

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: CHADEAYNE; Andrew R. Confirmation No.: 5317

Serial No.: 17/627,988 Group No.:

Filing or 371(c) Date: July 23, 2020 Examiner:

Entitled: Compositions Containing Toad Secretion Compounds

THIRD-PARTY PRE-ISSUANCE SUBMISSION

Examiner:

The following documents, which are also identified in the Form PTO/SB/429 filed herewith, are submitted for your consideration as being of potential relevance to the examination of the present application:

1. UTHAUG (2016) "A single inhalation of vapor from dried toad secretion containing 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting is related to sustained enhancement of satisfaction with life, mindfulness-related capacities, and a decrement of psychopathological symptoms" *Psychopharmacology*. 263:2653-2666
2. Int'l Pat. App. Pub. No. WO/2019/081764 "COMBINATION PRODUCT FOR THE TREATMENT OF NEUROLOGICAL AND/OR PSYCHIATRIC DISORDERS" (Published May 2, 2019)
3. DAI (2016) "A New Indole Alkaloid from the Toad Venom of *Bufo bufo gargarizans*" *Molecules*. 21(3):1-5
4. QI (2014) "Toad Glandular Secretions and Skin Extractions as Anti-Inflammatory and Anticancer Agents" *Evidence-Based Complementary and Alternative Medicine*. 2014:1-9
5. QI (2018) "The Development of Toad Toxins as Potential Therapeutic Agents" *Toxins*. 10(8):1-14
6. RODRIGUEZ (2017) "Toxins and pharmacologically active compounds from species of the family Bufonidae (Amphibia, Anura)" *Journal of Ethnopharmacology*. 198:235-254
7. ROSTELATO-FERREIRA (2014) "Presynaptic neuromuscular action of a methanolic extract from the venom of *Rhinella schneideri* toad" *Journal of Venomous Animals and Toxins including Tropical Diseases*. 20:1-5
8. SHEN (2010) "Psychedelic 5-Methoxy-N,N-dimethyltryptamine: Metabolism, Pharmacokinetics, Drug Interactions, and Pharmacological Actions" *Current Drug Metabolism*. 11(8):659-666
9. DAVIS (2018) "The epidemiology of 5-Methoxy-N,N-Dimethyltryptamine (5-MeO-DMT) use: Benefits, consequences, patterns of use, subjective effects, and reasons for consumption" *Journal of Psychopharmacology*. 32(7):779-792

Attached hereto is a claim chart providing a concise description of the relevance of each reference in the document list to the elements of the presently pending claims.

