IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	Confirmation No. 1807
Andrew R. CHADEAYNE	)	Group Art Unit: 1629
Application No: 17/095,430	)	Examiner: ANDERSON, James D.
Filed: November 11, 2020	)	
For: COMPOSITIONS AND METHODS COMPRISING	)	
A COMBINATION OF SEROTONERGIC DRUGS	)	Date: March 6, 2023

AMENDMENT AND RESPONSE TO OFFICE ACTION

Commissioner for Patents
United States Patent and Trademark Office
MAIL STOP: Amendment
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Commissioner:

In response to the Office Action dated November 7, 2022, Applicant respectfully requests examination of this application on the merits in view of the following amendments and remarks. A fee payment for a one-month extension of time is submitted with this response.

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

Remarks begin on page 4 of this paper.

AMENDMENTS

IN THE CLAIMS:

The present listing of claims replaces all prior listings or versions of claims in the present application.

1-18. (Canceled).

19. (Currently Amended) A method of treating a psychological disorder comprising administering a composition comprising a first serotonergic drug and a purified psilocybin derivative selected from the group consisting of 3-(2-dimethylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate, 4-hydroxy-N,N-dimethyltryptamine, [3-(2-trimethylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate, 4-hydroxy-N,N,N-trimethyltryptamine, [3-(2-methylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate, 4-hydroxy-N-methyltryptamine, [3-(aminoethyl)-1H-indol-4-yl] dihydrogen phosphate, 4-hydroxytryptamine, and their salts to a subject in need thereof.

20. (Previously Presented) The method of claim 19, wherein the first serotonergic drug comprises a Selective Serotonin Reuptake Inhibitor.

21. (Previously Presented) The method of claim 20, wherein the Selective Serotonin Reuptake Inhibitor is 90 – 100% pure.

22. (Previously Presented) The method of claim 21, wherein the Selective Serotonin Reuptake Inhibitor comprises escitalopram.

23. (Canceled).

24. (Currently Amended) The method of claim [[23]]19, wherein the purified psilocybin derivative ~~comprises~~ is 3-(2-Dimethylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate.

25. (Withdrawn- Currently Amended) The method of claim [[23]]19, wherein the purified psilocybin derivative ~~comprises~~ is 4-hydroxy-N,N-dimethyltryptamine.

26. (Canceled).

27. (Currently Amended) The method of claim [[26]]19, wherein the composition further comprises ~~comprising administering~~ an excipient.

28. (Previously Presented) The method of claim 19, wherein the first serotonerigic drug or the purified psilocybin derivative is in the form of a dried powder.

29. (Currently Amended) The method of claim 28, wherein the purified psilocybin derivative is in crystalline form.

30. (Previously Presented) The method of claim 19, wherein the purified psilocybin derivative is 90-100% pure.

31. (Currently Amended) The method of claim 28, wherein the first serotonergic drug is a ~~crystalline~~ Selective Serotonin Reuptake Inhibitor in crystalline form.

32. (Previously Presented) The method of claim 19, wherein the psychological disorder is chosen from an anxiety disorder, a compulsive disorder, addiction, and a depressive disorder.

REMARKS

1. The Status of the Claims

After entry of this amendment claims 19-22, 24, 25, and 27-32 will be pending in this application. Claim 25 is withdrawn from consideration as directed to non-elected subject matter. Claims 23 and 26 are canceled herein. Claim 19 is amended to recite "administering a composition comprising a first serotonergic drug and a purified psilocybin derivative." Claim 19 is also amended to recite the subject matter of claim 23. Claim 24 and withdrawn claim 25 are amended to depend from and conform to claim 19. Claim 27 is amended to depend from claim 19 and to recite "wherein the composition further comprises an excipient." Claims 29 and 31 are amended to recite "in crystalline form." The specification and claims as originally filed provide support for the claim amendments. *See, e.g.*, Specification (as-filed), ¶¶ [0027], [0039], [0041], [0042], [0045], [0052], [0066], [0282]. Thus, no new matter is added.

2. Information Disclosure Statement

Applicant thanks the Office for considering the cited references and for pointing out the discrepancy with regard to NPL Reference No. 3 (Carhart-Harris et al., 2016) cited in the IDS filed May 9, 2022. If the Office would like Applicant to submit an IDS citing both Carhart-Harris et al., Lancet Psychiatry, 2016, vol. 3, pages 619-627 (Year: 2016) and Carhart-Harris et al., Neuropsychopharmacology, 2017, vol. 42, pages 2105-2113 (Published Online May 17, 2017) (Year: 2017) to clarify the record, Applicant will do so.

