or processing.

**[0031]** After the acid addition, the aqueous and organic (non-aqueous) layers are  
separated, a concentrated acid is added to the separated aqueous layer to form an



1 aqueous reaction mixture. The aqueous reaction mixture is then heated to reflux for an appropriate period of time to complete the reaction.

**[0032]** The amount of concentrated acid added to separated aqueous layer to form the aqueous reaction mixture may be about 0.15 parts to about 1.5 part, for  
5 example about 0.2 part to about 0.5 part, or about 0.25 part to about 0.5 part with respect to 1 part of the separated aqueous layer. In some embodiments, the concentrated acid may be 12N hydrochloric acid (concentrated hydrochloric acid [ca37%]).

**[0033]** After reaction of the aqueous reaction mixture is complete, the aqueous  
10 reaction mixture is comprised of water, acid, and product (i.e., the protonated acyclic amine salt, e.g., protonated 3-(4-aminobutanyl-1-one)-pyridine).

**[0034]** After reaction of the aqueous reaction mixture is complete, the aqueous  
reaction mixture may be cooled to -10°C to 5°C. Then the acidic aqueous reaction  
mixture (or solution) may be made strongly basic (e.g., having a pH greater than 9)  
15 while keeping the temperature at an appropriate level to maintain the reaction. The result of this reaction is the myosamine reaction mixture, which is comprised of myosamine, base, water, and any remaining unreacted materials from the aqueous reaction mixture, as well as any contaminants natural to the reaction. The resulting basic aqueous reaction mixture is extracted with organic solvent, and then the  
20 solvent is distilled off to yield crude myosamine. In some embodiments, the organic solvent may be dichloromethane. In some embodiments, the amount of organic solvent may be about 1 part to about 10 parts with respect to the amount of the basic aqueous reaction mixture, for example about 1.5 parts to about 5 parts, or about 2 parts to about 4 parts with respect to the basic aqueous reaction mixture.

**[0035]** In some embodiments, the completed condensation reaction may be  
25 injected directly into a hot solution of hydrochloric acid (instead of the cold acid solution described above), resulting in a heterogeneous acid reaction mixture. The heterogeneous acid reaction mixture may be heated using an external bath to enable vigorous reflux, and the vigorous reflux may be continued until the reaction is  
30 complete. In embodiments of this hot acid alternative, the solvent for the condensation reaction mixture may be toluene or xylene, or a high boiling point solvent such as diglyme.

**[0036]** In order to reduce the crude myosamine product to a crude nornicotine  
product, a suitable hydrogenation catalyst is added in a suitable amount to the crude  
35 myosamine (3) in solution with an appropriate solvent to form a myosamine reaction mixture. To complete the reduction of myosamine to nornicotine, the myosamine reaction mixture is submitted to an atmosphere of hydrogen gas at a pressure

1 greater than or equal to ambient pressure, but not high enough to reduce the  
carbons in the pyridine ring.

**[0037]** In some embodiments, the solvent for the myosamine reaction mixture  
may be an alcoholic solvent, for example, ethanol or isopropanol, although other  
5 solvents known in the art of hydrogenation can also be employed. The amount of  
solvent may be about 3 parts to about 98 parts, for example about 4 parts to about  
60 parts, or about 5 parts to about 20 parts solvent with respect to 1 part crude  
myosamine. In some embodiments, the suitable hydrogenation catalyst may include  
10 10% palladium on carbon, but other catalysts common to the art of catalytic  
hydrogenation may also be employed, either as a co-catalyst, or as the sole catalyst.  
The pressure of the hydrogen gas can be about ambient pressure to about 100  
atmospheres, for example about ambient pressure to about 75 atmospheres, or  
about 10 to about 50 atmospheres.

**[0038]** In some embodiments, the myosamine reaction mixture may include a  
15 borohydride salt as the reducing agent rather than a hydrogenation catalyst, and the  
myosamine reaction mixture may undergo different reaction conditions suitable to  
effect reduction of the myosamine to nornicotine using the borohydride salt.

**[0039]** Completion of the reaction of the myosamine reaction mixture yields a  
crude nornicotine reaction mixture that includes nornicotine (reduction product),  
20 catalyst and solvent, as well as any unreacted starting material (crude myosamine)  
and unwanted reaction contaminants. Crude nornicotine product (4) is extracted  
from the crude nornicotine reaction mixture using known extraction methods.

**[0040]** Water, formic acid and formaldehyde are added to the crude nornicotine  
(4) product to form a crude nicotine reaction mixture. The crude nicotine reaction  
25 mixture is heated to an appropriate temperature for a duration which allows for  
completion of the methylation reaction that affords crude nicotine in good yield.

**[0041]** At the completion of the reaction of the crude nicotine reaction mixture, the  
resulting mixture contains crude RS-Nicotine product, solvent (water), and any  
unreacted starting material including formaldehyde and formic acid, as well as  
30 reaction contaminating by-products.

**[0042]** The product of the crude nicotine reaction mixture, i.e., crude RS-Nicotine,  
may be subjected to at least one high vacuum distillation to give pure (i.e., greater  
than 95% pure, for example greater than 97% pure, greater than 99% pure, or  
greater than 99.5% pure) RS-Nicotine as a clear, colorless non-viscous liquor in  
35 good overall yield.

**[0043]** The synthetic nicotine produced according to the above-described  
chemical synthesis is substantially free or completely free of certain contaminants  
typically found in the natural nicotine derived from tobacco leaves. In some



1       embodiments, the synthetic nicotine may be substantially free of these contaminants,  
such that the combined amount of these contaminants in the synthetic nicotine may  
be more than 0 wt% but less than 0.5 wt%, for example less than 0.2 wt%, less than  
0.01 wt%, less than 0.001 wt%, less than 0.0001 wt%, or less than 0.00001 wt%  
5       based on the total weight of the synthetic nicotine. As discussed above, "completely  
free" or "free" of these contaminants means that the synthetic nicotine includes no  
measurable amount of these contaminants, i.e., 0 wt% (or none). In some  
embodiments, the synthetic nicotine is substantially free or completely free of  
contaminants such as alkaloid compounds, which may be found in nicotine derived  
10       from tobacco. For example, the synthetic nicotine may be substantially free or  
completely free of one or more or all of nicotine-1'-N-oxide, nicotyrine, nornicotyrine,  
2',3-bipyridyl, anabasine, and anatabine. While these contaminants may be among  
the most common impurities or contaminants in tobacco-derived nicotine, other  
naturally occurring contaminants or impurities may be present in tobacco-derived  
15       nicotine, and the synthetic nicotine according to embodiments of the present  
invention is substantially free or completely free of those contaminants and impurities  
as well.

**[0044]**       However, while the synthetic nicotine according to embodiments of the  
present invention may be substantially free or completely free of certain  
20       contaminants normally found in tobacco-derived nicotine, as discussed above, the  
synthetic nicotine may include certain other impurities or contaminants resulting from  
the synthetic route. Although such contaminants and impurities may be present in  
the synthetic nicotine according to embodiments of the present invention, these  
impurities are not generally present in tobacco-derived or naturally sourced nicotine.  
25       Indeed, the contaminants/impurities found in naturally sourced (or tobacco-derived)  
nicotine are significantly different than those potentially found in the synthetic  
nicotine according to embodiments of the present invention. For example, the  
contaminants or impurities present in the synthetic nicotine according to  
embodiments of the present invention may include one or more or all of myosamine,  
30       nornicotine, water, and the solvents (discussed above) used in the various reactions  
of the synthesis scheme. Additionally, in some embodiments, the contaminants or  
impurities present in the synthetic nicotine may include one or more or all of 1-keto-  
5-methylamino, or 1-hydroxy-5-methylamino-2-pyridine. As used herein, the terms  
"synthetic contaminants," "synthetic impurities," and like terms, are used  
35       interchangeably, and refer to these contaminants and/or impurities found in the  
synthetic nicotine according to embodiments of the present invention but not typically  
found in naturally sourced (or tobacco-derived) nicotine.

1 **[0045]** For example, based on the total weight of the synthetic nicotine, the  
synthetic nicotine may include about 0 wt% (i.e., an undetectable, or unmeasurable  
amount) to about 5 wt%, for example about 0 wt% (i.e., an undetectable, or  
unmeasurable amount) to about 1 wt%, about 0 wt% (i.e., an undetectable, or  
5 unmeasurable amount) to about 0.5 wt% myosamine. In some embodiments, based  
on the total weight of the synthetic nicotine, the synthetic nicotine may include about  
0 wt% (i.e., an undetectable, or unmeasurable amount) to about 5 wt%, for example  
about 0 wt% (i.e., an undetectable, or unmeasurable amount) to about 3 wt%, or  
about 0 wt% (i.e., an undetectable, or unmeasurable amount) to about 1 wt%  
10 nornicotine. In some embodiments, based on the total weight of the synthetic  
nicotine, the synthetic nicotine may include about 0 wt% (i.e., an undetectable, or  
unmeasurable amount) to about 5 wt%, for example about 0 wt% (i.e., an  
undetectable, or unmeasurable amount) to about 3 wt%, or about 0 wt% (i.e., an  
undetectable, or unmeasurable amount) to about 1 wt% solvent. Also, in some  
15 embodiments, based on the total weight of the synthetic nicotine, the synthetic  
nicotine may include about 0 wt% (i.e., an undetectable, or unmeasurable amount) to  
about 5 wt%, for example about 0 wt% (i.e., an undetectable, or unmeasurable  
amount) to about 3 wt%, or about 0 wt% (i.e., an undetectable, or unmeasurable  
amount) to about 1 wt% water.

20 **[0046]** The above-described synthesis of nicotine produces a racemic mixture,  
i.e., a 50-50 mixture of the R and S isomers of nicotine. Thus, in some  
embodiments, the synthetic nicotine includes a ratio of the R-isomer to the S-isomer  
of 1:1. However, in some embodiments, the ratio of the R-isomer to the S-isomer can  
be manipulated through further resolution of the synthetic nicotine. For example, the  
25 synthetic nicotine may have a ratio of the R-isomer to the S-isomer of about 1:1 to  
about 1:1000, about 1:1.1 to about 1:100, about 1:2 to about 1:5, about 1:4 to about  
1:9, or about 1:5 to about 1:7. In some embodiments, the synthetic nicotine may  
include a ratio of the R-isomer to the S-isomer of about 1:1 to about 1000:1, about  
1.1:1 to about 100:1, about 2:1 to about 5:1, about 4:1 to about 9:1, or about 5:1 to  
30 about 7:1.