U.S.S.N. 17/627,988 Pending Claims	References																																																																								
<p>1. A composition comprising two purified toad secretion tryptamines chosen from the following 5-MeO-DMT, 5-MeO-NMT, 5-Methoxytryptamine, bufobutanoic Acid, bufobutarginine, bufoserotonin A, bufoserotonin B, bufoserotonin C, bufotenidine, bufotenin, bufotenin Oxide, bufotenine-O-Sulphate, bufoviridine, dET, dMT, n-Acetylserotonin, n'-Formylserotonin, n-Methylserotonin, o-Methylbufoviridine, serotonin, tryptamine, and bufopyramide or the salts of these toad secretion tryptamines.</p>	<p>1. UTHAUG (2016) “A single inhalation of vapor from dried toad secretion containing 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting is related to sustained enhancement of satisfaction with life, mindfulness-related capacities, and a decrement of psychopathological symptoms” <i>Psychopharmacology</i>. 263:2653-2666</p> <p>From page 2657</p> <p>Table 2 Overview of compound concentrations in milligrams or micrograms per 1 g of secretion) in samples of dried secretion from the <i>Bufo alvarius</i> toad</p> <table border="1" data-bbox="527 583 1258 730"> <thead> <tr> <th>Sample</th> <th>5-MeO-DMT [mg/g]</th> <th>Bufotenin [mg/g]</th> <th>DMT [mg/g]</th> <th>NMT [μg/g]</th> <th>DET [μg/g]</th> <th>NMe-5HT [mg/g]</th> <th>Bufogenin [mg/g]</th> <th>Bufotalidin [mg/g]</th> <th>5-MeO-Tryptophol [μg/g]</th> <th>5-HO-Tryptophol [μg/g]</th> <th>5-MIAA [μg/g]</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>265.9</td> <td>0.642</td> <td>0.016</td> <td>ND</td> <td><LOQ</td> <td>0.028</td> <td><LOQ</td> <td><LOQ</td> <td>0.696</td> <td>ND</td> <td>ND</td> </tr> <tr> <td>2</td> <td>203.6</td> <td>0.600</td> <td>0.032</td> <td>ND</td> <td><LOQ</td> <td>0.014</td> <td>0.005</td> <td><LOQ</td> <td>2.357</td> <td>ND</td> <td>ND</td> </tr> <tr> <td>3</td> <td>274.3</td> <td>1.179</td> <td>0.029</td> <td>ND</td> <td><LOQ</td> <td>0.050</td> <td>0.013</td> <td><LOQ</td> <td>1.307</td> <td>ND</td> <td>ND</td> </tr> <tr> <td>4</td> <td>283.3</td> <td>3.530</td> <td>0.022</td> <td>ND</td> <td><LOQ</td> <td>0.171</td> <td>0.011</td> <td><LOQ</td> <td>0.997</td> <td>ND</td> <td>ND</td> </tr> <tr> <td>5</td> <td>307.3</td> <td>1.436</td> <td>0.041</td> <td>ND</td> <td>0.415</td> <td>0.064</td> <td>0.008</td> <td><LOQ</td> <td>3.053</td> <td>ND</td> <td>ND</td> </tr> </tbody> </table> <p>ND not determined <LOQ under the limit of quantification</p> <p>2. Int'l Pat. App. Pub. No. WO/2019/081764 “COMBINATION PRODUCT FOR THE TREATMENT OF NEUROLOGICAL AND/OR PSYCHIATRIC DISORDERS” (Published May 2, 2019)</p> <p>From claim 3 “The combination product for use according to anyone of claims 1 -2 wherein the compound described by formula (I) is selected from the group consisting of N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, N,N-diethyltryptamine, N,N-dipropyltryptamine and N,N-diisopropyltryptamine.”</p> <p>From pages 16-17, lines 34-8 “The term "substantially pure" refers to any compound that has been separated from its surrounding environment and has been enriched in a sample. A compound is substantially pure if the compound made up at least 50, 55, 60, 70, 75, 85, 90 or 95 % of a sample at any point. Preferably, the compound made up at least 95 % of a sample at any point. The compound is substantially pure before it is mixed with other components such as another active ingredient or pharmaceutically acceptable carriers and/or diluents. Further, when the purity is measured in solution, the one or more solvents used are not included in the calculation of the purity of the compound in the sample. The purity may be measured through any common method known in the art. For example, the purity of the compound in the sample may be determined through high-performance liquid chromatography (HPLC). In a preferred embodiment, the purity of a substantially pure compound in a sample is determined through HPLC.”</p> <p>3. DAI (2016) “A New Indole Alkaloid from the Toad Venom of <i>Bufo bufo gargarizans</i>” <i>Molecules</i>. 21(3):1-5</p> <p>From abstract “A new indole alkaloid named bufobutarginine (1), along with three known bufotenines, namely, serotonin (2), bufotenidine (3), and</p>	Sample	5-MeO-DMT [mg/g]	Bufotenin [mg/g]	DMT [mg/g]	NMT [μ g/g]	DET [μ g/g]	NMe-5HT [mg/g]	Bufogenin [mg/g]	Bufotalidin [mg/g]	5-MeO-Tryptophol [μ g/g]	5-HO-Tryptophol [μ g/g]	5-MIAA [μ g/g]	1	265.9	0.642	0.016	ND	<LOQ	0.028	<LOQ	<LOQ	0.696	ND	ND	2	203.6	0.600	0.032	ND	<LOQ	0.014	0.005	<LOQ	2.357	ND	ND	3	274.3	1.179	0.029	ND	<LOQ	0.050	0.013	<LOQ	1.307	ND	ND	4	283.3	3.530	0.022	ND	<LOQ	0.171	0.011	<LOQ	0.997	ND	ND	5	307.3	1.436	0.041	ND	0.415	0.064	0.008	<LOQ	3.053	ND	ND
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bufotenine (4), were isolated from the water extract of toad venom. Their structures were elucidated by spectral methods.”

4. QI (2014) “Toad Glandular Secretions and Skin Extractions as Anti-Inflammatory and Anticancer Agents” Evidence-Based Complementary and Alternative Medicine. 2014:1-9

From **page 4**

Table 1

Chemical properties of Chansu and Huachansu.

Objective	Method	Compounds	Reference
Chansu	HPLC and LC-DAD-MS/MS	gamabufotalin arenobufagin telocinobufagin bufotalin cinobufotalin bufalin cinobufagin resibufogenin	[69]
Chansu	High-speed counter-current chromatography	arenobufagin telocinobufagin bufotalin cinobufotalin bufalin resibufogenin cinobufagin	[70]

Chansu	HPLC/APCI-MS/MS	bufalin arenobufagin bufotalin telocinobufagin ψ -Bufarenogin bufotalinin cinobufotalin gamabufotalin	[71]
Huachansu	HPLC	bufalin, cinobufagin resibufogenin	[72]
Huachansu	HPLC-QqQ MS	bufalin cinobufagin recinobufagin cinobufotalin telocinobufagin, gamabufotalin arenobufagin, bufotalin	[73]

5. QI (2018) “The Development of Toad Toxins as Potential Therapeutic Agents” Toxins. 10(8):1-14

From pages 2-3

Table 1. The identification of significant bioactive compounds in different species of toads.

Name	Classification	Formula	Species of Toad			
			<i>B. b. gargarizans</i>	<i>B. marinus</i>	<i>B. alvarius</i>	<i>B. melanosticus</i>
Bufalin	Bufadienolides	C ₂₄ H ₃₄ O ₄	+	+	+	+
Cinobufagin	Bufadienolides	C ₂₆ H ₃₄ O ₆	+	–	–	–
Arenobufagin	Bufadienolides	C ₂₄ H ₃₂ O ₆	+	+	+	+
Gamabufotalin	Bufadienolides	C ₂₄ H ₃₄ O ₅	+	–	+	+
Telocinobufagin	Bufadienolides	C ₂₄ H ₃₄ O ₅	+	+	+	+
Marinobufagin	Bufadienolides	C ₂₄ H ₃₂ O ₅	+	+	+	+

Table 1. Cont.