3. The Rejections under 35 U.S.C. § 112(b)

a. Claims 19-22 and 26-32

The Office rejected claims 19-22 and 26-32 under 35 U.S.C. § 112(b) or 35 U.S.C. § 112 (pre-AIA), second paragraph, as indefinite. *See* Office Action at 4-5. The Office stated that "the term 'derivative' in claim 19, appearing in the expression 'a purified psilocybin derivative', is a relative term which renders the claims indefinite." *Id.* at 5. The Office further stated that "'derivative' does not particularly point out the degree or type of derivation that a given compound may have in relation to the parent compound (psilocybin) and still be considered a 'psilocybin derivatives' as intended by Applicant." *Id*.

Solely to accelerate prosecution, claim 19 is amended to recite the subject matter of claim 23, a claim not rejected as indefinite. Claim 19 is amended to recite "a purified psilocybin derivative selected from the group consisting of 3-(2-dimethylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate, 4-hydroxy-N,N-dimethyltryptamine, [3-(2-trimethylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate, 4-hydroxy-N,N,N-trimethyltryptamine, [3-(2-methylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate, 4-hydroxy-

N-methyltryptamine, [3-(aminoethyl)-1H-indol-4-yl] dihydrogen phosphate, 4-hydroxytryptamine, and their salts," thereby mooting this rejection. Thus, Applicant respectfully requests that the Office withdraw this rejection.

b. Claim 27

The Office rejected claim 27 under 35 U.S.C. § 112(b) or 35 U.S.C. § 112 (pre-AIA), second paragraph, as indefinite. *See* Office Action at 5-6. The Office stated that "[c]laim 27 recites the method of claim 26, 'comprising administering an excipient'" and that "[i]t is unclear exactly what is intended to be administered by claim 27." *Id.* at 5. The Office further stated that "it is unclear if by 'comprising administering an excipient' Applicant intends the 'combination of the first serotonergic drug and the purified psilocybin derivative' recited in claim 26 to be in a single composition comprising the first serotonergic drug, the purified psilocybin derivative, and an excipient" and "[a]lternatively, it is unclear if Applicant merely intends to further administer 'an excipient' in a totally separate composition." *Id.* at 5-6.

Solely to accelerate prosecution, claim 19 is amended to recite "administering a composition comprising a first serotonergic drug and a purified psilocybin derivative"; claim 26 is canceled; and claim 27 is amended to depend from claim 19 and recite "wherein the composition further comprises an excipient," thereby mooting this rejection. Thus, Applicant respectfully requests that the Office withdraw this rejection.

c. Claims 29 and 31

The Office rejected claims 29 and 31 under 35 U.S.C. § 112(b) or 35 U.S.C. § 112 (pre-AIA), second paragraph, as indefinite. *See* Office Action at 6. The Office stated that "[a] person of ordinary skill in the art would understand that 'crystalline' means the compound is a solid material arranged in a highly ordered microscopic structure, forming a crystal lattice that extends in all directions." *Id.* The Office further stated that "[i]t is unclear if claims 29 and 31 are therefore intended to limit the administering of the purified psilocybin and/or Selective Serotonin Reuptake Inhibitor to the solid, crystalline forms thereof or if Applicant intends that claims 29 and 31 merely require that the composition administered is made using a crystalline psilocybin derivative and/or crystalline Selective Serotonin Reuptake Inhibitor." *Id.*

Solely to accelerate prosecution, claims 29 and 31 are amended to recite that the purified psilocybin derivative and the Selective Serotonin Reuptake Inhibitor are "in crystalline form," thereby mooting this rejection. Thus, Applicant respectfully requests that the Office withdraw this rejection.

4. The Rejection under 35 U.S.C. § 112(a)

The Office rejected claims 29 and 31 under 35 U.S.C. § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. *See* Office Action at 6-9. The Office stated that "[n]ewly added claim 29 recites that the purified psilocybin is crystalline," that "[n]ewly added claim 31 recites that the first serotonergic drug is a crystalline Selective Serotonin Reuptake Inhibitor," and that "[t]hese claims introduce new matter." *Id*. at 7.

Applicant respectfully traverses this rejection for the following reasons.

Claim 28, the claim from which claims 29 and 31 depend, recites "wherein the first serotonergic drug or the purified psilocybin derivative is in the form of a dried powder." The Specification discloses that "the compositions disclosed herein are in the form of a dried powder" and that "the compounds disclosed herein are in a dried powder form, e.g., a psilocybin derivative, a cannabinoid, a terpene, etc." *See* Specification (as-filed) at ¶¶ [0039], [0045]. The Specification further discloses that "a dried powder is composed of particles with a crystalline structure;" that "a dried powder is composed of pure crystals;" and that "the term 'purified' refers to a compound or composition that has been crystallized." *Id.* at ¶¶ [0041], [0042], [0052].

