A tobacco product contains tobacco material enriched with anatabine or a salt or derivative thereof. In some aspects, the tobacco material has very low levels of tobacco specific nitrosamines (TSNA), such as having a collective content of N'-nitrosonornicotine (NNN), 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK), N'-nitrosoanatabine (NAT) and N'-nitrosoanabasine (NAB) which is about 0.3 μg/g or less. The tobacco product may be a smoking product, such as cigarettes, cigars, or pipe tobacco; or a smokeless product, such as chewing tobacco, snuff, snus, tobacco-containing gum or lozenges, or a dissolvable powdered tobacco-based smokeless product.
ANATABINE-ENRICHED TOBACCO PRODUCTS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. §119(e) to U.S. Application No. 61/528,377, filed Aug. 29, 2011, the disclosure of which is hereby incorporated by reference in its entirety.

BACKGROUND

[0002] In addition to the major alkaloid nicotine, tobacco also contains the minor alkaloids nornicotine, anabasine, and anatabine. The minor tobacco alkaloids, particularly anatabine, have been shown to exhibit beneficial effects such as monoamine oxidase inhibitory activity, as described in Williams U.S. Pat. No. 6,350,479.

SUMMARY

[0003] In one aspect, a tobacco product comprises a tobacco material enriched with anatabine or a salt or derivative thereof. The tobacco product may have an anatabine content, for example, which is about 0.1 wt. % to about 10 wt. % above the anatabine content in the tobacco material.

[0004] In some aspects, the tobacco material has very low levels of tobacco specific nitrosamines (TSNA). For example, the tobacco material may have a collective content of N-nitrosornicotine (NNN), 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK), N-nitrosanatabine (NAT) and N-nitrosoanabasine (NAB) which is about 0.3 μg/g or less.

[0005] In some embodiments, the tobacco material may be partially or wholly denicotinized. Anatabine or a salt or derivative thereof may be added to the tobacco material, for example, to partially or wholly replace any nicotine that is removed from the tobacco material.

[0006] The tobacco product may be a smoking product, such as cigarettes, cigars, pipe tobacco, or the like; or a smokeless product, such as chewing tobacco, snuff, snus, tobacco-containing gum or lozenges, dissolvable powdered tobacco-based smokeless products, or the like.

DETAILED DESCRIPTION

[0007] The tobacco products described herein generally contain tobacco material enriched with anatabine or a salt or derivative thereof. Unless otherwise clear from context, all percentages herein are expressed as percent by weight based on the total dry weight of the tobacco material.

Tobacco Material

[0008] Tobacco material may be provided from cured tobacco stems, lamina, or both. Any variety may be used, including flue or bright varieties, burley, oriental varieties, and the like, either individually or in combination with one or more other varieties. Often, flue or bright varieties of tobacco are used, e.g., Virginia flue. Tobacco stems generally have higher amounts of fibrous components than are present in lamina. Stems typically have less bitterness than lamina. Lamina generally is easier to mill and has higher concentrations of soluble components.

[0009] First, tobacco is grown and harvested. The tobacco is then cured and removed from the curing barn. If only the stem or lamina is used, the stem or lamina may be separated from the rest of the leaf either before or after curing.

[0010] In some embodiments, tobacco material is cured using a process designed to obtain very low levels of tobacco-specific nitrosamines (TSNA). For example, a microwave process may be used to substantially prevent the formation of nitrosamines during curing. U.S. Pat. No. 5,803,081 and WO 98/05226 describe the use of microwaves to substantially prevent the formation of nitrosamines U.S. Pat. No. 6,311,695 describes the use of high frequency electromagnetic energy (electron beam, gamma, etc.) applied to uncurd tobacco to substantially prevent the formation of nitrosamines. Alternatively, tobacco can be cured in a controlled environment that avoids anaerobic condition, as described in U.S. Pat. No. 6,202,649, to substantially prevent the formation of nitrosamines. Williams U.S. Pat. No. 8,151,804 describes a process of subjecting uncurd tobacco to a controlled environment while at least a majority of the tobacco is still in a green state. U.S. Pat. No. 5,803,081, U.S. Pat. No. 6,202,649, U.S. Pat. No. 6,311,695, and U.S. Pat. No. 8,151,804 are each hereby incorporated by reference in their entirety.