Name	Classification	Formula	Species of Toad			
			<i>B. b. gargarizans</i>	<i>B. marinus</i>	<i>B. alvarius</i>	<i>B. melanosticus</i>
Bufotenine	Indolealkylamine	C ₁₂ H ₁₆ N ₂ O	+	+	+	+
Bufotenidine	Indolealkylamine	C ₁₃ H ₁₈ N ₂ O	+	–	–	–
Dehydrobufotenine	Indolealkylamine	C ₁₂ H ₁₄ N ₂ O	+	+	–	+
Bufothionine	Indolealkylamine	C ₁₂ H ₁₅ N ₂ O ₃ S	+	+	+	–
5-methoxytryptamine	Indolealkylamine	C ₁₁ H ₁₄ N ₂ O	–	+	+	–
Indole-3-acetic acid	Indolealkylamine	C ₁₀ H ₉ NO ₂	–	–	+	–

+: Present; –: Not present.

2. A composition of claim 1, wherein the molar ratio of the first purified toad secretion tryptamine to the second purified toad secretion tryptamine in the composition is from about 0.1:100 to about 100:0.1, from about 1:100 to about 100:1, from about 1:50 to about 50:1, from about 1:25 to about 25:1, from about 1:20 to about 20:1, from about 1:10 to about 10:1, from about 1:5 to about 5:1, from about 1:2 to about 2:1, or about 1:1.

1. UTHAUG (2016) “A single inhalation of vapor from dried toad secretion containing 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting is related to sustained enhancement of satisfaction with life, mindfulness-related capacities, and a decrement of psychopathological symptoms” *Psychopharmacology*. 263:2653-2666

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3. A formulation comprising a composition of claim 1 and an excipient.

4. QI (2014) “Toad Glandular Secretions and Skin Extractions as Anti-Inflammatory and Anticancer Agents” *Evidence-Based Complementary and Alternative Medicine*. 2014:1-9

From **page 3** “One of the most widely used commercial preparation is Huachansu (Cinobufacini), which is a **sterilized hot water extract of dried toad skin**”

2. Int’l Pat. App. Pub. No. WO/2019/081764 “COMBINATION PRODUCT FOR THE TREATMENT OF NEUROLOGICAL AND/OR PSYCHIATRIC DISORDERS” (Published May 2, 2019)

From **claim 6** “The combination product for use according to any one of claims 1 -5 wherein the combination product is a **composition**, or the compound described by formula (I) and the 5-HT_{2A} receptor antagonist are physically separated.”

5. RODRIGUEZ (2017) “Toxins and pharmacologically active compounds from species of the family Bufonidae (Amphibia, Anura)” *Journal of Ethnopharmacology*. 198:235-254

From **chart 1, page 237** : Preparation of the Remedy: “**Toad ashes mixed with rancid fat**”; “**Ashes of a toad (the biggest that can be found) mixed with a**

half ounce of ashes from verbena, romero leaves, and serpentaria root“; “crushed toad skin mixed with garlic in lukewarm water”

2. Int’l Pat. App. Pub. No. WO/2019/081764 “COMBINATION PRODUCT FOR THE TREATMENT OF NEUROLOGICAL AND/OR PSYCHIATRIC DISORDERS” (Published May 2, 2019)

From **page 16, lines 9-28** “As used herein, "**pharmaceutically acceptable carrier**" or "pharmaceutically acceptable diluent" means any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed and, without limiting the scope of the present invention, include: additional buffering agents; preservatives; co-solvents; antioxidants, including ascorbic acid and methionine; chelating agents such as EDTA; metal complexes (e.g., Zn-protein complexes); biodegradable polymers, such as polyesters; salt-forming counterions, such as sodium, polyhydric sugar alcohols; amino acids, such as alanine, glycine, glutamine, asparagine, histidine, arginine, lysine, ornithine, leucine, 2-phenylalanine, glutamic acid, and threonine; organic sugars or sugar alcohols, such as lactitol, stachyose, mannose, sorbose, xylose, ribose, ribitol, myoinisitol, myoinisitol, galactose, galactitol, glycerol, cyclitols (e.g., inositol), polyethylene glycol; sulfur containing reducing agents, such as urea, glutathione, thiocetic acid, sodium thioglycolate, thioglycerol, [alpha]-monothioglycerol, and sodium thio sulfate; low molecular weight proteins, such as human serum albumin, bovine serum albumin, gelatin, or other immunoglobulins; and hydrophilic polymers, such as polyvinylpyrrolidone. Other pharmaceutically acceptable carriers, **excipients**, or stabilizers, such as those described in Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980) may also be included.”

4. A pharmaceutical formulation comprising a composition of claim 1 and a pharmaceutically acceptable excipient, wherein the first purified toad secretion tryptamine and the second purified toad secretion tryptamine are each present in a therapeutically effective amount.