**[0047]** In some exemplary embodiments, for example, the synthetic nicotine  
includes a ratio of the S-isomer to the R-isomer of less than 50:1, for example 45:1  
or lower, 40:1 or lower, or 35:1 or lower. In some embodiments, the synthetic  
nicotine may include a ratio of the R-isomer to the S-isomer of less than 50:1, for  
35 example 45:1 or lower, 40:1 or lower, or 35:1 or lower. Additionally, in some  
embodiments, the synthetic nicotine may include the R-isomer in an amount greater  
than 5 wt%, for example, greater than 7 wt%, or greater than 10 wt%. In some  
embodiments, the synthetic nicotine may include the S-isomer in an amount greater



1 than 5 wt%, for example, greater than 7 wt%, or greater than 10 wt%. In some  
embodiments, the synthetic nicotine includes more R-isomer than S-isomer, and in  
some embodiments, the synthetic nicotine includes more S-isomer than R-isomer.

**[0048]** This ratio of R/S isomers in the synthetic product is yet another  
5 characteristic that distinguishes the synthetic nicotine according to embodiments of  
the present invention from natural or tobacco-derived nicotine. Indeed, a simple test  
to determine chirality of the sample can be performed in order to determine whether  
the sample includes natural nicotine or a synthetic nicotine according to  
embodiments of the invention. Techniques for determining chirality or optical  
10 rotation of a sample are known to those of ordinary skill in the art, and the ordinary  
artisan would be readily capable of selecting an appropriate technique and carrying  
out that technique to determine chirality or optical rotation. One nonlimiting example  
of such a technique is high performance liquid chromatography (HPLC) using a  
chiral column. For example, the optical rotation of the sample may first be  
15 determined by any suitable technique (which are known to those of ordinary skill in  
the art), and then the sample may be run through the chiral column and the results  
compared to the USP standard for tobacco-derived or natural nicotine.

**[0049]** The synthetic nicotine containing the racemic mixture of R and S isomers  
may be resolved to have these relative amounts of the R and S isomers by any  
20 suitable resolution techniques, which techniques are known to those skilled in the art  
(e.g., crystallization, chromatography, etc.). Additionally, in some embodiments, the  
synthesized nicotine may be fully resolved to yield either pure R-isomer or pure S-  
isomer. As used herein, the term "pure" as used in defining the isomeric composition  
of the synthetic nicotine, refers to a percentage of the identified isomer of greater  
25 than 97%, for example greater than 98%, and in some embodiments greater than  
99%. For example, a "pure S isomer" synthetic nicotine includes a synthetic nicotine  
that has been resolved to include a ratio of S isomer to R isomer of greater than  
97:3, for example greater than 98:2, and in some embodiments, greater than 99:1.  
Similarly, a "pure R isomer" synthetic nicotine includes a synthetic nicotine that has  
30 been resolved to include a ratio of R isomer to S isomer of greater than 97:3, for  
example greater than 98:2, and in some embodiments, greater than 99:1. In some  
embodiments, however, a pure R isomer may include 100% R isomer with 0% S  
isomer, and a pure S isomer may include 100% S isomer with 0% R isomer.

**[0050]** As noted above, any suitable resolution technique may be used to resolve  
35 the synthetic nicotine composition, which techniques are known to those of ordinary  
skill in the art. Some nonlimiting examples of resolution techniques include those  
described in Divi et al., U.S. Patent Publication No. 2012/0197022, filed April 6,  
2011, Aceto, et al., *J. Med. Chem.*, "Optically Pure (+)-Nicotine from (±)-Nicotine and



1 Biological Comparisons with (-)-Nicotine vol. 22, pgs. 174-177 (1979), and DeTraglia  
et al., "Separation of D-(+)-Nicotine from a Racemic Mixture by Stereospecific  
Degradation of the L-(-) Isomer with *Pseudomonas putida*," *Applied and*  
5 *Environmental Microbiology*, vol. 39, pgs. 1067-1069 (1980), the entire contents of  
all of which are incorporated herein by reference. For example, as described in  
Aceto et al., resolution of the racemic mixture may be accomplished using D-tartaric  
acid, and as described in DeTraglia et al., resolution can be accomplished using  
*pseudomonas putida*. In addition, in some embodiments, resolution of the racemic  
mixture may be accomplished using (+)-O,O'-di-*p*-toluoyl-D-tartaric acid.

10 Additionally, as described in Divi et al., resolution of the racemic mixture may be  
accomplished by diastereomeric salt formation using dibenzoyl-D-tartaric acid and  
dibenzoyl-L-tartaric acid to achieve separation.

**[0051]** In some embodiments, however, the racemic mixture may be blended or  
mixed with suitable added amounts of pure R isomer or pure S isomer, which pure  
15 isomers would typically be prepared via enantioselective synthetic pathways.  
Notably, naturally sourced nicotine (i.e., that derived from tobacco leaves) generally  
has an undetectable or small amount of the R isomer, and typically the naturally  
sourced tobacco mainly includes the S isomer. Indeed, naturally sourced tobacco  
typically has an S to R isomer ratio of greater than 50:1.

20 **[0052]** As discussed above, according to some embodiments of the present  
invention, the synthetic nicotine may include a mixture of the R and S isomers,  
whether racemic or otherwise. As would be understood by those of ordinary skill in  
the art, tobacco-derived (or naturally sourced) nicotine typically has greater than 95  
wt% of the S isomer, and therefore is optically active. Indeed, when measured using  
25 a standard polarimeter, the tobacco-derived nicotine (having 95 wt% or greater S  
nicotine isomer) registers a negative optical rotation which is typically greater than  
125°. In contrast, according to embodiments of the present invention, the synthetic  
nicotine may include a racemic (or 1:1) mixture of the R and S isomers, yielding a  
nicotine having no optical rotation. Additionally, in embodiments of the present  
30 invention in which the synthetic nicotine includes a non-racemic mixture of the R and  
S isomers, the synthetic product will register an optical rotation that is different from  
the optical rotation of tobacco-derived nicotine (i.e., due to the presence of the R  
isomer, which generally has an opposite optical rotation than that of the S isomer).

**[0053]** As discussed above, tobacco-derived (or naturally sourced) nicotine may  
35 include one or more or all of the following impurities: nicotine-1'-N-oxide, nicotyrine,  
nornicotyrine, 2',3-bipyridyl, cotinine, anabasine, anatabine, nornicotine, and  
myosamine. For example, tobacco derived nicotine may comprise 99.5 wt%  
nicotine, 0.1 wt% nornicotine, 0.15 wt% myosamine, and 0.1 wt% cotinine.



1 According to some embodiments of the present invention, as described above, the  
nicotine replacement composition or NRT composition may include both the  
synthetic nicotine described above and an amount of naturally sourced (or tobacco-  
derived) nicotine. In these embodiments of the nicotine replacement composition  
5 including the naturally sourced nicotine, the portion of the composition making up the  
tobacco-derived nicotine may include these components (or contaminants) in, e.g.,  
the above amounts. However, as would be appreciated by those of ordinary skill in  
the art, because the naturally sourced nicotine (or tobacco-derived nicotine) makes  
up only a portion of the nicotine replacement composition or NRT composition, the  
10 amount of these natural tobacco contaminants in the overall nicotine replacement  
composition is significantly lower than the amounts reported above, and significantly  
lower than the amounts in comparable compositions using larger portions of (or all)  
naturally sourced nicotine.

**[0054]** In embodiments including a mixture of synthetic nicotine and naturally-  
15 sourced or tobacco derived nicotine, the nicotine product of the nicotine replacement  
composition may include more synthetic nicotine than tobacco-derived nicotine. For  
example, in such a mixture, based on the total weight of the nicotine product, the  
nicotine product may include 50 wt% or more synthetic nicotine, for example 60 wt%  
or more synthetic nicotine or 70 wt% or more synthetic nicotine. In some  
20 embodiments, for example, in embodiments including a mixture of synthetic nicotine  
and tobacco-derived nicotine, based on the total weight of the nicotine product, the  
nicotine product of the nicotine replacement composition may include 80 wt% or  
more synthetic nicotine, for example 90 wt% or more synthetic nicotine, or 95 wt% or  
more synthetic nicotine.

25 **[0055]** In addition to the nicotine product (i.e., the synthetic nicotine and/or  
naturally sourced nicotine) discussed above, the composition for use in nicotine  
replacement products or therapies (i.e., the nicotine replacement composition or  
NRT composition) may further comprise, consist essentially of, or consist of one or  
more pharmaceutically acceptable excipients, additives and/or carriers (e.g.,  
30 solvents). Nonlimiting examples of such excipients, additives and/or carriers (e.g.,  
solvents) include water, organic solvents, resins or polymers (e.g., edible or  
biocompatible resins or polymers), elastomers, gum bases, and the like, sweetening  
and/or flavoring agents, pH adjusting agents and the like. Nonlimiting examples of  
carriers or solvents that may be used in liquid nicotine replacement compositions  
35 (such as, for example, those intended for inhalation through a vaping device, or  
those housed in a reservoir in certain transdermal nicotine delivery patches) include  
water, and alcohols such as 1,2-propylene glycol (PG or MPG), ethanol, ethyl  
acetate, 1-3 propanediol, glycerin (e.g., vegetable glycerin) and the like. The solvent



1 may include a single solvent or may include a combination of two or more solvents.  
The amount of solvent present may be selected based on the NRT product in which  
the composition is used. In some embodiments, for example in embodiments in  
which the composition remains liquid, the amount of solvent present may be about  
5 50 wt% to about 99.99 wt %, for example about 75 wt% to about 99 wt%, or about 85  
wt% to about 98 wt% based on the total weight of the composition.

**[0056]** In some embodiments, for example, in embodiments in which the nicotine  
replacement composition is a liquid (e.g., a liquid composition that can be inhaled  
through a vaping device, or a liquid composition that is housed in a reservoir of a  
10 nicotine patch), the nicotine replacement composition may include water as a  
solvent. The amount of water present in the nicotine replacement composition may  
vary depending on the NRT product in which the composition is used. In some  
embodiments, for example, in embodiments in which the nicotine replacement  
composition is a liquid composition that can be inhaled through a vaping device, the  
15 water may be present in an amount of about 0.1 to about 10 wt%, for example about  
0.5 to about 5 wt %, based on the total weight of the nicotine replacement  
composition.

**[0057]** In some embodiments, the nicotine replacement composition may include  
glycerin as a solvent, and the glycerin may be a Kosher vegetable glycerin having a  
20 purity greater than 99%, for example greater than 99.5%, or greater than 99.9%.  
The glycerin may be odorless, colorless and have a slightly sweet taste.

**[0058]** In some embodiments, the nicotine replacement composition may include  
propylene glycol as a solvent, and the propylene glycol may be USP grade and have  
a purity greater than 99%, for example greater than 99.5%, or greater than 99.99%.  
25 The propylene glycol may be odorless and colorless, and essentially tasteless. In  
some embodiments, the nicotine replacement composition may include a solvent  
that comprises, consists essentially of, or consists of glycerin and propylene glycol.