[0011] In some embodiments, the tobacco material has a collective content of N-nitrosornicotine (NNN), 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK), N-nitrosanatabine (NAT) and N-nitrosoanabasine (NAB) which is 0.3 μg/g or less, often 0.2 μg/g or less, and in some cases 0.1 μg/g or less, less than about 0.09 μg/g, less than about 0.07 μg/g, or less than about 0.05 μg/g, 0.03 μg/g, 0.015 μg/g, or even lower.

[0012] In some embodiments, the tobacco material has an NNK content of about 0.05 μg/g or less, often about 0.01 μg/g or less, in some cases about 0.002 μg/g or less. The tobacco material may have an NNK content of about 0.1 μg/g or less, about 0.05 μg/g or less, about 0.03 μg/g or less, about 0.015 μg/g or less, about 0.01 μg/g or less, or even lower.

[0013] After curing, before or after milling or extracting, the tobacco material may be subjected to a sterilization technique. The sterilization technique typically irradiates the tobacco to destroy any microbes remaining on the tobacco in order to prevent or substantially prevent the further formation of nitrosamines. Any suitable radiation may be used such as, but not limited to, microwaves, gamma rays or electron beams. U.S. Pat. No. 6,311,695, discussed above, describes the use of electron beams.

[0014] In some embodiments, the tobacco material may be partially or wholly denicotinized. For example, about 5 wt. % or more (e.g., about 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 wt. %) of nicotine present in the tobacco material may be removed. Methods for denicotinizing tobacco materials are known to persons skilled in the art, as described, e.g., in U.S. Pat. No. 5,119,835, the disclosure of which is hereby incorporated by reference. In some embodiments, for example, tobacco material may be enriched with anatabine (or a salt or derivative thereof) to partially or wholly replace any nicotine that is removed from the tobacco material.

Anatabine and Anatabine Derivatives

[0015] In some aspects, tobacco material is enriched with a compound of Formula I, or a pharmaceutically acceptable salt thereof:
wherein:

- R represents hydrogen or C₁-C₉ alkyl;
- R' represents hydrogen or C₁-C₇ alkyl; and
- X represents halogen or C₁-C₉ alkyl.

In some embodiments,

- R represents hydrogen or C₁-C₉ alkyl;
- R' represents hydrogen or C₁-C₇ alkyl; and
- X represents halogen or C₁-C₉ alkyl.

The dotted line within the piperidine ring represents a carbon/carbon or carbon/nitrogen double bond within that ring, or two conjugated double bonds within that ring. One of the two conjugated double bonds can be a carbon/nitrogen double bond, or both of the conjugated double bonds can be carbon/carbon double bonds. When a carbon/nitrogen double bond is present, R is absent; and either (i) "a" is an integer ranging from 1-4, usually 1-2, and "b" is an integer ranging from 0-8, usually 0-4; or (ii) "a" is an integer ranging from 0-4, usually 0-2, and "b" is an integer ranging from 1-8, usually 1-4. When a carbon/nitrogen double bond is not present, R is present; "a" is an integer ranging from 0-4, usually 1-2; and "b" is an integer ranging from 0-8, usually 0-4 or 1-2. The term "alkyl," as used herein, encompasses both straight chain and branched alkyl. The term "halogen" encompasses fluorine (F), chlorine (Cl), bromine (Br), and iodine (I).