1. UTHAUG (2016) “A single inhalation of vapor from dried toad secretion containing 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting is related to sustained enhancement of satisfaction with life, mindfulness-related capacities, and a decrement of psychopathological symptoms” Psychopharmacology. 263:2653-2666

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Table 2 Overview of compound concentrations in milligrams or micrograms per 1 g of secretion) in samples of dried secretion from the *Bufo alvarius* toad

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<p>5. A pharmaceutical composition of claim 4 further comprising a therapeutically effective amount of a serotonergic drug, a purified psilocybin derivative, a purified cannabinoid, or a purified terpene.</p>	<p>2. Int'l Pat. App. Pub. No. WO/2019/081764 "COMBINATION PRODUCT FOR THE TREATMENT OF NEUROLOGICAL AND/OR PSYCHIATRIC DISORDERS" (Published May 2, 2019)</p> <p>From claim 4 "The combination product for use according to any one of claims 1 -3 wherein the 5-HT2A receptor antagonist is selected from the group consisting of Methiothepin, Ritanserin, Ketanserin, Flibanserin, Methysergide, Trazodone, Nefazodone, Cinitapride, Cyproheptadine, Brexpiprazole, Cariprazine, Agomelatine, Pimavanserin, Eplivanserin, Volinanserin, Altanserin, Setoperone, LY-367,265, 1 -(1 -Naphthyl)piperazine, SB 206553, Pirenperone, SB-215505, Metergoline, Deramciclane, Amperozide, Glemanserin, 5-MeO-NBpBrT, Adatanserin, AM DA, Cinanserin, Fananserin, Ifersanserin, AC-90179, LY86057, GSK-215083, Cyamemazine, Mesulergine, BF-1 , LY215840, Sergolexole, Spiramide, LY53857, Amesergide, LY108742, Pipamperone, LY314228 and 5-I- 91 150."</p>																																																																								
<p>6. A pharmaceutical composition of claim 4, wherein the therapeutically effective amount of each tryptamine separately ranges from about 0.5 mg-about 200 mg, about 1 mg-about 100 mg, about 2 mg-about 50 mg, about 5 mg-about 25 mg, or 25 mg.</p>	<p>1. UTHAUG (2016) "A single inhalation of vapor from dried toad secretion containing 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting is related to sustained enhancement of satisfaction with life, mindfulness-related capacities, and a decrement of psychopathological symptoms" <i>Psychopharmacology</i>. 263:2653-2666</p> <p>From page 2657</p> <table border="1" data-bbox="527 934 1258 1134"> <caption>Table 2 Overview of compound concentrations in milligrams or micrograms per 1 g of secretion) in samples of dried secretion from the <i>Bufo alvarius</i> toad</caption> <thead> <tr> <th>Sample</th> <th>5-MeO-DMT [mg/g]</th> <th>Bufofenin [mg/g]</th> <th>DMT [mg/g]</th> <th>NMT [μg/g]</th> <th>DET [μg/g]</th> <th>NMe-5HT [mg/g]</th> <th>Bufofenin [mg/g]</th> <th>Bufofenidin [mg/g]</th> <th>5-MeO-Tryptophol [μg/g]</th> <th>5-HO-Tryptophol [μg/g]</th> <th>5-MIAA [μg/g]</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>265.9</td> <td>0.642</td> <td>0.016</td> <td>ND</td> <td><LOQ</td> <td>0.028</td> <td><LOQ</td> <td><LOQ</td> <td>0.696</td> <td>ND</td> <td>ND</td> </tr> <tr> <td>2</td> <td>203.6</td> <td>0.600</td> <td>0.032</td> <td>ND</td> <td><LOQ</td> <td>0.014</td> <td>0.005</td> <td><LOQ</td> <td>2.357</td> <td>ND</td> <td>ND</td> </tr> <tr> <td>3</td> <td>274.3</td> <td>1.179</td> <td>0.029</td> <td>ND</td> <td><LOQ</td> <td>0.050</td> <td>0.013</td> <td><LOQ</td> <td>1.307</td> <td>ND</td> <td>ND</td> </tr> <tr> <td>4</td> <td>283.3</td> <td>3.530</td> <td>0.022</td> <td>ND</td> <td><LOQ</td> <td>0.171</td> <td>0.011</td> <td><LOQ</td> <td>0.997</td> <td>ND</td> <td>ND</td> </tr> <tr> <td>5</td> <td>307.3</td> <td>1.436</td> <td>0.041</td> <td>ND</td> <td>0.415</td> <td>0.064</td> <td>0.008</td> <td><LOQ</td> <td>3.053</td> <td>ND</td> <td>ND</td> </tr> </tbody> </table> <p>ND not determined < LOQ under the limit of quantification</p> <p>From page 2656 "Some facilitators reported having administered around 20–30 mg of dried toad secretion, while others reported to administer up to 100–120 mg."</p>	Sample	5-MeO-DMT [mg/g]	Bufofenin [mg/g]	DMT [mg/g]	NMT [μ g/g]	DET [μ g/g]	NMe-5HT [mg/g]	Bufofenin [mg/g]	Bufofenidin [mg/g]	5-MeO-Tryptophol [μ g/g]	5-HO-Tryptophol [μ g/g]	5-MIAA [μ g/g]	1	265.9	0.642	0.016	ND	<LOQ	0.028	<LOQ	<LOQ	0.696	ND	ND	2	203.6	0.600	0.032	ND	<LOQ	0.014	0.005	<LOQ	2.357	ND	ND	3	274.3	1.179	0.029	ND	<LOQ	0.050	0.013	<LOQ	1.307	ND	ND	4	283.3	3.530	0.022	ND	<LOQ	0.171	0.011	<LOQ	0.997	ND	ND	5	307.3	1.436	0.041	ND	0.415	0.064	0.008	<LOQ	3.053	ND	ND
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<p>9. A method of treating a psychological disorder, a compulsive disorder, or a depressive disorder comprising the step of administering to a person in need thereof an effective dose of a composition of claim 1.</p>	<p>1. UTHAUG (2016) “A single inhalation of vapor from dried toad secretion containing 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting is related to sustained enhancement of satisfaction with life, mindfulness-related capacities, and a decrement of psychopathological symptoms” <i>Psychopharmacology</i>. 263:2653-2666</p> <p>From page 2659: “Mixed model analysis revealed the main effects of session on depression ($F_{2,55.943} = 4.348$; $p = 0.018$), anxiety ($F_{2,55.033} = 8.875$; $p < 0.001$), and stress ($F_{2,51.874} = 6.225$; $p = 0.004$), the three subscales of the DASS-21. Separate contrast revealed that subjective ratings of depression, anxiety, and stress decreased within 24 h following the inhalation of the vapor from dried toad secretion containing 5-MeO-DMT, but failed to reach significance until 4 weeks later ($p = 0.015$, Hedges”</p> <p>9. DAVIS (2018) “The epidemiology of 5-Methoxy-N,N-Dimethyltryptamine (5-MeO-DMT) use: Benefits, consequences, patterns of use, subjective effects, and reasons for consumption” <i>Journal of Psychopharmacology</i>. 32(7):1-29</p> <p>From page 29</p>