Solely to accelerate prosecution, claims 29 and 31 are amended to recite that the purified psilocybin derivative and the Selective Serotonin Reuptake Inhibitor are "in crystalline form." Claim 29 is supported by the Specification because the purified psilocybin derivative of claim 28 is in the form of a dried powder and the dried powder is composed of particles with a crystalline structure or pure crystals, and thus in crystalline form. *See id.* at ¶¶ [0041], [0042], [0045]. Additionally, because the purified psilocybin derivative of claim 29 is purified, the Specification supports "purified" as a compound that has been crystallized. *Id.* at ¶ [0052]. Thus, a purified psilocybin derivative in crystalline form is supported by the Specification.

Claim 31 is supported by the Specification because the first serotonergic drug of claim 28, which is a Selective Serotonin Reuptake Inhibitor, is in the form of a dried powder and the dried powder is composed of particles with a crystalline structure or pure crystals, and thus in crystalline form. *See id.* at ¶¶ [0041], [0042], [0045]. The specification discloses that "a first purified terpene modulates the activity of a neurotransmitter activity modulator, e.g., a serotonergic drug, an adrenergic drug, a dopaminergic drug, a psilocybin derivative, etc." and that "a serotonergic drug is a selective serotonin reuptake inhibitor." *Id.* at ¶¶ [0249], [0253]. Thus, a Selective Serotonin Reuptake Inhibitor in crystalline form is supported by the Specification.

Applicant respectfully contends that claims 29 and 31 are supported by the Specification and do not add new matter. For these reasons, Applicant respectfully requests that the Office withdraw this rejection.

5. The Rejections under 35 U.S.C. § 103

The Office rejected claims 19-24 and 26-32 under 35 U.S.C. § 103 as unpatentable over Griffiths et al., Journal of Psychopharmacology, 2016, vol. 30, no. 12, pages 1181-1197 ("Griffiths"), Carhart-Harris et al., Lancet Psychiatry, 2016, vol. 3, pages 619-627 ("Carhart-Harris 2016"), Shirota et al., J. Nat. Prod., 2003, vol. 66, pages 885-887 ("Shirota"), and GB 2571696 B to Compass Pathways Limited ("GB '696") in view of US 2005/0137255 A1 to Petersen et al. ("US '255") and Carhart-Harris et al., Neuropsychopharmacology, 2017, vol. 42, pages 2105-2113 ("Carhart-Harris 2017"). *See* Office Action at 9-15.

Applicant respectfully traverses this rejection for the following reasons.

The Office asserted that Griffiths "teach[es] that psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer." *See* Office Action at 10 (citing Griffiths at Abstract). Griffiths does not teach or suggest administering a purified psilocybin derivative, let alone administering a composition comprising a first serotonergic drug and a purified psilocybin derivative, as in the claimed invention. Griffiths does not even mention the use of a serotonergic drug. Thus, a person of ordinary skill in the art would not have reached the claimed invention from Griffiths.

The Office also asserted that Carhart-Harris 2016, which was cited by Griffiths, "teach[es] administering two oral doses of psilocybin (10 mg and 25 mg, 7 days apart) to patients with treatment resistant depression." *See* Office Action at 10-11 (citing Carhart-Harris 2016 at Summary). Carhart-Harris 2016 does not teach or suggest administering a purified psilocybin derivative, as in the claimed invention. Carhart-Harris 2016 teaches away from administering a composition comprising a first serotonergic drug and a purified psilocybin derivative. Carhart-Harris 2016 teaches that "[s]erotonergic antidepressants have been found to down-regulate the primary receptor target of psilocybin (the 5-HT_{2A} receptor) and attenuate subjective responses to psychedelics have previously bee reported in individuals chronically medicated with serotonergic antidepressants." *See* Carhart-Harris 2016, p. 627. Thus, the person of ordinary skill in the art would not have reached the claimed invention from Carhart-Harris 2016.

The Office conceded that Griffiths and Carhart-Harris 2016 "do not expressly disclose that the psilocybin administered therein was 'purified', purified psilocybin, specifically highly purified crystalline

psilocybin was known in the art" and asserted that "[i]t would be obvious to a person or ordinary skill in the art that a therapeutic agent intended to be administered to subjects should be as pure as possible." *See* Office Action at 11. Applicant respectfully disagrees. As disclosed in the Specification, at the time of the invention, "[d]espite a handful of studies utilizing purified psilocybin as a single active pharmaceutical ingredient, virtually no work has been done formulating psilocybin into drug products for treating mental disorders"; "[a]side from a few studies on purified psilocybin, no efforts [had] been made to modulate its properties with formulating agents or other ingredients"; and "no efforts [had] been made to formulate particular combinations or doses of psilocybin derivatives or combinations with other active molecules." *See* Specification (as-filed) at ¶ [0008]. Even assuming *arguendo* that the person of ordinary skill in the art would have suggested administering a purified psilocybin derivative, there was no motivation to administer a composition comprising a purified psilocybin derivative and a first serotonergic drug. Carhart-Harris 2016 teaches away from doing so by teaching that "patients may be required to withdraw from concurrent antidepressant medication before receiving psilocybin and this should only ever be done with care." *See* Carhart-Harris 2016 at p. 627.