Table I below illustrates non-limiting examples of anatabine derivatives falling within Formula I:

<table>
<thead>
<tr>
<th>R</th>
<th>R' (position)</th>
<th>X (position)</th>
<th>a</th>
<th>b</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>CH₃ (3)</td>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>CH₃</td>
<td>—</td>
<td>CH₃ (5)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>CH₂CH₃</td>
<td>CH₂CH₃ (4)</td>
<td>—</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>CH₂</td>
<td>CH₂ (2)</td>
<td>—</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>CH₂CH₂</td>
<td>CH₂ (4)</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CH₃</td>
<td>CH₂CH₂ (5)</td>
<td></td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Compounds of Formula I may be present in the form of a racemic mixture or, in some cases, as an isolated enantiomer, such as illustrated below in Formula IA.

An example of a compound of Formula I is anatabine. Compounds of Formula I are sometimes referred to herein as "anatabine or derivatives thereof." The chemical structure of anatabine (1,2,3,6-tetrahydro[2,3]bipyridinyl) is illustrated below, in which * designates an asymmetric carbon.

Anatabine exists in tobacco and certain foods, including green tomatoes, green potatoes, ripe red peppers, tomatillos, and sundried tomatoes, as a racemic mixture of R-(+)-anatabine and S-(-)-anatabine, whose structures are illustrated below.

An example of a compound of Formula IA is S-(-)-anatabine. In some embodiments anatabine is provided in the form of a pharmaceutically acceptable (or food grade) salt of anatabine. Anatabine may be adsorbed on a cation exchange resin such as polyethacrilic acid (Amberlite IRP64 or Purolite C115HMR), as described in U.S. Pat. No. 3,901,248, the disclosure of which is hereby incorporated by reference in its entirety. Such cation exchange resins have been used commercially, for example, in nicotine replacement therapy, e.g., nicotine polacrilex.

Unless otherwise clear from context, the term “anatabine” as used herein refers collectively to anatabine, either as a racemic mixture or an enantiomer, and pharmaceutically acceptable salts of either of them. In general, salts may provide improved chemical purity, stability, solubility, and/or bioavailability relative to anatabine in its native form. Non-limiting examples of possible anatabine salts are described in P. H. Stahl et al., Handbook of Pharmaceutical Salts: Properties, Selection and Use, Weinheim/Zürich:Wiley-VCH/VHCA, 2002, including salts of 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-hydroxymethanesulfonic acid, 2-oxoglutaric acid, 4-acetumidobenzoic acid, 4-aminosalicylic acid, acetic acid, adipic acid, ascorbic acid (L), aspartic acid (L), benzenesulfonic acid, benzoic acid, camphoric acid (+), camphor-10-sulfonic acid (+), capric acid (decanoic acid), caproic acid (hexanoic acid), caprylic acid (octanoic acid), carboxylic acid, cinnamic acid, citric acid, cyclameric acid, dodecylsulfate acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid (D), gluconic acid (D), glucoronic acid (D), glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, laetic acid.
(DL), lactobionic acid, lauric acid, maleic acid, malic acid (-L), malonic acid, mandelic acid (DL), methanesulfonic acid, naphtalene-1,5-disulfonic acid, naphtalene-2-sulfonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmic acid, pamoic acid, phosphoric acid, propionic acid, pyroglutamic acid (-L), salicylic acid, sebacic acid, stearic acid, succinic acid, sulfurous acid, tartaric acid (+L), thiocyanic acid, toluenesulfonic acid (p), and undecylenic acid.

[0030] Anatabine (and other compounds of Formula I) may be prepared synthetically, such as via a benzophenonetin pathway, as described in Puthiaparampel et al. U.S. Pat. No. 8,207,346, the disclosure of which is incorporated herein by reference in its entirety.

[0031] As an alternative to preparing anatabine synthetically, anatabine can be obtained by extraction from tobacco or other plants, such as members of the Solanaceae family, such as datura, mandrake, belladonna, capsicum, potato, nicotiana, eggplant, and petunia. For example, a tobacco extract may be prepared from cured tobacco stems, lamina, or both. In the extraction process, cured tobacco material is extracted with a solvent, typically water, ethanol, steam, or carbon dioxide. The resulting solution contains the soluble components of the tobacco, including anatabine. Anatabine may be purified from the other components of the tobacco using suitable techniques such as liquid chromatography. Other details of extracting anatabine from tobacco are described in Williams et al. U.S. Pat. No. 8,241,680, the disclosure of which is hereby incorporated by reference in its entirety.