**[0059]** In some embodiments, for example, in embodiments in which the nicotine  
replacement composition is intended for use in a resinous or polymeric transdermal  
30 nicotine delivery patch, the nicotine replacement composition may include a resin or  
polymer as a carrier. Any suitable resin or polymer may be used so long as it is  
compatible with the nicotine replacement composition intended to be housed,  
embedded or impregnated in the carrier. As the nicotine patch is intended to be in  
contact with a user's skin, the resin or polymer should also be biocompatible and  
35 non-irritating (or only moderately irritating) to the skin. Nonlimiting examples of  
suitable such polymers and/or resins include polyurethane polymers, methacrylate  
polymers, ethylene acrylic acid polymers, and the like. Some nonlimiting examples  
of suitable methacrylate polymers include polymethyl methacrylate and polybutyl



1 methacrylate, and nonlimiting examples of suitable polyurethanes include polyether  
and polyester polyurethanes. As would be understood by those of ordinary skill in  
the art, the amount of the polymer or resin will depend on the desired loading level of  
the nicotine replacement composition, and the skilled artisan would be readily  
5 capable of selecting an appropriate amount of polymer to contain, embed or  
otherwise house the desired amount of the nicotine replacement composition in the  
polymer matrix.

**[0060]** In some embodiments, for example, in embodiments in which the nicotine  
replacement composition is intended for use in a nicotine gum, the nicotine  
10 replacement composition may include a gum base or similar polymer, or an  
elastomer as a carrier or solvent. Any suitable gum base or polymer may be used so  
long as it is compatible with the nicotine replacement composition intended to be  
housed, embedded or impregnated in the carrier. As the nicotine gum is intended to  
be chewed by the user, the gum base or polymer should also be edible and  
15 biocompatible. Any suitable gum base that is insoluble in water and/or saliva may be  
used, and such gum bases are well known to those of ordinary skill in the art.  
Indeed, those of ordinary skill in the art would be readily capable of selecting an  
appropriate polymer or gum base for use in a nicotine gum. Nonlimiting examples of  
suitable such polymers and/or gum bases include natural and synthetic elastomers  
20 and rubbers, and mixtures thereof. Some nonlimiting examples of suitable naturally  
occurring polymers include plant derived polymers such as, for example, chicle,  
jelutong, gutta percha, crown gum, and mixtures thereof. Some nonlimiting  
examples of suitable synthetic elastomers include butadiene-styrene copolymers,  
isobutylene and isoprene copolymers (e.g., butyl rubbers), polyethylene,  
25 polyisobutylene, polyvinyl esters such as polyvinylacetate, and mixtures thereof. As  
would be understood by those of ordinary skill in the art, the amount of the polymer  
or gum base will depend on the desired loading level of the nicotine replacement  
composition and the desired rate of release of the nicotine replacement composition  
(e.g., during chewing), and the skilled artisan would be readily capable of selecting  
30 an appropriate amount of polymer or gum base to contain, embed or otherwise  
house the desired amount of the nicotine replacement composition in the polymer  
matrix.

**[0061]** Additionally, any suitable elastomer solvent may be used, and such  
elastomer solvents are known to those of ordinary skill in the art. Nonlimiting  
35 examples of suitable such elastomer solvents include rosins and resins, and  
mixtures thereof. Some nonlimiting examples of suitable elastomer solvents include  
methyl, glycerol, and pentaerythritol esters of rosins or modified rosins, such as  
hydrogenated, dimerized or polymerized rosins, and mixtures thereof. For example,

1 the elastomer solvent may include a pentaerythritol ester of a partially hydrogenated  
wood rosin, a pentaerythritol ester of a wood rosin, a glycerol ester of a wood rosin,  
a glycerol ester of a partially dimerized rosin, a glycerol ester of a polymerized rosin,  
5 a glycerol ester of a tall oil rosin, a glycerol ester of a wood rosin and a partially  
hydrogenated wood rosin and partially hydrogenated methyl ester of rosin, such as  
polymers of alpha-pinene or beta-pinene, and terpene resins including polyterpenes  
and mixtures thereof. As would be understood by those of ordinary skill in the art,  
the amount of the elastomer solvent will depend on the desired loading level of the  
10 nicotine replacement composition and the desired rate of release of the nicotine  
replacement composition (e.g., during chewing), and the skilled artisan would be  
readily capable of selecting an appropriate amount of elastomer solvent to contain,  
embed or otherwise house the desired amount of the nicotine replacement  
composition in the carrier.

**[0062]** In some embodiments, the pH of the nicotine replacement composition  
15 may be adjusted (e.g., to improve the taste or experience of a nicotine gum or vaping  
liquid, or the feel or irritation of a transdermal nicotine delivery patch) by the addition  
of pharmacologically or pharmaceutically acceptable acids as pH adjusting agents.  
In some embodiments, the acid pH adjusting agent may be an inorganic acid.  
Nonlimiting examples of suitable inorganic acid pH adjusting agents include:  
20 hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid and/or phosphoric acid.  
In some embodiments, the inorganic acid may include hydrochloric acid and/or  
sulfuric acid (i.e., an inorganic acid or a mixture of inorganic acids).

**[0063]** In some embodiments, the acid pH adjusting agent may be an organic  
acid. Nonlimiting examples of suitable organic acids include: lactic acid, ascorbic  
25 acid, citric acid, malic acid, tartaric acid, maleic acid, succinic acid, fumaric acid,  
acetic acid, formic acid and/or propionic acid, and the like. In some embodiments,  
for example, the organic acid may be lactic acid, ascorbic acid, fumaric acid and/or  
citric acid (i.e., an organic acid or a mixture of organic acids). For example, in some  
embodiments, the organic acid includes citric acid and/or lactic acid.

30 **[0064]** In some embodiments, the acid pH adjusting agent may be an acid which  
forms an acid addition salt with the active substance. Also, if desired, a single acid  
pH adjusting agent may be used, or a mixture of two or more acid pH adjusting  
agents may be used. Indeed, some acids have additional properties that make them  
desirable for inclusion in the vaping composition. For example, some acids may  
35 have pH adjusting (or acidifying) properties in addition to auxiliary or additional  
properties, such as, e.g. flavoring properties or antioxidant properties. Some  
nonlimiting examples of such dual function acids include citric acid and ascorbic  
acid.



1 **[0065]** In some embodiments, the pH adjusting agent may be basic, or the  
nicotine replacement composition may include an additional pH adjusting agent that  
is basic (e.g., in addition to the acidic pH adjusting agent). For example, a basic pH  
adjusting agent may be used or desired to more precisely titrate the pH of the  
5 nicotine replacement composition. Accordingly, in some embodiments, the pH  
adjusting agent may include (or further include) a basic pH adjusting agent, which  
may include a pharmacologically acceptable base. Nonlimiting examples of suitable  
such bases include alkali metal hydroxides and alkali metal carbonates. In some  
embodiments, the alkali ion in the alkali metal hydroxides or carbonates may be  
10 sodium. In embodiments in which such a basic pH adjusting agent is used, as would  
be understood by those of ordinary skill in the art, care must be taken to ensure that  
the resulting salts, which are then contained in the finished pharmaceutical  
formulation, are pharmacologically compatible with the abovementioned acid of the  
acid pH adjusting agent.

15 **[0066]** As would be understood by those skilled in the art, the amount of the pH  
adjusting agent (whether acid or base) will depend on the desired target pH and the  
starting pH of the composition. Indeed, pH adjustment and titration techniques and  
addition amounts are well within the knowledge and skill of the ordinary artisan in  
this field.

20 **[0067]** In some embodiments, as discussed above, the nicotine replacement  
composition may further include a pharmacologically or pharmaceutically acceptable  
excipient. The excipient may include any of a number of compounds, some  
nonlimiting examples of which include antioxidants, such as ascorbic acid (which can  
also be used to adjust the pH as discussed above), vitamin A, vitamin E, tocopherols  
25 and similar vitamins or provitamins occurring in the human body.

**[0068]** Other nonlimiting examples of suitable excipients include preservatives,  
which can be added to protect the formulation from contamination by, for example,  
pathogenic bacteria. Any suitable preservative may be used, including those known  
in the art. Some nonlimiting examples of suitable preservatives include butylated  
30 hydroxyl toluene, benzalkonium chloride, benzoic acid or benzoates such as sodium  
benzoate. In some embodiments, the preservative may include benzalkonium  
chloride. Any suitable amount of the preservative may also be used, which amount  
(or concentration) would be known to those skilled in the art.

**[0069]** Additional nonlimiting examples of suitable excipients include plasticizers  
35 and softeners, which can be added to adjust the viscosity of the nicotine replacement  
composition. In some embodiments, for example, in embodiments in which the  
nicotine replacement composition is intended for use in a nicotine gum, the nicotine  
replacement composition may include a plasticizer and/or softener in order to

1 improve the texture and bite of the gum during chewing. Any suitable plasticizers  
and/or softeners can be used, including those known in the art. However, in  
embodiments in which the nicotine replacement composition is intended for use in an  
edible product (such as, for example, in a nicotine gum), the plasticizers and/or  
5 softeners should be fit for human consumption, non-toxic and biocompatible. Some  
nonlimiting examples of suitable plasticizers and/or softeners include lecithin, mono-  
and di-glycerides, lanolin, stearic acid, sodium stearate, potassium stearate, glycerol  
triacetate, glycerol monostearate, glycerin, waxes (such as, for example beeswax),  
fats and oils (such as, for example, soybean and/or cottonseed oils). Any suitable  
10 amount of the plasticizer and/or softener may be used, which amount (or  
concentration) would be known to those of ordinary skill in the art. Also, the desired  
viscosity or softness of the composition may vary depending on the intended  
application of the nicotine replacement composition, and those of ordinary skill in the  
art would be readily capable of selecting an appropriate plasticizer and/or softener  
15 and an appropriate amount of these excipients in order to achieve the desired  
properties.

**[0070]** As discussed above, fats and oils can be included in the nicotine  
replacement composition as a plasticizer and/or softener. However, the fats and oils  
may also be included in the nicotine replacement composition as an encapsulating  
20 agent that encapsulates or surrounds the active ingredient, i.e., the nicotine product.  
This encapsulation can aid in creating a uniform product, and provide added shelf-  
life by improving the stability of the nicotine replacement composition. Nonlimiting  
examples of suitable such fats and oils for encapsulation include vegetable and  
animal fats and oils, such as, for example, stearine, mono- and di-glyceride-based  
25 fats. In some embodiments, for example, the encapsulating agent may include  
stearine, canola oil, cottonseed oil, soybean oil, medium chain triglycerides oils,  
mono-, di- and tri-glyceride-based fatty acid oils. Any suitable amount of the  
encapsulating agent may be used, which amount (or concentration) would be known  
to those of ordinary skill in the art. Also, the desired properties of the composition  
30 may vary depending on the intended application of the nicotine replacement  
composition, and those of ordinary skill in the art would be readily capable of  
selecting an appropriate encapsulating agent and an appropriate amount of these  
excipients in order to achieve the desired properties.