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Condition	% had condition ^a	% better ^b	% same ^b	% worsened ^b
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Asthma	12	24	73	4
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Forgetfulness	28	27	69	4
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Chronic anger	21	76	20	4
Eating disorder	10	39	59	2
Bipolar disorder	8	50	47	3
PTSD	21	79	18	3
ADHD	22	35	61	4
Autism	4	48	52	0
OCD	11	53	37	10
Alcoholism or hazardous drinking	22	66	31	3
Drug use disorder	33	60	35	5

Abbreviations: PTSD = Posttraumatic Stress Disorder, ADHD = Attention Deficit Hyperactivity Disorder, OCD = Obsessive Compulsive Disorder

^aProportion is out of the total sample (n range from 476-490)

^bOnly including responses from those who endorsed having the condition

5. QI (2018) “The Development of Toad Toxins as Potential Therapeutic Agents” *Toxins*. 10(8):1-14

From **page 7**: “Recently, IAAs in toad toxins are considered as potential therapeutic compounds in developing new agents for treating several **neurologic disorders**, such as schizophrenia, **depression**, anxiety, **obsessive–compulsive disorders**, and chronic pain conditions, due to their potential 5-HT2A receptor selectivity in the CNS.”

2. Int’l Pat. App. Pub. No. WO/2019/081764 “COMBINATION PRODUCT FOR THE TREATMENT OF NEUROLOGICAL AND/OR PSYCHIATRIC DISORDERS” (Published May 2, 2019)

From **claim 9** “The combination product according to anyone of claims 2-8 for use in the treatment and/or prevention of a **disorder** selected from the group consisting of acquired brain injury, ataxia, brain tumor, dementia, dystonia, epilepsy, functional and dissociative neurological symptoms, meningitis, motor neuron disease, multiple sclerosis, muscular dystrophy, myalgic encephalomyelitis, Parkinson's disease, progressive supranuclear palsy, Huntington's disease, Alzheimer's disease, fronto-temporal dementia, vascular dementia, cognitive decline associated with aging, spina bifida, hydrocephalus, spinal injury, stroke, Tourette syndrome, transverse myelitis, panic disorder, agoraphobia, social anxiety disorder, phobias, post-traumatic stress disorder, obsessive compulsive disorder, generalized anxiety disorder, bipolar disorder, depression, anorexia nervosa, binge eating disorder, bulimia nervosa, psychosis, schizophrenia, substance addiction and personality disorders.”

10. A method of treating a psychological disorder, a compulsive disorder, or a

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depressive disorder comprising the step of administering to a person in need thereof a pharmaceutical formulation of claim 4.

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Abbreviations: PTSD = Posttraumatic Stress Disorder, ADHD = Attention Deficit Hyperactivity Disorder, OCD = Obsessive Compulsive Disorder

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11. A formulation comprising a composition of claim 2 and an excipient.

5. QI (2014) “Toad Glandular Secretions and Skin Extractions as Anti-Inflammatory and Anticancer Agents” *Evidence-Based Complementary and Alternative Medicine*. 2014:1-9

From **page 3** “One of the most widely used commercial preparation is Huachansu (Cinobufacini), which is a **sterilized hot water extract of dried toad skin**”

2. Int'l Pat. App. Pub. No. WO/2019/081764 "COMBINATION PRODUCT FOR THE TREATMENT OF NEUROLOGICAL AND/OR PSYCHIATRIC DISORDERS" (Published May 2, 2019)

From **claim 6** "The combination product for use according to any one of claims 1 -5 wherein the combination product is a **composition**, or the compound described by formula (I) and the 5-HT2A receptor antagonist are physically separated."