[0032] As part of the purification process, tobacco material may be substantially denicotinized to remove a majority of other alkaloids such as nicotine, nornicotine, and anabasine. Denicotinizing is usually carried out prior to extraction of anatabine. Methods that may be used for denicotinizing tobacco materials are described, for example, in U.S. Pat. No. 5,119,835, the disclosure of which is hereby incorporated by reference. In general, tobacco alkaloids may be extracted from tobacco material with carbon dioxide under supercritical conditions. The tobacco alkaloids may then be separated from the carbon dioxide by dissolving an organic acid or a salt thereof, such as potassium mononitrate, in the carbon dioxide.

[0033] In some aspects, an isolated form of anatabine is used. An “isolated form of anatabine,” as used herein, refers to anatabine that either has been prepared synthetically or has been substantially separated from plant materials in which it occurs naturally. The isolated form of anatabine should have a very high purity (including enantiomeric purity in the case where an enantiomer is used). In the case of synthetic anatabine, for example, purity refers to the ratio of the weight of anatabine to the weight of the end reaction product. In the case of isolating anatabine from plant material, for example, purity refers to the ratio of the weight of anatabine to the total weight of the anatabine-containing extract. Usually, the level of purity is at least about 95%, more usually at least about 96%, about 97%, about 98%, or higher. For example, the level of purity may be about 98.5%, 99.0%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, or higher.

[0034] The amount of anatabine, or salt or derivative thereof, added to the tobacco material may vary over a wide range, but often ranges from about 0.1 wt. % to about 10 wt. % above the anatabine content in the tobacco material, based on the total weight of the tobacco material. For example, anatabine or a salt or derivative thereof may be added to the tobacco material in an amount of about 0.2 wt. % to about 9 wt. % above the anatabine content in the tobacco material, or from about 0.3 wt. % to about 8 wt. %, from about 0.5 wt. % to about 6 wt. %, from about 0.7 wt. % to about 5 wt. %, from about 0.8 wt. % to about 4 wt. %, or from about 1 wt. % to about 3 wt. % above the anatabine content in the tobacco material, based on the total weight of the tobacco material.

[0035] By way of example and without limitation, the amount of anatabine, or salt or derivative thereof, added to the tobacco material per single unit of tobacco product may range from about 0.01 mg to about 2 g, from about 0.1 mg to about 1 g, from about 0.5 mg to about 1 g, from about 1 mg to about 500 mg, from about 2 mg to about 400 mg, from about 3 mg to about 300 mg, from about 4 mg to about 250 mg, from about 5 mg to about 200 mg, from about 6 mg to about 150 mg, from about 7 mg to about 100 mg, from about 8 mg to about 75 mg, from about 9 mg to about 50 mg, or from about 10 mg to about 40 mg.

[0036] In addition to being enriched with anatabine or a salt or derivative thereof as described herein, the tobacco material may also be enriched with other components, including other minor tobacco alkaloids such as nornicotine and anabasine. Such other components may be added, for example, in the amounts listed above for anatabine and its salts and derivatives.

[0037] Any suitable technique may be used for adding anatabine or a salt or derivative thereof (and optionally other alkaloids) to the tobacco material, depending on such factors as the state of the tobacco material and the type of tobacco product ultimately prepared. For example, during a process of preparing cigarettes, anatabine may be provided in a solvent, such as ethanol, and sprayed onto or otherwise mixed with tobacco material in whole leaf or shredded leaf form. When the tobacco material is in the form of a powder, such as when preparing dissolvable smokeless tobacco products, anatabine may be dry blended with other ingredients prior to compressing the powder into a solid bit. Alternatively, anatabine may be added to a liquid tobacco extract which is subsequently dried into a powder used to prepare a smokeless tobacco product.