**[0071]** Other nonlimiting examples of suitable excipients include fillers, which can  
35 be added to adjust the properties of the nicotine replacement composition. In some  
embodiments, for example, in embodiments in which the nicotine replacement  
composition is intended for use in a nicotine gum, the nicotine replacement  
composition may include a filler in order to improve the texture and bite of the gum



1 and the chewability. The filler may also be added to adjust the release of nicotine  
from the composition, and the absorption of nicotine by the user. Any suitable fillers  
can be used, including those known in the art. However, in embodiments in which  
the nicotine replacement composition is intended for use in an edible product (such  
5 as, for example, in a nicotine gum), the fillers should be fit for human consumption,  
non-toxic and biocompatible. Some nonlimiting examples of suitable fillers include  
calcium carbonate, magnesium silicate (i.e., talc), dicalcium phosphate, metallic  
mineral salts (such as, for example, alumina, aluminum hydroxide, and aluminum  
silicates), and mixtures thereof. Any suitable amount of the filler may be used, which  
10 amount (or concentration) would be known to those of ordinary skill in the art. Also,  
the desired properties of the composition may vary depending on the intended  
application of the nicotine replacement composition, and those of ordinary skill in the  
art would be readily capable of selecting an appropriate filler and an appropriate  
amount of these excipients in order to achieve the desired properties.

15 **[0072]** In some embodiments, the nicotine replacement composition may further  
comprise a sweetening and/or flavoring agent. Any suitable such sweetener and/or  
flavoring agent may be used, some nonlimiting examples of which include sugars,  
sugar substitutes, sugar alcohols, peppermint, menthol, wintergreen, spearmint,  
propolis, eucalyptus, cinnamon, oils or the like. Some additional nonlimiting  
20 examples of suitable flavorants or sweeteners include those derived from fruits,  
tobacco itself, liquor, coffee and confectionaries. The amount of the sweetener  
and/or flavorant may be about 0 wt% (e.g. no flavorant is present, or no flavorant is  
added) to about 40 wt%, for example about 1 wt% to about 30 wt%, about 5 wt% to  
about 20 wt%, or about 10 wt% to about 15 wt%, based on the total weight of the  
25 nicotine replacement composition. In some embodiments, the amount of the  
sweetener and/or flavorant may be about 10 wt% based on the total weight of the  
nicotine replacement composition.

**[0073]** It has been surprisingly found that the nicotine replacement compositions  
according to embodiments of the present invention including a portion of synthetic  
30 nicotine has suitable and/or enhanced physiological activity on the human system,  
including neuroactivity, as well as suitable and/or enhanced sensory appeal (e.g.,  
mouthfeel, throatfeel, etc.) as compared to compositions including only nicotine  
derived from tobacco (or naturally sourced nicotine) as the nicotine component.  
Indeed, smoker/vaporizer users have found that the compositions according to  
35 embodiments of the present invention including at least a portion of synthetic  
nicotine to be preferable to compositions using only nicotine derived from tobacco (or  
naturally sourced nicotine) as the nicotine component.

1 **[0074]** Also, because the nicotine replacement compositions described herein  
have fewer of the contaminants associated with tobacco-derived nicotine, smaller  
amounts (if any at all) of sweeteners and/or flavorants are needed in the  
compositions. In particular, smaller amounts of sweeteners and/or flavorants are  
5 needed to mask the bitterness and smell of comparable compositions comprising  
only tobacco-derived nicotine as the nicotine component. In some embodiments, the  
nicotine replacement composition is substantially free of sweeteners and/or  
flavorants.

**[0075]** Using smaller amounts of sweeteners and/or flavorants (or substantially no  
10 sweeteners and/or flavorants) provides certain benefits to the nicotine replacement  
products. For example, smaller amounts of sweeteners and/or flavorants (or  
substantially no sweeteners and/or flavorants) provides a mechanical benefit to  
electronic vaping devices. Specifically, the use of smaller amounts of sweeteners  
and/or flavorants leads to less wear on the coil or heating element of the vaporizer.  
15 Because sweeteners and/or flavorants tend to be sticky, oily or more viscous than  
the other components in the nicotine replacement composition, the addition of larger  
amounts of sweeteners and/or flavorants causes the coil (or heating element) to  
work harder to heat the nicotine replacement composition. Also, because of the  
sticky, oily, viscous properties of the sweeteners and/or flavorants, compositions  
20 having larger amounts of sweeteners and/or flavorants tend to have larger amounts  
of buildup on the coil, which also increases wear on the coil, and decreases the  
working life of the coil (and device). In contrast, in the nicotine replacement  
compositions according to embodiments of the present invention, smaller amounts of  
the sweeteners and/or flavorants are used, reducing the wear on the coil, and the  
25 potential for buildup on the coil. As a result, the nicotine replacement compositions  
according to embodiments of the present invention can increase the working life of  
the coil or heating element, and thus the life of the vaping device.

**[0076]** Additionally, in embodiments of nicotine replacement products that are  
edible (such as, for example, a nicotine gum or other confection), smaller amounts of  
30 sweeteners reduces the amount of sugars in the product, which makes the product  
more appealing to many consumers or users. Indeed, increased amounts of  
sweeteners may lead to several undesirable human health consequences, such as  
weight gain, compromised immune system, diabetes and other chronic diseases, as  
well as a variety of dental concerns. Accordingly, the smaller amounts of  
35 sweeteners in the nicotine replacement compositions according to embodiments of  
the present invention yield a healthier option for treating nicotine addiction. Also, the  
reduced amount of flavorants in the nicotine replacement compositions according to



1       embodiments of the present invention leads to products with a more pleasant taste  
that is less intensely flavored, which appeals to a large number of users.

**[0077]**       In some embodiments, the nicotine replacement composition may be  
intravenously injected. In such embodiments, the injectable composition may  
5       include any of the nicotine replacement compositions described herein in which the  
carrier is a pharmaceutically acceptable carrier suitable for intravenous delivery,  
which pharmaceutically acceptable carriers are well known to those of ordinary skill  
in the art.

**[0078]**       In accordance with aspects of embodiments of the present invention, a (1)  
10       50-50 RS synthetic nicotine provides the same or better sensory impact as “S”  
nicotine derived from tobacco. Similarly, a (2) racemic synthetic nicotine is  
neurologically effective, and in many cases exhibits superior neurological effect to  
that of tobacco-derived (“S”) nicotine. Also, the above-disclosed blends of synthetic  
RS nicotine with synthetic or non-synthetic tobacco-derived nicotine, according to  
15       embodiments of the present invention, have improved sensory impact as well as  
neurological impact on the user as compared to nicotine replacement compositions  
having only tobacco-derived nicotine as the source of nicotine. Additionally, having  
fewer tobacco alkaloids in the nicotine replacement composition increases the shelf  
life of the composition and maintains visual clarity of product (e.g., a colorless or  
20       transparent appearance).

**[0079]**       The nicotine replacement compositions according to embodiments of the  
present invention, especially those that are completely free of any tobacco-derived  
nicotine or its associated impurities, have reduced carcinogenesis, or are not  
carcinogenic. Indeed, synthetic nicotine is not carcinogenic, as discussed in  
25       Carmella, et al., “Evidence for endogenous formation of tobacco-specific  
nitrosamines in rats treated with tobacco alkaloids and sodium nitrite,”  
*Carcinogenesis*, vol. 18, no. 3, pp 587-592 (1997), the entire content of which is  
incorporated herein by reference. In contrast, tobacco-derived nicotine is  
carcinogenic due to the presence of the contaminants discussed herein.  
30       Accordingly, in some embodiments, the nicotine replacement compositions  
(regardless of isomeric composition) are non-carcinogenic.

**[0080]**       According to some embodiments of the present invention, a nicotine  
replacement therapy product (NRT product) utilizes the nicotine replacement  
compositions described above. Any suitable NRT product may use the nicotine  
35       replacement compositions according to embodiments of the present invention, some  
nonlimiting examples of which include a transdermal nicotine replacement delivery  
patch (also referred to herein as a “nicotine patch” or “transdermal nicotine delivery  
patch”), a nicotine replacement gum (also referred to herein as a “nicotine gum”), a

1 nicotine replacement chewing tobacco (e.g., a composition having properties similar  
to conventional chewing tobacco), a nicotine replacement snuff (e.g., a composition  
having properties similar to conventional snuff), a nicotine replacement strip (e.g., a  
composition having properties similar to conventional dissolvable tobacco), a  
5 nicotine replacement oral spray, and a lotion, balm, salve or other type of rub  
incorporating a nicotine replacement composition. Several variations of these  
nicotine replacement therapy products are well known to those of ordinary skill in the  
art, and the NRT products according to embodiments of the present invention are the  
same as the known products except that the nicotine source is replaced with the  
10 nicotine replacement compositions described herein. As the structure, function, and  
manufacturing methods for each of these NRT products is well known to those of  
ordinary skill in the art, those of ordinary skill in the art would be readily capable of  
replacing the existing nicotine source with the nicotine replacement compositions  
according to embodiments of the present invention.

15 **[0081]** By way of example, a NRT product according to embodiments of the  
present invention includes a transdermal nicotine replacement delivery patch. The  
transdermal nicotine replacement delivery patch may have a similar structure and  
composition to the patches disclosed in U.S. Patent No. 4,943,435 to Baker et al.,  
and titled "Prolonged Activity Nicotine Patch," the entire content of which is  
20 incorporated herein by reference. However, the transdermal nicotine replacement  
delivery patch uses the nicotine replacement compositions according to  
embodiments of the present invention in place of the "nicotine" described in the  
patent document. For example, a transdermal nicotine replacement delivery patch  
according to embodiments of the present invention may include an impermeable  
25 support layer, a nicotine replacement composition layer, and either a release liner or  
a nicotine replacement composition permeable layer. The impermeable support  
layer may include any suitable material that is both capable of supporting the  
nicotine replacement composition layer and that prevents or minimizes the  
permeation of the nicotine replacement composition through the impermeable  
30 support layer. Indeed, while the term "impermeable" is intended to convey that the  
nicotine replacement composition generally does not permeate through the  
impermeable support layer it is understood that the impermeable support layer may  
not be perfectly impermeable, and that some, negligible amounts of the nicotine  
replacement composition may permeate through the layer over time. Suitable  
35 materials for the impermeable support layer are well known to those of ordinary skill  
in the art, and any of these materials may be used in the transdermal nicotine  
delivery patch according to embodiments of the present invention. Some nonlimiting  
examples of suitable impermeable support layer materials include polyesters,



1     aluminized polyesters, metal foils, metallized polyfoils, composite foils or films  
containing polyester, polytetrafluoroethylene materials, and the like.