From **page 16, lines 9-28** "As used herein, "**pharmaceutically acceptable carrier**" or "pharmaceutically acceptable diluent" means any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed and, without limiting the scope of the present invention, include: additional buffering agents; preservatives; co-solvents; antioxidants, including ascorbic acid and methionine; chelating agents such as EDTA; metal complexes (e.g., Zn-protein complexes); biodegradable polymers, such as polyesters; salt-forming counterions, such as sodium, polyhydric sugar alcohols; amino acids, such as alanine, glycine, glutamine, asparagine, histidine, arginine, lysine, ornithine, leucine, 2-phenylalanine, glutamic acid, and threonine; organic sugars or sugar alcohols, such as lactitol, stachyose, mannose, sorbose, xylose, ribose, ribitol, myoinisitol, myoinisitol, galactose, galactitol, glycerol, cyclitols (e.g., inositol), polyethylene glycol; sulfur containing reducing agents, such as urea, glutathione, thiocetic acid, sodium thioglycolate, thioglycerol, [alpha]-monothioglycerol, and sodium thio sulfate; low molecular weight proteins, such as human serum albumin, bovine serum albumin, gelatin, or other immunoglobulins; and hydrophilic polymers, such as polyvinylpyrrolidone. Other pharmaceutically acceptable carriers, **excipients**, or stabilizers, such as those described in Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980) may also be included."

12. A pharmaceutical formulation comprising a composition of claim 2 and a pharmaceutically acceptable excipient, wherein the first purified toad secretion tryptamine and the second purified toad secretion tryptamine are each present in a

1. UTHAUG (2016) "A single inhalation of vapor from dried toad secretion containing 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting is related to sustained enhancement of satisfaction with life, mindfulness-related capacities, and a decrement of psychopathological symptoms" Psychopharmacology. 263:2653-2666

From **page 2657**

Table 2 Overview of compound concentrations in milligrams or micrograms per 1 g of secretion) in samples of dried secretion from the *Bufo alvarius* toad

Sample	5-MeO-DMT [mg/g]	Bufofenin [mg/g]	DMT [mg/g]	NMT [µg/g]	DET [µg/g]	NMe-5HT [mg/g]	Bufofenin [mg/g]	Bufofenidin [mg/g]	5-MeO-Tryptophol [µg/g]	5-HO-Tryptophol [µg/g]	5-MIAA [µg/g]
1	265.9	0.642	0.016	ND	<LOQ	0.028	<LOQ	<LOQ	0.696	ND	ND
2	203.6	0.600	0.032	ND	<LOQ	0.014	0.005	<LOQ	2.357	ND	ND
3	274.3	1.179	0.029	ND	<LOQ	0.050	0.013	<LOQ	1.307	ND	ND
4	283.3	3.530	0.022	ND	<LOQ	0.171	0.011	<LOQ	0.997	ND	ND
5	307.3	1.436	0.041	ND	0.415	0.064	0.008	<LOQ	3.053	ND	ND