**Additives**

[0038] The tobacco product may also contain other ingredients such as sweeteners, flavorants, coloring agents, fillers, and the like. Non-limiting examples of flavorants include eucalyptus, propolis, spearmint, menthol, wintergreen, and the like. Examples of citrus flavors are described in U.S. Pat. No. 4,832,059 (Lorillard); and examples of carbocyclic alkyl ethers are described in U.S. Pat. No. 5,414,142 (Lorillard), the disclosures of each of which are incorporated by reference in their entirety.

[0039] Typically, the amounts of individual additives ranges from 0 wt. % to about 15 wt. %, often from about 0.5 wt. % to about 10 wt. %, and usually from about 1 wt. % to about 5 wt. %, based on the total weight of the tobacco material.

**Tobacco Products**

[0040] The enriched tobacco material may be formed into a tobacco product using techniques well known to those skilled in the art. Non-limiting examples of smoking products include cigarettes, cigars, pipe tobacco, and the like. Non-limiting examples of smokeless products include chewing
tobacco, snuff, snus, tobacco-containing gum or lozenges, dissolvable powdered tobacco-based smokeless products, and the like.

[0041] Methods for preparing cigarettes, cigars, pipe tobacco, chewing tobacco, and the like are well known to persons skilled in the art, and the details of such processes form no part of the present invention.

[0042] In one embodiment, a smokeless tobacco product comprises a solid bit prepared by compressing powdered tobacco. The powdered tobacco may be produced from cured tobacco stems, lamina, or both. Cured tobacco material may be pulverized, e.g., milled, to form a powdered tobacco. Alternatively, an extract of the tobacco material may be dried to form a powder. The solid bit may contain, for example, from about 10 wt. % to about 80 wt. % of powdered tobacco, often from about 25 wt. % to about 75 wt. %.

[0043] In the extraction process, cured tobacco material is typically extracted with a solvent, typically water or steam. The resulting solution contains the water-soluble components of the tobacco, including nicotine. The solution is then dried and ground, as needed, to form a powdered tobacco. Prior to forming the bit, the powdered tobacco may be processed to form larger particles, such as by granulation or by rolling and grinding. Such processes provide particles, which are more readily formed into bits, and form bits, which do not disintegrate during handling and in the package. Moreover, larger particles are easier to handle than the smaller particles and are less prone to form "dust" associated with small powder particles.

[0044] The bit may be processed and packaged by any suitable means. The bit is placed in the mouth and allowed to dissolve, releasing the nicotine and other tobacco components. Any material that does not dissolve is easily swallowed along with the dissolved components. That is, for example, a bit formed from whole leaf pulverized tobacco, will disintegrate and dissolve in the mouth, such that any insoluble components are in the form of very small particles that are easily swallowed with the saliva.

[0045] Other details of preparing dissolvable smokeless tobacco products are described in Williams U.S. Pat. No. 6,834,654, the disclosure of which is hereby incorporated by reference in its entirety.

EXAMPLE 1

[0046] This example illustrates preparing a dissolvable smokeless tobacco product containing powdered tobacco enriched with anatabine citrate.

[0047] Virginia flue tobacco is pulverized into a powder and spray-dried together with flavors and other components in a fluidized bed granulator, as described in Example 1 of U.S. Pat. No. 6,834,654. Synthetic anatabine citrate is added to the fluidized bed granulator together with the other ingredients. The resulting powder is compressed into 600 mg solid bits each containing about 0.4 mg of anatabine from anatabine citrate in addition to approximately 0.3 mg anatabine from the Virginia flue tobacco.

EXAMPLE 2

[0048] This example illustrates preparing cigarettes containing tobacco material enriched with anatabine citrate. A solution of synthetic anatabine citrate is sprayed onto shredded Virginia flue tobacco together with menthol and other flavors. Cigarettes are formed from the tobacco material using conventional techniques. Anatabine citrate is added in an amount equivalent to 0.6 mg of anatabine per cigarette, in excess of the quantity of anatabine present from the Virginia flue tobacco (approximately 0.3 mg per cigarette). While the invention has been described with respect to specific examples including presently preferred modes of carrying out the invention, those skilled in the art will appreciate that there are numerous variations and permutations of the above described systems and techniques that fall within the spirit and scope of the invention as set forth in the appended claims.