5     **[0082]**     The nicotine replacement composition layer may include any of the  
nicotine replacement compositions according to embodiments of the present  
invention, and may be a liquid, or may be embedded in a resinous or polymeric  
matrix. When the nicotine replacement composition is provided as a liquid, the  
nicotine replacement composition layer may be a reservoir housing the nicotine  
10    replacement composition, and the patch may include the nicotine replacement  
composition permeable layer. When the nicotine replacement composition is  
embedded in a resinous or polymeric matrix, the matrix makes up the nicotine  
replacement composition layer, and the patch includes the release liner releasably  
attached to the nicotine replacement composition layer (i.e., the matrix). In some  
embodiments, however, when the nicotine replacement composition layer is a  
reservoir housing the nicotine replacement composition, the patch may include both  
15    the nicotine replacement composition permeable layer (or membrane) and a release  
liner releasably attached to the nicotine replacement composition permeable layer.

20    **[0083]**     In embodiments in which the nicotine replacement composition layer is a  
reservoir housing the nicotine replacement composition, the nicotine replacement  
composition may include any of the nicotine replacement compositions in liquid form  
described herein. Additionally, the nicotine replacement composition permeable  
layer may be any suitable material capable of permeating the nicotine replacement  
composition at the desired permeation rate. Suitable materials for the nicotine  
replacement composition permeable layer are well known to those of ordinary skill in  
the art, and any of these materials may be used in the transdermal nicotine delivery  
25    patch according to embodiments of the present invention. Indeed, those of ordinary  
skill in the art would be readily capable of selecting a suitable material for the  
nicotine replacement composition permeable layer based on the desired composition  
permeation rate, and compatibility with the components of the nicotine replacement  
compositions. Some nonlimiting examples of suitable nicotine replacement  
30    composition permeable layer materials include various polyethylenes, polyamides  
and ethylene vinyl acetate copolymers.

35    **[0084]**     Also, release liners are well known in the art, and any suitable release liner  
material may be used in connection with embodiments of the transdermal nicotine  
replacement deliver patch. In some embodiments, for example, the release liner  
may be any suitable silicone release liner.

**[0085]**     As another example, a NRT product according to embodiments of the  
present invention includes a nicotine replacement gum. The nicotine replacement  
gum may have a similar structure and composition to the gums disclosed in U.S.

1 Patent No. 6,344,222 to Cherukuri et al., and titled "Medicated Chewing Gum  
Delivery System for Nicotine," the entire content of which is incorporated herein by  
reference. However, the nicotine replacement gum uses the nicotine replacement  
compositions according to embodiments of the present invention in place of the  
5 "nicotine" described in the patent document. For example, as described herein, a  
nicotine replacement composition for use in a nicotine replacement gum according to  
embodiments of the present invention may include the nicotine product described  
herein in addition to a gum base, polymer and/or elastomer solvent as a carrier. The  
nicotine replacement gum may also include a plasticizer and/or softener, a  
10 sweetener and/or flavorant, a preservative, a pH adjusting agent, and/or a filler.

**[0086]** In another example, a NRT product according to embodiments of the  
present invention includes a nicotine replacement spray (e.g., an oral spray). The  
nicotine replacement spray may include any of the nicotine replacement  
compositions according to embodiments of the present invention in a sprayable,  
15 aerosolizable, atomizable or nebulizable form. For example, the nicotine  
replacement composition may be a liquid composition having a viscosity suitable for  
forcing through an atomizer, aerosolizer, nebulizer or other spraying device.

**[0087]** In some examples, NRT products according to embodiments of the  
present invention include a nicotine replacement chewing tobacco, a nicotine  
20 replacement snuff (e.g., inhalable nicotine replacement product, such as, for  
example, powder) or a nicotine replacement strip (e.g., dissolvable nicotine  
replacement product, such as, for example, a gelatinized sheet as a mouth strip or a  
vaporizable film). These nicotine replacement products may include any of the  
nicotine replacement compositions according to embodiments of the present invention  
25 embedded, impregnated, or otherwise housed in a polymeric or resinous carrier,  
e.g., a carrier including polymer or resin particles or fibers. The polymeric matrix  
housing the nicotine replacement composition may be first impregnated or  
embedded with the nicotine replacement composition, and then further processed to  
mimic the physical properties of conventional chewing tobacco, snuff or strips. For  
30 example, the resulting matrix may be cut, pulverized or otherwise mechanically  
processed to resemble the shape, structure, mouthfeel, texture and chew of  
conventional chewing tobacco, snuff or strips. Alternatively, the polymer or resin  
may be first processed to the desired shape, e.g., particles or fibers, and then  
impregnated or embedded with the nicotine replacement composition. Additionally,  
35 the polymer(s) of the matrix may be selected to mimic the chemical properties of  
conventional chewing tobacco, snuff or strips, such as melting or softening  
temperature, so that the matrix with embedded nicotine replacement composition  
has the same or similar mouth experience as conventional chewing tobacco, snuff or



1 strips. Any suitable polymer or resin may be used for the polymer or resin matrix,  
and may differ depending on the type of NRT product. Some nonlimiting examples  
of polymers suitable for mimicking the properties of conventional tobacco derived  
chewing tobacco and/or snuff include algae-derived cellulose materials or polymers.

5 **[0088]** In addition, in some embodiments, for example, when the NRT product is  
a dissolvable nicotine product (e.g., a nicotine replacement strip, such as a  
gelatinized sheet as a mouth strip or a vaporizable film), the polymer or resin may be  
soluble in water and/or saliva. Any suitable non-tobacco polymer may be used for  
this purpose, and the dissolvable nicotine replacement product may be  
10 manufactured using techniques known in the art, as well as food-grade solvents that  
can be later removed by any suitable means, e.g., heat or vacuum.

**[0089]** In another example, a NRT product according to embodiments of the  
present invention includes a nicotine replacement rub, e.g., a lotion, balm, salve, oil,  
ointment or the like. The nicotine replacement rub may include any of the nicotine  
15 replacement compositions according to embodiments of the present invention in any  
form suitable for external application to a user's skin. For example, the nicotine  
replacement composition may be a liquid or solid composition dissolved or diluted in  
a carrier suitable for application to the skin, e.g., a biocompatible oil base, wax base,  
lotion base, balm base, salve base, ointment base or the like. The various  
20 components of external rubs (e.g., lotions, oils, balms, salves, ointments, etc.) are  
well known to those of ordinary skill in the art, and the skilled artisan would be readily  
capable of selecting appropriate components for the desired NRT product.

**[0090]** According to some embodiments of the present invention, a method of  
treating nicotine addiction comprises administering a nicotine replacement  
25 composition according to embodiments of the present invention to a user. The  
nicotine replacement composition may be administered via a nicotine replacement  
therapy product. Additionally, in some embodiments, the administration may include  
administering a first nicotine replacement composition having a first concentration of  
the nicotine product in the composition, and then administering a second nicotine  
30 replacement composition having a second concentration of the nicotine product in  
the composition, where the second concentration of the nicotine product is lower  
than the first concentration of the nicotine product. Additional administrations of  
additional nicotine replacement compositions with additional concentrations of the  
nicotine product may also be administered after administration of the second nicotine  
35 replacement composition, where each additional concentration of the nicotine  
becomes lower with each successive administration.

**[0091]** As discussed in the Examples section below, humans may have different  
neurophysiological responses to the R and S isomers of nicotine, and therefore



1 different neurophysiological responses to various mixtures of the R and S isomers. The differences reported in the below Examples section in membrane receptor binding properties of the R and S isomers may also affect psychoactive neuronal pathways as well as addictive responses. Indeed, the different assay results  
5 observed in the membrane bound nicotine receptors primarily responsible for addictive response may suggest that the R isomer of nicotine can be used as an effective treatment for addiction, e.g., an effective means for smoking cessation. Additionally, given the neurophysiological differences between the R and S isomers of nicotine, a NRT product that includes all R isomer, or different levels of R isomer  
10 in the nicotine replacement composition may be used as a way to control the dose of active nicotine (i.e., S isomer). Accordingly, in some embodiments of the present invention, a method of treating nicotine addiction (or method of promoting smoking cessation) may include administering a nicotine replacement composition according to embodiments of the present invention in which at least a portion of the nicotine  
15 product includes R-Nicotine to a user. The nicotine replacement composition may be administered via a nicotine replacement therapy product. Additionally, in some embodiments, the administration may include administering a first nicotine replacement composition having a first concentration of R-isomer in the nicotine product in the composition, and then administering a second nicotine replacement  
20 composition having a second concentration of R-isomer in the nicotine product in the composition, where the second concentration of R-isomer in the nicotine product is greater than the first concentration of R-isomer in the nicotine product. Additional administrations of additional nicotine replacement compositions with additional concentrations of R-isomer in the nicotine product may also be administered after  
25 administration of the second nicotine replacement composition, where each additional concentration of R-isomer in the nicotine becomes greater with each successive administration. With such a treatment regimen of stepped increases in the amount of R isomer in the nicotine replacement compositions, the R isomer serves to control the dose of active (i.e., S isomer) nicotine.

30 **[0092]** It is understood that while some embodiments of the method of treating nicotine addiction (or the method of promoting smoking cessation) may include the administration of a composition including some R-isomer, these methods do not require the presence of R-isomer. Indeed, according to some embodiments of the present invention, the method of treating nicotine addiction (or promoting smoking  
35 cessation) includes administering a nicotine replacement composition according to embodiments of the present invention in which the nicotine product includes only S-Nicotine to a user. The nicotine replacement composition may be administered via a nicotine replacement therapy product. Additionally, in some embodiments, the



1 administration may include administering a first nicotine replacement composition  
having a first concentration of S-isomer in the nicotine product in the composition,  
and then administering a second nicotine replacement composition having a second  
concentration of S-isomer in the nicotine product in the composition, where the  
5 second concentration of S-isomer in the nicotine product is lower than the first  
concentration of R-isomer in the nicotine product. Additional administrations of  
additional nicotine replacement compositions with additional concentrations of S-  
isomer in the nicotine product may also be administered after administration of the  
second nicotine replacement composition, where each additional concentration of S-  
10 isomer in the nicotine becomes lower with each successive administration. With  
such a treatment regimen of stepped decreases in the amount of S isomer in the  
nicotine replacement compositions, the increasing amount of R isomer as the  
treatment regimen progresses serves to control the dose of active (i.e., S isomer)  
nicotine.