ND not determined
< LOQ under the limit of quantification

therapeutically effective amount.																																																																									
13. A pharmaceutical composition of claim 12 further comprising a therapeutically effective amount of a serotonergic drug, a purified psilocybin derivative, a purified cannabinoid, or a purified terpene.	<p>2. Int'l Pat. App. Pub. No. WO/2019/081764 "COMBINATION PRODUCT FOR THE TREATMENT OF NEUROLOGICAL AND/OR PSYCHIATRIC DISORDERS" (Published May 2, 2019)</p> <p>From claim 4 "The combination product for use according to any one of claims 1 -3 wherein the 5-HT2A receptor antagonist is selected from the group consisting of Methiothepin, Ritanserin, Ketanserin, Flibanserin, Methysergide, Trazodone, Nefazodone, Cinitapride, Cyproheptadine, Brexpiprazole, Cariprazine, Agomelatine, Pimavanserin, Eplivanserin, Volinanserin, Altanserin, Setoperone, LY-367,265, 1 -(1 -Naphthyl)piperazine, SB 206553, Pirenperone, SB-215505, Metergoline, Deramciclane, Amperozide, Glemanserin, 5-MeO-NBpBrT, Adatanserin, AM DA, Cinanserin, Fananserin, Ifersanserin, AC-90179, LY86057, GSK-215083, Cyamemazine, Mesulergine, BF-1 , LY215840, Sergolexole, Spiramide, LY53857, Amesergide, LY108742, Pipamperone, LY314228 and 5-I- 91 150."</p>																																																																								
14. A pharmaceutical composition of claim 5, wherein the therapeutically effective amount of each tryptamine separately ranges from about 0.5 mg-about 200 mg, about 1 mg-about 100 mg, about 2 mg-about 50 mg, about 5 mg-about 25 mg, or 25 mg.	<p>1. UTHAUG (2016) "A single inhalation of vapor from dried toad secretion containing 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting is related to sustained enhancement of satisfaction with life, mindfulness-related capacities, and a decrement of psychopathological symptoms" <i>Psychopharmacology</i>. 263:2653-2666</p> <p>From page 2657</p> <p>Table 2 Overview of compound concentrations in milligrams or micrograms per 1 g of secretion) in samples of dried secretion from the <i>Bufo alvarius</i> toad</p> <table border="1" data-bbox="527 1087 1258 1234"> <thead> <tr> <th>Sample</th> <th>5-MeO-DMT [mg/g]</th> <th>Bufofenin [mg/g]</th> <th>DMT [mg/g]</th> <th>NMT [μg/g]</th> <th>DET [μg/g]</th> <th>NMe-5HT [mg/g]</th> <th>Bufofenin [mg/g]</th> <th>Bufofalinin [mg/g]</th> <th>5-MeO-Tryptophol [μg/g]</th> <th>5-HO-Tryptophol [μg/g]</th> <th>5-MIAA [μg/g]</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>265.9</td> <td>0.642</td> <td>0.016</td> <td>ND</td> <td><LOQ</td> <td>0.028</td> <td><LOQ</td> <td><LOQ</td> <td>0.696</td> <td>ND</td> <td>ND</td> </tr> <tr> <td>2</td> <td>203.6</td> <td>0.600</td> <td>0.032</td> <td>ND</td> <td><LOQ</td> <td>0.014</td> <td>0.005</td> <td><LOQ</td> <td>2.357</td> <td>ND</td> <td>ND</td> </tr> <tr> <td>3</td> <td>274.3</td> <td>1.179</td> <td>0.029</td> <td>ND</td> <td><LOQ</td> <td>0.050</td> <td>0.013</td> <td><LOQ</td> <td>1.307</td> <td>ND</td> <td>ND</td> </tr> <tr> <td>4</td> <td>283.3</td> <td>3.530</td> <td>0.022</td> <td>ND</td> <td><LOQ</td> <td>0.171</td> <td>0.011</td> <td><LOQ</td> <td>0.997</td> <td>ND</td> <td>ND</td> </tr> <tr> <td>5</td> <td>307.3</td> <td>1.436</td> <td>0.041</td> <td>ND</td> <td>0.415</td> <td>0.064</td> <td>0.008</td> <td><LOQ</td> <td>3.053</td> <td>ND</td> <td>ND</td> </tr> </tbody> </table> <p>ND not determined < LOQ under the limit of quantification</p>	Sample	5-MeO-DMT [mg/g]	Bufofenin [mg/g]	DMT [mg/g]	NMT [μ g/g]	DET [μ g/g]	NMe-5HT [mg/g]	Bufofenin [mg/g]	Bufofalinin [mg/g]	5-MeO-Tryptophol [μ g/g]	5-HO-Tryptophol [μ g/g]	5-MIAA [μ g/g]	1	265.9	0.642	0.016	ND	<LOQ	0.028	<LOQ	<LOQ	0.696	ND	ND	2	203.6	0.600	0.032	ND	<LOQ	0.014	0.005	<LOQ	2.357	ND	ND	3	274.3	1.179	0.029	ND	<LOQ	0.050	0.013	<LOQ	1.307	ND	ND	4	283.3	3.530	0.022	ND	<LOQ	0.171	0.011	<LOQ	0.997	ND	ND	5	307.3	1.436	0.041	ND	0.415	0.064	0.008	<LOQ	3.053	ND	ND
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17. A method of treating a psychological disorder, a compulsive disorder, or a depressive disorder comprising the step of administering to a person in need thereof an effective dose of a composition of claim 2.

1. UTHAUG (2016) “A single inhalation of vapor from dried toad secretion containing 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting is related to sustained enhancement of satisfaction with life, mindfulness-related capacities, and a decrement of psychopathological symptoms” *Psychopharmacology*. 263:2653-2666

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Shyness	48	60	37	3
Chronic anger	21	76	20	4
Eating disorder	10	39	59	2
Bipolar disorder	8	50	47	3
PTSD	21	79	18	3
ADHD	22	35	61	4
Autism	4	48	52	0
OCD	11	53	37	10
Alcoholism or hazardous drinking	22	66	31	3
Drug use disorder	33	60	35	5

Abbreviations: PTSD = Posttraumatic Stress Disorder, ADHD = Attention Deficit Hyperactivity Disorder, OCD = Obsessive Compulsive Disorder

^aProportion is out of the total sample (n range from 476-490)

^bOnly including responses from those who endorsed having the condition

5. QI (2018) “The Development of Toad Toxins as Potential Therapeutic Agents” Toxins. 10(8):1-14

From **page 7** “Recently, IAAs in toad toxins are considered as potential therapeutic compounds in developing new agents for treating several **neurologic disorders**, such as schizophrenia, **depression**, anxiety, **obsessive-compulsive disorders**, and chronic pain conditions, due to their potential 5-HT2A receptor selectivity in the CNS.”

2. Int’l Pat. App. Pub. No. WO/2019/081764 “COMBINATION PRODUCT FOR THE TREATMENT OF NEUROLOGICAL AND/OR PSYCHIATRIC DISORDERS” (Published May 2, 2019)

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19. A method of treating a psychological disorder, a compulsive disorder, or a depressive disorder comprising the step of administering to a person in need thereof a pharmaceutical formulation of claim 5.