What is claimed is:

1. A tobacco product comprising tobacco material enriched with a compound of Formula I or a salt thereof:

\[ \text{Formula I} \]

wherein:
- \( R \) represents hydrogen or \( C_1-C_5 \) alkyl;
- \( R' \) represents hydrogen or \( C_1-C_5 \) alkyl;
- \( X \) represents halogen or \( C_1-C_5 \) alkyl;
- the dotted line within the piperidine ring represents a carbon/carbon or carbon/nitrogen double bond with that ring, or two conjugated double bonds within that ring; wherein one of the two conjugated double bonds is a carbon/nitrogen double bond, or both of the conjugated double bonds are carbon/carbon double bonds; wherein when a carbon/nitrogen double bond is present, \( R \) is absent; and either (i) \( "a" \) is an integer ranging from 1-4 and \( "b" \) is an integer ranging from 0-8; or (ii) \( "a" \) is an integer ranging from 0-4 and \( "b" \) is an integer ranging from 1-8; and wherein when a carbon/nitrogen double bond is not present, \( R \) is present; \( "a" \) is an integer ranging from 0-4; and \( "b" \) is an integer ranging from 0-8.

2. The tobacco product of claim 1 wherein the tobacco material has a collective content of \( N\)-nitrosornornicotine (NNN), \( 4-(N\text{-nitrosomethylamino})-1-(3\text{-pyridyl})-1\text{-butanone (NNK)}, \) \( N\text{-nitrosoanatabine (NAT)} \) and \( N\text{-nitrosoanabasine (NAB)} \) which is 0.3 mg/g or less.

3. The tobacco product of claim 1 wherein the collective content is 0.2 mg/g or less.

4. The tobacco product of claim 4 wherein the collective content is 0.1 mg/g or less.

5. A tobacco product of claim 1 wherein the content of \( 4-(N\text{-nitrosomethylamino})-1-(3\text{-pyridyl})-1\text{-butanone (NNK)} \) is 0.05 mg/g or less.

6. The tobacco product of claim 5 wherein the content of \( 4-(N\text{-nitrosomethylamino})-1-(3\text{-pyridyl})-1\text{-butanone (NNK)} \) is 0.01 mg/g or less.

7. The tobacco product of claim 1 wherein the tobacco material consists essentially of Virginia flue cured tobacco.

8. The tobacco product of claim 1 wherein the compound of Formula I is anatabine or a salt thereof.

9. The tobacco product of claim 8 wherein anatabine or a salt thereof is present in an amount of about 0.1 wt. % to about 10 wt. % above the anatabine content in the tobacco material, based on the total weight of the tobacco material.
10. The tobacco product of claim 9, wherein anatabine or a salt thereof is present in an amount of about 0.5 wt. % to about 5 wt. % above the anatabine content in the tobacco material, based on the total weight of the tobacco material.

11. The tobacco product of claim 1 which is a smoking product selected from the group consisting of cigarettes, cigars, and pipe tobacco.

12. The tobacco product of claim 11 which is a cigarette.

13. The tobacco product of claim 1 which is a smokeless product selected from the group consisting of chewing tobacco, snuff, snus, tobacco-containing gum or lozenges, and dissolvable powdered tobacco-based smokeless products.

14. The tobacco product of claim 13 which is a dissolvable powdered tobacco-based smokeless product.

15. The tobacco product of claim 1 wherein the tobacco material is partially denicotinized.

16. The tobacco product of claim 1 wherein the tobacco material is wholly denicotinized.

17. The tobacco product of claim 1 wherein the tobacco material is further enriched with a compound selected from the group consisting of nornicotine, anabasine, and combinations thereof.

* * * * *