## 15 **EXAMPLES**

**[0093]** The following Examples are provided for illustrative purposes only, and are  
not intended to limit the scope of any of the embodiments of the present invention.

### **SYNTHESIS EXAMPLE 1 - R,S NICOTINE SYNTHESIS**

**[0094]** 1 equivalent of potassium hydride was added to a stirred solution of 1-  
20 vinyl-2-pyrrolidinone (2) in dry THF under a nitrogen atmosphere. The reaction  
mixture was stirred at room temperature for about 20 minutes, then ethyl nicotinate  
(1equivalent) was added and the resulting mixture was stirred for 24 hours at 65  
degrees centigrade. The reaction was cooled and then acidified with 5% HCl, and  
then concentrated HCl was added and the resulting solution was refluxed for 48  
25 hours. The pH was adjusted to 13 with sodium hydroxide, and the aqueous and  
organic layers of the resulting biphasic solution were separated three times using  
equal volumes of dichloromethane. The combined extracts from the separation were  
dried over sodium sulfate, filtered and the solvent evaporated to give an amorphous  
material. The amorphous material was taken up in 3 parts ethanol, and then  
30 palladium-on-carbon was added (about 10%) and the resulting mixture was  
subjected to hydrogen pressure for 6 hours (greater than 25 atmospheres). The  
resulting residue was diluted with more ethanol and filtered through celite. The  
solvent was evaporated to dryness under vacuum with minimal heat, and then the  
residue was taken up in a formic acid/formaldehyde solution (1:1). The resulting  
35 mixture was heated to an internal temperature of 90 degrees Celsius and maintained  
at this temperature over a period of 12 hours, and then cooled and neutralized with  
sodium hydroxide to a pH of greater than 10, and then extracted with

1 dichloromethane and dried over sodium sulfate, filtered and concentrated to give a brown oil. This oil was vacuum distilled to give pure RS Nicotine.

### SYNTHESIS EXAMPLE 2 - R,S NICOTINE SYNTHESIS

5 **[0095]** 1.2 equivalent of sodium hydride was added to a stirred solution of 1-vinyl-2-pyrrolidinone (**2**) in dry THF/DMF (3/1) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for about 20 minutes, then ethyl nicotinate (1 equivalent) was added, and the resulting mixture was stirred for 24 hours at 65 degrees centigrade. The reaction was cooled and then acidified with 5% HCl, and  
10 then concentrated HCl was added, and the resulting mixture was refluxed for 48 hours. The pH was adjusted to 6 with sodium hydroxide, and then excess dichloromethane was added and the layers were separated. The aqueous layer was extracted twice with excess dichloromethane, and the extracts were combined and washed with water, and then dried over sodium sulfate. The solution was then  
15 filtered and the solvent removed using vacuum to yield a brownish solid. This solid was dissolved in ethanol (about 5 to about 10 parts), and then 0.5 parts palladium on carbon was added and the resulting mixture was subjected to hydrogen pressure for 6 hours (greater than 25 atmospheres). The resulting residue was diluted with more ethanol and filtered through celite. The solvent was evaporated to dryness under  
20 vacuum with minimal heat, and then the residue was taken up in 3 parts formic acid and 3 parts formaldehyde, and the resulting solution was heated to an internal temperature of about 90 to about 95 degrees centigrade and maintained at this temperature over a period of 24 hours. The reaction was cooled and then vacuum distilled to yield pure RS nicotine as a clear, colorless non-viscous oil.

25

### SYNTHESIS EXAMPLE 3 - R,S NICOTINE SYNTHESIS

**[0096]** 1 equivalent of potassium hydride was added to a stirred solution of 1-vinyl-2-pyrrolidinone (**2**) in dry DMF under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for about 20 minutes, then ethyl nicotinate  
30 (1 equivalent) was added and the resulting mixture was stirred for 24 hours at 65 degrees centigrade. The reaction was cooled and then acidified with 5% HCl and then refluxed for 48 hours. The pH was adjusted to 6 with sodium hydroxide, and then a suspension of sodium borohydride in isopropanol was added in excess and the reaction mixture was stirred for 24 hours at room temperature. The reaction  
35 mixture was then acidified to a pH of about 3 with 5% HCl, and then stirred for about 15 minutes. 10 parts dichloromethane was added and the layers were separated. The organic layer was dried over sodium sulfate and filtered, and then 1.1 equivalents of potassium carbonate was added, and then 1.1 equivalents of methyl



1 iodide was added and the reaction mixture was stirred for 24 hours and filtered, and  
the solvent was removed to yield an oil which was vacuum distilled to yield pure RS  
nicotine.

#### 5 SYNTHESIS EXAMPLE 4 - R,S NICOTINE SYNTHESIS

**[0097]** 1 equivalent of potassium hydride was added to a stirred solution of 1-  
vinyl-2-pyrrolidinone (2) in dry THF under a nitrogen atmosphere. The reaction  
mixture was stirred at room temperature for about 20 minutes, then ethyl nicotinate  
(1 equivalent) was added and the resulting mixture was stirred for 24 hours at 65  
10 degrees centigrade. The reaction was cooled and then acidified with 5% HCl and  
then concentrated HCl was added and the resulting mixture was refluxed for 48  
hours. The pH was adjusted to 6 with sodium hydroxide, and then a suspension of  
sodium borohydride in isopropanol was added in excess and the reaction mixture  
was stirred for 24 hours at room temperature. About 10 parts formic acid and about  
15 10 parts formaldehyde were then added, and the resulting solution was stirred at  
about 100 degrees centigrade for 24 hours, cooled, and then brought to a pH of  
about 12 by addition of a sodium hydroxide solution. The layers were then  
separated and the aqueous layer was washed many times with dichloromethane.  
The organic extracts were dried over sodium sulfate and the solvent was removed.  
20 The resulting crude oil was vacuum distilled to yield pure RS nicotine as a clear and  
colorless non viscous liquor.

#### SYNTHESIS EXAMPLE 5 - R,S NICOTINE SYNTHESIS

**[0098]** 1.2 equivalents of sodium hydride (60% dispersion in oil) was added to a  
25 stirred solution of 1-vinyl-2-pyrrolidinone (2) in toluene, and then a concentrated  
solution of ethyl nicotinate (1 equivalent) in toluene was added drop-wise over 20  
min. The resulting mixture was heated to reflux for 3 hours. This crude reaction  
mixture was cooled in an ice bath, and then excess concentrated hydrochloric acid  
was added and the resulting solution was heated to an internal temperature of about  
30 85 to about 110 degrees Celsius and maintained at this temperature over a period of  
12 hours. The reaction mixture was then cooled to room temperature, and the upper  
toluene layer removed. Sodium hydroxide was added to the acidic aqueous layer  
until the pH was greater than 12, and then the pH was adjusted to about 8 with HCl.  
2.5 equivalents of sodium borohydride solution in isopropanol (stabilized with sodium  
35 hydroxide) were added to the stirred solution, and the resulting mixture was stirred  
for 6 hours (until the reaction was completed). Excess formic acid and formaldehyde  
was then added, and the resulting mixture was refluxed for 10 hours, and then  
brought to neutral or slightly basic pH with sodium hydroxide, and then the solvents

1 were removed by vacuum and the remaining residue was vacuumed distilled to yield  
pure R,S, Nicotine (boiling point = 74 to 76 degrees Celsius @ 0.5mmHg).

#### SYNTHESIS EXAMPLE 6 - MYOSAMINE SYNTHESIS

5 **[0099]** Sodium hydride (1.25 Kg, 31.2 mole) was added to a stirred solution of  
toluene (10L) in an inert atmosphere (dry nitrogen or argon gas) and stirred for about  
15 minutes at room temperature. Then, a solution of n-vinyl pyrrolidinone (2kg,  
18.02 mole) in 1L of toluene was added over 15 minutes via funnel addition, and the  
10 resulting mixture was stirred at ambient temperature for about 15 minutes. Then, a  
solution of ethyl nicotinate (2.5Kg, 16.56 mole) in 2L toluene was added in portions  
over a two hour period. The mildly effervescent exothermic reaction mixture turned a  
light rose color and then a light green precipitant formed as the exothermic reaction  
maintained itself at about 60 to about 65 °C. After the addition was complete, the  
15 reaction mixture was heated to an internal temperature of about 85°C and  
maintained at this temperature for about 16 hours, then cooled to room temperature  
yielding a greenish heterogeneous mixture. This greenish heterogeneous mixture  
flows well and can be pumped through a ½" polyethylene tubing using a diaphragm  
pump. The greenish heterogeneous mixture was added, in about 250mL portions, to  
20 25L of a boiling solution of 6N HCl. The addition took place with vigorous  
effervescence, which subsided within a few minutes after addition of the aliquot of  
the reaction mixture to the hot HCl. After all the reaction mixture was added, the  
resulting dark brown biphasic mixture was stirred under reflux for an additional hour.  
Then, the reaction mixture was cooled, and the layers were separated. The aqueous  
25 layer was cooled, made basic (i.e., having a pH greater than 10) using NaOH (50%),  
and then extracted 3 times with 8L of dichloromethane. The solvent was then  
removed via vacuum distillation (temperature of the bath was about 45 degrees  
centigrade) to yield crude myosamine as a dark brown, non-viscous oil.

#### SYNTHESIS EXAMPLE 7 – NORNICOTINE SYNTHESIS

30 **[00100]** The total crude myosamine from Synthesis Example 6 was taken up in  
16L of ethanol. 250 grams of 10% palladium-on-carbon was added, and the  
resulting mixture was stirred in a hydrogen atmosphere for 12 hours, followed by  
filtering using celite, and washing with ethanol. The ethanol was removed by  
vacuum to give crude nornicotine as a dark brown non-viscous oil.

35

#### SYNTHESIS EXAMPLE 8 - R,S NICOTINE SYNTHESIS

**[00101]** 2.0 Kg of formaldehyde (37%) and 1.5Kg of formic acid (85%) were added  
to the crude nornicotine from Synthesis Example 7. The resulting brown solution



1 was heated to an internal temperature of 85 degrees centigrade and maintained at  
this temperature for 15 hours, and then cooled to ambient temperature. The  
resulting solution was chilled to about 5 degrees centigrade, and then made basic by  
addition of NaOH. The resulting solution was then extracted 3 times with 8L of  
5 dichloromethane, and the solvent was removed by vacuum. Pure R,S-nicotine was  
obtained using high vacuum distillation (i.e., 75 to 76 @ 0.5mmHg) to yield a clear,  
colorless non-viscous oil (about 31% overall yield from ethyl nicotinate).