1. UTHAUG (2016) “A single inhalation of vapor from dried toad secretion containing 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting is related to sustained enhancement of satisfaction with life, mindfulness-related capacities, and a decrement of psychopathological symptoms” *Psychopharmacology*. 263:2653-2666

From **page 2659** “Mixed model analysis revealed the main effects of session on **depression** ($F_{2,55.943} = 4.348$; $p = 0.018$), anxiety ($F_{2,55.033} = 8.875$; $p < 0.001$), and stress ($F_{2,51.874} = 6.225$; $p = 0.004$), the three subscales of the DASS-21. Separate contrast revealed that subjective ratings of depression, anxiety, and stress decreased within 24 h following the inhalation of the vapor from dried toad secretion containing 5-MeO-DMT, but failed to reach significance until 4 weeks later ($p = 0.015$, Hedges’^a)”

9. DAVIS (2018) “The epidemiology of 5-Methoxy-N,N-Dimethyltryptamine (5-MeO-DMT) use: Benefits, consequences, patterns of use, subjective effects, and reasons for consumption” *Journal of Psychopharmacology*. 32(7):1-29

From **page 29**

Table 6.
Medical and psychiatric conditions and change in symptoms (better, same, worse) following 5-MeO-DMT use

Condition	% had condition ^a	% better ^b	% same ^b	% worsened ^b
High blood pressure	9	15	78	7
Coronary artery disease	1	0	100	0
Asthma	12	24	73	4
Other lung disease	2	22	78	0
Chronic fatigue syndrome	8	58	37	5
Forgetfulness	28	27	69	4
Depression	61	77	22	2
Anxiety	63	69	27	5
Shyness	48	60	37	3
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Abbreviations: PTSD = Posttraumatic Stress Disorder, ADHD = Attention Deficit Hyperactivity Disorder, OCD = Obsessive Compulsive Disorder

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From **page 7** “Recently, IAAs in toad toxins are considered as potential therapeutic compounds in developing new agents for treating several **neurologic disorders**, such as schizophrenia, **depression**, anxiety, **obsessive–compulsive disorders**, and chronic pain conditions, due to their potential 5-HT_{2A} receptor selectivity in the CNS.”

	<p>2. Int'l Pat. App. Pub. No. WO/2019/081764 "COMBINATION PRODUCT FOR THE TREATMENT OF NEUROLOGICAL AND/OR PSYCHIATRIC DISORDERS" (Published May 2, 2019)</p> <p>From claim 9 "The combination product according to anyone of claims 2-8 for use in the treatment and/or prevention of a disorder selected from the group consisting of acquired brain injury, ataxia, brain tumor, dementia, dystonia, epilepsy, functional and dissociative neurological symptoms, meningitis, motor neuron disease, multiple sclerosis, muscular dystrophy, myalgic encephalomyelitis, Parkinson's disease, progressive supranuclear palsy, Huntington's disease, Alzheimer's disease, fronto-temporal dementia, vascular dementia, cognitive decline associated with aging, spina bifida, hydrocephalus, spinal injury, stroke, Tourette syndrome, transverse myelitis, panic disorder, agoraphobia, social anxiety disorder, phobias, post-traumatic stress disorder, obsessive compulsive disorder, generalized anxiety disorder, bipolar disorder, depression, anorexia nervosa, binge eating disorder, bulimia nervosa, psychosis, schizophrenia, substance addiction and personality disorders."</p>
<p>20. A method of treating a psychological disorder, a compulsive disorder, or a depressive disorder comprising the step of administering to a person in need thereof a pharmaceutical formulation of claim 6.</p>	<p>1. UTHAUG (2016) "A single inhalation of vapor from dried toad secretion containing 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting is related to sustained enhancement of satisfaction with life, mindfulness-related capacities, and a decrement of psychopathological symptoms" <i>Psychopharmacology</i>. 263:2653-2666</p> <p>From page 2659 "Mixed model analysis revealed the main effects of session on depression ($F_{2,55.943} = 4.348$; $p = 0.018$), anxiety ($F_{2,55.033} = 8.875$; $p < 0.001$), and stress ($F_{2,51.874} = 6.225$; $p = 0.004$), the three subscales of the DASS-21. Separate contrast revealed that subjective ratings of depression, anxiety, and stress decreased within 24 h following the inhalation of the vapor from dried toad secretion containing 5-MeO-DMT, but failed to reach significance until 4 weeks later ($p = 0.015$, Hedges")</p> <p>9. DAVIS (2018) "The epidemiology of 5-Methoxy-N,N-Dimethyltryptamine (5-MeO-DMT) use: Benefits, consequences, patterns of use, subjective effects, and reasons for consumption" <i>Journal of Psychopharmacology</i>. 32(7):1-29</p> <p>From page 29</p>

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Electronic Acknowledgement Receipt

EFS ID:	47001134
Application Number:	17627988
International Application Number:	
Confirmation Number:	5317
Title of Invention:	COMPOSITIONS CONTAINING TOAD SECRETION COMPOUNDS
First Named Inventor/Applicant Name:	Andrew R. CHADEAYNE
Customer Number:	92049
Filer:	Taylor Kurtzweil
Filer Authorized By:	
Attorney Docket Number:	205.0003-US00
Receipt Date:	10-NOV-2022
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Time Stamp:	15:06:25
Application Type:	

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$90
RAM confirmation Number	E2022A0F06220942
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2	Third-Party Submission Under 37 CFR 1.290	Third-party-preissuance-submission.pdf	72536 908fe8948593e1e6e21961ec159ae5218ebd2bc4	no	5
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