#### SYNTHESIS EXAMPLE 9 - SYNTHESIS OF NORNICOTINE

10 **[00102]** The total crude myosamine from Synthesis Example 6 was taken up in  
16L methanol and 4L of acetic acid. The resulting solution was cooled to an internal  
temperature of -40 degrees centigrade, and then 700 grams of sodium borohydride  
(granular) was added in portions over 1 hour. The reaction mixture was allowed to  
warm to room temperature with stirring, and was then submitted to vacuum  
15 distillation to remove most of the solvent. The resulting liquor was added to 25L of  
water, and the resulting solution was brought to a pH greater than 10 with NaOH.  
The resulting solution was extracted three times with 15L of dichloromethane, and  
the combined extracts were subjected to medium vacuum distillation to give crude  
nornicotine as a crude non-viscous dark brown colored oil.

20

#### SYNTHESIS EXAMPLE 10 - SYNTHESIS OF R,S NICOTINE

**[00103]** A solution of N-vinyl pyrrolidinone (4.5kg) in 2.5Kg of toluene was added to  
2.5 Kg of Sodium Hydride (60% dispersion in mineral oil) as a stirred suspension in  
20L of toluene. The resulting mixture was stirred for about 15 minutes at room  
25 temperature. 5Kg of ethyl nicotinate in 10Kg of toluene was added to the resulting  
mixture in portions and by a constant slow stream of liquor (light golden color). The  
exothermic reaction was controlled at an internal temperature of about 60°C by  
controlling the rate of addition of the ethyl nicotinate – toluene solution. After  
addition of about one third of the ethyl nicotinate, a green precipitate was formed.  
30 After addition was completed, the green heterogeneous mixture was heated to an  
internal temperature of about 85 °C and maintained at this temperature for about 12  
hours. The resulting solution was injected into a precooled solution of 30L of 4N HCl  
at 0°C followed by vigorous stirring for about 5 minutes. The layers were separated,  
and the toluene layer was washed once with 2.5Kg of 4N HCl. 8L of concentrated  
35 HCl was added to the combined acidic aqueous layers, and the reaction mixture  
was heated to boiling and maintained at this temperature for about 3 hours (or until  
the reaction was completed, as determined by thin layer chromatography (TLC)).  
The reaction mixture was cooled to 0°C, and then neutralized with 50% sodium

1 hydroxide solution while not allowing the internal temperature to go above 35 to 40  
degrees centigrade. The pH was made very basic by addition of a sodium hydroxide  
solution (50%) until the pH reached 11 to 13 (as indicated by a blue color change on  
litmus paper). The resulting solution was extracted 4 times with 15L of  
5 dichloromethane, and the combined extracts were subjected to medium vacuum  
distillation to yield myosamine as a non-viscous brownish oil.

**[00104]** 40L of anhydrous ethanol was added to the crude myosamine product,  
and the resulting solution was added to 2Kg of 10% palladium-on-carbon. The  
resulting mixture was subjected to hydrogen pressure of 50 atm. The reaction was  
10 completed within 12 hours. The resulting heterogeneous mixture was filtered  
through celite, and then washed twice with 10L of ethanol. The combined ethanolic  
solutions of the crude nornicotine product was subjected to vacuum distillation (29  
inches Hg) at below 50°C, and then the crude dark brown oil was taken up in 10L  
water. A solution of 5L of formaldehyde solution (37%) with 4L of formic acid (85%)  
15 was added to the resulting solution, and the mixture was heated to an internal  
temperature of 90 °C and maintained at this temperature for 20 hours. The reaction  
mixture was cooled to -5 °C, and then made basic (i.e., a pH greater than 10) by  
addition of a sodium hydroxide solution (50%). The basic liquor was then extracted  
3 times with 15L of dichloromethane, and the combined extracts were subjected to  
20 med vacuum distillation to yield crude RS-Nicotine product as a dark brown oil. The  
dark brown oil was high vacuum distilled twice to yield RS-Nicotine having a purity  
that meets the requirements of the USP purity test.

**[00105]** In a study of the differences between synthetic nicotine according to  
embodiments of the present invention and tobacco-derived nicotine,  
25 electrophysiology-based HTS assay was used to evaluate and compare the activity  
of different nicotine forms on two nicotinic ACh receptors (nAChRs), i.e.,  $\alpha 7$  and  
 $\alpha 4\beta 2$ . The nicotinic forms subjected to this assay included an S nicotine available  
from Sigma-Aldrich Corporation, St. Louis, MO, a synthetic RS racemic mixture of R  
and S isomers according to embodiments of the present invention, a synthetic S  
30 nicotine according to embodiments of the present invention, a synthetic RS mixture  
including 75% S and 25% R isomers according to embodiments of the present  
invention, a synthetic R nicotine according to embodiments of the present invention,  
a synthetic RS mixture including 25% S and 75% R isomers according to  
embodiments of the present invention, an S nicotine available from Alchem  
35 Laboratories Corporation, Alachua, FL, and a reference nicotine available from  
Sigma-Aldrich. The results of the assay are provided in Tables 1 and 2 below, which  
show the obtained  $EC_{50}$ ,  $IC_{50}$ ,  $E_{max}$  and Hill slope values of receptor activation and  
inhibition.



1 Table 1 -  $\alpha 4\beta 2$  nAChRs activation and inhibition

| Composition                         | Agonist Effect       |                            |           | Antagonist Effect          |           |
|-------------------------------------|----------------------|----------------------------|-----------|----------------------------|-----------|
|                                     | E <sub>max</sub> , % | EC <sub>50</sub> , $\mu$ M | Hillslope | IC <sub>50</sub> , $\mu$ M | Hillslope |
| 5 Sigma-Aldrich S nicotine          | 91                   | 3.11                       | -0.84     | 0.01                       | 0.94      |
| Synthetic RS racemic nicotine       | 96                   | 9.91                       | -0.77     | 0.03                       | 1.27      |
| Synthetic S nicotine                | 91                   | 3.54                       | -0.88     | 0.01                       | 0.93      |
| 10 Synthetic 75% S / 25% R nicotine | 99                   | 5.15                       | -0.76     | 0.02                       | 1.04      |
| Synthetic R nicotine                | 28                   | 10.79                      | -0.87     | 0.14                       | 0.67      |
| Synthetic 25% S / 75% R nicotine    | 80                   | 9.30                       | -0.90     | 0.04                       | 1.11      |
| Alchem S nicotine                   | 103                  | 3.71                       | -0.81     | 0.01                       | 1.01      |
| 15 Ref. nicotine (Sigma-Aldrich)    | 100                  | 4.13                       | -0.80     | 0.01                       | 0.85      |

20 Table 2 -  $\alpha 7$  nAChRs activation and inhibition

| Composition                         | Agonist Effect       |                            |           | Antagonist Effect          |           |
|-------------------------------------|----------------------|----------------------------|-----------|----------------------------|-----------|
|                                     | E <sub>max</sub> , % | EC <sub>50</sub> , $\mu$ M | Hillslope | IC <sub>50</sub> , $\mu$ M | Hillslope |
| 20 Sigma-Aldrich S nicotine         | 104                  | 1.20                       | -2.49     | 0.80                       | 2.76      |
| Synthetic RS racemic nicotine       | 108                  | 2.07                       | -1.97     | 1.20                       | 3.38      |
| 25 Synthetic S nicotine             | 102                  | 1.07                       | -3.36     | 0.84                       | 5.83      |
| Synthetic 75% S / 25% R nicotine    | 102                  | 1.39                       | -2.64     | 0.99                       | 5.16      |
| Synthetic R nicotine                | 110                  | 5.81                       | -2.37     | 4.07                       | 2.55      |
| 30 Synthetic 25% S / 75% R nicotine | 105                  | 2.69                       | -2.35     | 2.39                       | 4.70      |
| Alchem S nicotine                   | 97                   | 1.00                       | -3.15     | 0.73                       | 3.06      |
| Ref. nicotine (Sigma-Aldrich)       | 100                  | 1.21                       | -2.23     | 0.92                       | 10.02     |

35 **[00106]** As can be seen in the above Tables 1 and 2, the synthetic R nicotine according to embodiments of the present invention appears to be a full, weak agonist at human  $\alpha 7$  nAChRs, but only a partial agonist at human  $\alpha 4\beta 2$  nAChRs, suggesting a selectivity of the nicotine isomers at different types of nAChRs, which is surprising

1 and unexpected. For example, these results may suggest different  
 neurophysiological responses to the R and S isomers of nicotine, and therefore  
 different neurophysiological responses to various mixtures of the R and S isomers.  
 These differences in the neurophysiological response may be responsible for the  
 5 different sensory experiences reported in Tables 1 and 2 above, and these  
 differences in membrane receptor binding properties of the R and S isomers may  
 also affect psychoactive neuronal pathways as well as addictive responses.

**[00107]** In a second study of the differences between synthetic nicotine according  
 to embodiments of the present invention and tobacco-derived nicotine,  
 10 electrophysiology-based HTS assay was used to evaluate and compare the activity  
 of different nicotine forms on two additional nicotinic ACh receptors (nAChRs), i.e.,  
 $\alpha 6/3\beta 2\beta 3$  and  $\alpha 3\beta 4\alpha 5$ . The nicotinic forms subjected to this assay included an S  
 nicotine available from Sigma-Aldrich Corporation, St. Louis, MO, a synthetic RS  
 racemic mixture of R and S isomers according to embodiments of the present  
 15 invention, a synthetic S nicotine according to embodiments of the present invention,  
 a synthetic RS mixture including 75% S and 25% R isomers according to  
 embodiments of the present invention, a synthetic R nicotine according to  
 embodiments of the present invention, a synthetic RS mixture including 25% S and  
 75% R isomers according to embodiments of the present invention, an S nicotine  
 20 available from Alchem Laboratories Corporation, Alachua, FL, and a reference  
 nicotine available from Sigma-Aldrich. The results of the assay are provided in  
 Tables 3 and 4 below, which show the obtained  $EC_{50}$ ,  $IC_{50}$ ,  $E_{max}$  and Hill slope values  
 of receptor activation and inhibition.

Table 3 -  $\alpha 6/3\beta 2\beta 3$  nAChRs activation and inhibition

| Composition                         | Agonist Effect   |                        |            | Antagonist Effect      |            |
|-------------------------------------|------------------|------------------------|------------|------------------------|------------|
|                                     | $E_{max}$ ,<br>% | $EC_{50}$ ,<br>$\mu M$ | Hill slope | $IC_{50}$ ,<br>$\mu M$ | Hill slope |
| Sigma-Aldrich S nicotine            | 100              | 1.23                   | -0.69      | 0.02                   | 0.96       |
| Synthetic RS racemic<br>nicotine    | 91               | 3.56                   | -0.67      | 0.03                   | 1.36       |
| Synthetic S nicotine                | 97               | 0.94                   | -0.70      | 0.01                   | 1.10       |
| Synthetic 75% S / 25% R<br>nicotine | 103              | 2.28                   | -0.65      | 0.01                   | 0.68       |
| Synthetic R nicotine                | 70               | 3.87                   | -0.92      | 0.10                   | 1.07       |
| Synthetic 25% S / 75% R<br>nicotine | 94               | 3.39                   | -0.75      | 0.01                   | 0.62       |
| Alchem S nicotine                   | 95               | 1.27                   | -0.81      | 0.01                   | 0.97       |
| Ref. nicotine (Sigma-               | 100              | 1.20                   | -0.74      | 0.0057                 | 0.72       |



1 Aldrich)

Table 4 -  $\alpha 3\beta 4\alpha 5$  nAChRs activation and inhibition

| 5  | Composition                      | Agonist Effect          |                               |           | Antagonist Effect             |           |
|----|----------------------------------|-------------------------|-------------------------------|-----------|-------------------------------|-----------|
|    |                                  | E <sub>max</sub> ,<br>% | EC <sub>50</sub> ,<br>$\mu$ M | Hillslope | IC <sub>50</sub> ,<br>$\mu$ M | Hillslope |
|    | Sigma-Aldrich S nicotine         | 84                      | 28.63                         | -1.91     | 0.26                          | 1.38      |
|    | Synthetic RS racemic nicotine    | 65                      | 32.30                         | -2.13     | 0.44                          | 1.52      |
| 10 | Synthetic S nicotine             | 96                      | 28.57                         | -1.48     | 0.27                          | 1.11      |
|    | Synthetic 75% S / 25% R nicotine | 96                      | 42.25                         | -1.65     | 0.44                          | 1.65      |
|    | Synthetic R nicotine             | 21                      | 54.28                         | -2.37     | 2.54                          | 0.95      |
| 15 | Synthetic 25% S / 75% R nicotine | 51                      | 41.31                         | -1.97     | 0.82                          | 1.17      |
|    | Alchem S nicotine                | 87                      | 29.26                         | -1.46     | 0.33                          | 1.34      |
|    | Ref. nicotine (Sigma-Aldrich)    | 100                     | 29.22                         | -1.48     | 0.3004                        | 1.59      |

20 **[00108]** As can be seen in the above Tables 3 and 4, the synthetic R nicotine according to embodiments of the present invention appears to be a full, weak agonist at human  $\alpha 6/3\beta 2\beta 3$  nAChRs, but only a partial, weak agonist at human  $\alpha 3\beta 4\alpha 5$  nAChRs, suggesting a selectivity of the nicotine isomers at different types of nAChRs, which is surprising and unexpected. For example, like the results discussed above for the  $\alpha 7$  and  $\alpha 4\beta 2$  nAChRs, these results may suggest different neurophysiological responses to the R and S isomers of nicotine, and therefore different neurophysiological responses to various mixtures of the R and S isomers. As discussed above in connection with the results for the  $\alpha 7$  and  $\alpha 4\beta 2$  nAChRs, these differences in the neurophysiological response may be responsible for the different sensory experiences, and these differences in membrane receptor binding properties of the R and S isomers may also affect psychoactive neuronal pathways as well as addictive responses.

30 **[00109]** As discussed above, nicotine replacement compositions according to embodiments of the present invention include a synthetic nicotine source that improves the sensory experience, while also providing certain health and economic benefits. For example, while natural or tobacco derived nicotine typically has a foul taste, and is malodorous and carcinogenic, the nicotine replacement compositions according to embodiments of the present invention are non-carcinogenic and do not have the foul taste and smell characteristic of tobacco derived nicotine.

1 **[00110]** Also, because tobacco-derived nicotine compositions typically include  
contaminants that are the byproducts of extraction from tobacco leaves, these  
compositions may spoil sooner than the nicotine replacement compositions  
according to embodiments of the present invention incorporating synthetic nicotine  
5 sources. Indeed, nicotine replacement compositions according to embodiments of  
the present invention have improved shelf life or shelf stability than their tobacco-  
derived or natural counterparts.

**[00111]** Additionally, while tobacco-derived nicotine compositions for certain  
applications typically include large amounts of sweeteners and flavorants to mask  
10 the foul taste of the tobacco-derived nicotine, the nicotine replacement compositions  
according to embodiments of the present invention need not use so much sweetener  
and/or flavorant. As discussed above, this reduction in the amount of sweetener  
and/or flavorant can improve the sensory experience and decrease the health  
consequences typically associated with tobacco derived nicotine.

15 **[00112]** While certain exemplary embodiments of the present disclosure have been  
illustrated and described, those of ordinary skill in the art will recognize that various  
changes and modifications can be made to the described embodiments without  
departing from the spirit and scope of the present invention, and equivalents thereof,  
as defined in the claims that follow this description. For example, although certain  
20 components may have been described in the singular, i.e., "a" flavorant, "a" solvent,  
and the like, one or more of these components in any combination can be used  
according to the present disclosure.

**[00113]** Also, although certain embodiments have been described as "comprising"  
or "including" the specified components, embodiments "consisting essentially of" or  
25 "consisting of" the listed components are also within the scope of this disclosure. For  
example, while embodiments of the present invention are described as including a  
nicotine source that comprises a synthetic nicotine, a nicotine source consisting  
essentially of or consisting of a synthetic nicotine is also within the scope of this  
disclosure. Accordingly, the nicotine source may consist essentially of the synthetic  
30 nicotine. In this context, "consisting essentially of" means that any additional  
components in the nicotine source will not materially affect the user experience in  
terms of taste or neurological effect. For example, a nicotine source consisting  
essentially of the synthetic nicotine may exclude any measurable or detectable  
amount of the contaminants or impurities described herein as normally associated  
35 with tobacco-derived nicotine.

**[00114]** As used herein, unless otherwise expressly specified, all numbers such as  
those expressing values, ranges, amounts or percentages may be read as if  
prefaced by the word "about," even if the term does not expressly appear. Further,



1 the word "about" is used as a term of approximation, and not as a term of degree,  
and reflects the penumbra of variation associated with measurement, significant  
figures, and interchangeability, all as understood by a person having ordinary skill in  
the art to which this disclosure pertains. Any numerical range recited herein is  
5 intended to include all sub-ranges subsumed therein. Plural encompasses singular  
and vice versa. For example, while the present disclosure may describe "a" flavorant  
or "a" solvent, a mixture of such flavorants or solvents can be used. When ranges  
are given, any endpoints of those ranges and/or numbers within those ranges can be  
combined within the scope of the present disclosure. The terms "including" and like  
10 terms mean "including but not limited to," unless specified to the contrary.

**[00115]** Notwithstanding that the numerical ranges and parameters set forth herein  
may be approximations, numerical values set forth in the Examples are reported as  
precisely as is practical. Any numerical value, however, inherently contains certain  
errors necessarily resulting from the standard variation found in their respective  
15 testing measurements. The word "comprising" and variations thereof as used in this  
description and in the claims do not limit the disclosure to exclude any variants or  
additions.

20

25

30

35

## 1 WHAT IS CLAIMED IS:

1. A composition suitable for use in a nicotine replacement product, the composition comprising:

5 a nicotine product comprising a synthetic nicotine substantially free of one or more of nicotine-1'-N-oxide, nicotyrine, nornicotyrine, cotinine, 2',3-bipyridyl, anabasine, N-methyl anatabine, N-methyl anabasine, anabasine, and/or anatabine, and

one or more pharmaceutically acceptable excipients, additives and/or carriers.

10

2. The composition of claim 1, wherein the synthetic nicotine comprises pure S-nicotine, or a mixture of R-nicotine and S-nicotine.

15

3. The composition of claim 2, wherein the mixture of R-nicotine and S-nicotine comprises a racemic mixture of R-nicotine and S-nicotine.

4. The composition of claim 2, wherein the mixture of R-nicotine and S-nicotine comprises more R-nicotine than S-nicotine.

20

5. The composition of claim 1, wherein the composition is non-carcinogenic.

6. The composition of claim 1, further comprising a sweetener and/or a flavorant.

25

7. The composition of claim 1, wherein the composition is substantially free of sweeteners and/or flavorants.

30

8. The composition of claim 1, wherein the one or more of nicotine-1'-N-oxide, nicotyrine, nornicotyrine, 2',3-bipyridyl, anabasine, N-methyl anatabine, N-methyl anabasine, cotinine, anabasine, and/or anatabine are present in the composition in a combined amount of less than 0.5 wt% based on the total weight of the composition.

35

9. The composition of claim 1, wherein the one or more pharmaceutically acceptable excipients, additives and/or solvents comprises water, an organic solvent, a resin, a polymer, an elastomer, a gum base, a pH adjusting agent, a sweetener, a flavorant, a filler, a plasticizer, a softener, an antioxidant, an



1 encapsulating agent and/or a preservative.

10. A nicotine replacement therapy product, comprising:  
the composition of claim 1; and  
5 an atomizer for atomizing the composition.

11. A nicotine replacement therapy product, comprising:  
the composition of claim 1;  
a matrix comprising a resin, a polymer or a gum base, the composition of  
10 claim 1 being embedded or impregnated in the matrix; and  
a support, the matrix and the composition embedded or impregnated in the  
matrix being supported on the support.

12. A nicotine replacement therapy product, comprising:  
15 the composition of claim 1;  
a reservoir housing the composition of claim 1;  
a support; and  
a permeable membrane, the reservoir housing the composition between the  
support and the permeable membrane.

20 13. A nicotine replacement therapy product, comprising:  
the composition of claim 1; and  
a carrier comprising a resin, a polymer or a gum base.

25 14. The nicotine replacement therapy product of claim 13, further  
comprising a plasticizer and/or a softener.

15. A nicotine replacement therapy product, comprising the composition of  
claim 1 impregnated or embedded in polymer particles or fibers.

30 16. The nicotine replacement therapy product according to claim 15,  
wherein the polymer particles or fibers are soluble in water and/or saliva.

17. A method of treating nicotine addiction, the method comprising  
35 administering the nicotine replacement composition of claim 1 to a user.

18. The method of claim 17, wherein the administering the nicotine  
replacement composition comprises administering a first nicotine replacement

1 composition having a first concentration of the nicotine product, and then  
administering a second nicotine replacement composition having a second  
concentration of the nicotine product, the second concentration being lower than the  
first concentration.

5  
19. The method of claim 17, wherein at least a portion of the nicotine  
product includes R-Nicotine.

10  
20. The method of claim 19, wherein the administering the nicotine  
replacement composition comprises a first nicotine replacement composition having  
a first concentration of R-isomer in the nicotine product, and then administering a  
second nicotine replacement composition having a second concentration of R-  
isomer in the nicotine product, the second concentration of R-isomer being greater  
than the first concentration of R-isomer.

15

20

25

30

35