The Office further asserted that Shirota "[t]eaches large-scale synthesis of psilocybin that does not require chromatographic purification." *See* Office Action at 11-12 (citing Shirota at Abstract). Shirota does not teach or suggest a method of treating psychological disorders comprising administering a composition comprising a first serotonergic drug and a purified psilocybin derivative, as in the claimed invention. Shirota does not mention administering a serotonergic drug, let alone in combination with a purified psilocybin derivative. Thus, the person of ordinary skill in the art would not have reached the claimed invention by looking to Shirota.

The Office also asserted that GB '696 "also teaches the large-scale synthesis production of psilocybin, specifically for use in medicine." *See* Office Action at 12 (citing GB '696 at ¶ [0001]). Although GB '696 teaches a method of treating drug resistant depression comprising administering to a subject in need thereof an effective does of a high purity, crystalline psilocybin, GB '696 does not teach or suggest administering a first serotonergic drug with a purified psilocybin derivative, as in the claimed invention. *See* GB '696 at ¶ [0059]. GB '696 does not even mention the use of a serotonergic drug. Thus, the person of ordinary skill in the art would not have reached the claimed invention from looking at GB '696.

The Office conceded that the combined teachings of Griffiths, Carhart-Harris, Shirota, and GB '696 "do not disclose administering purified psilocybin in combination with a serotonergic drug to treat depression" and attempts to cure this deficiency with US '255 and Carhart-Harris 2017. *See* Office Action at 12. The Office further asserted that US '255 "teaches crystalline escitalopram hydrobromide, a novel

crystalline form of escitalopram hydrobromide referred to as Form I. *Id.* at 13 (citing US '255 at Abstract). Although US '255 teaches a method of treating an escitalopram-treatable disorder, such as depression, by administering a pharmaceutical composition comprising crystalline escitalopram hydrobromide, a serotonergic drug, there is no teaching or suggestion to administer a composition comprising a first serotonergic drug and a purified psilocybin derivative. *See* US '255 at ¶ [0012]. US '255 does not even mention psilocybin, let alone purified psilocybin derivatives. Thus, the person of ordinary skill in the art would not have reached the claimed invention from US '255.

Moreover, the Office asserted that "[t]he claimed invention, i.e., treatment of depression comprising administering a first serotonergic drug (e.g., the SSRI escitalopram) and a purified psilocybin derivative (e.g., psilocybin), is the result of combining equivalents known for the same purpose, i.e., combining two therapeutics having anti-depressant activity" and that "[a]s both psilocybin and escitalopram were known to reduce depressive symptoms when administered individually, when combined they would also be expected to reduce depressive symptoms." *See* Office Action at 13-14. Although the Office "acknowledges that the prior art questions whether administration of an SSRI should be discontinued before administering psilocybin to a depressed subject," the Office concludes that "[a] totality of the evidence weighs in favor of obviousness of the claimed invention, despite the 'anecdotal' evidence that SSRIs might potentially attenuate 'psychedelic effects." *Id.* at 14.

Applicant respectfully disagrees. Like the teaching away of Carhart-Harris 2016 above, Carhart-Harris 2017 also teaches away from administering a serotonergic drug with a psilocybin derivative. Carhart-Harris 2017 teaches that "chronic antidepressant medication strategies appear to have a muting effect on psilocybin's acute and putative antidepressant effects (Bonson et al, 1996; Bonson and Murphy, 1996), implying that treating medication-heavy, treatment-resistant depressed patients with psilocybin will be especially challenging (Carhart-Harris et al, 2016a.b)." *See* Carhart-Harris 2017 at 2107. Thus, at the time of the invention, the person of ordinary skill in the art would not have been motivated to administer a composition comprising a first serotonergic drug and a purified psilocybin derivative.

Even assuming *arguendo* that the cited references individually teach administering either a purified psilocybin derivative ***or*** a serotonergic drug to treat a psychological disorder, none of the cited references teach or suggest, let alone motivate, the person of ordinary skill in the art to administer a composition comprising ***both*** a purified psilocybin derivative and a serotonergic drug to treat a psychological disorder. Yet the Office concluded that administering both a first serotonergic drug and a purified psilocybin derivative is obvious, despite two of the cited references teaching away from combining both a psilocybin derivative and a serotonergic drug. Based on the teachings of Carhart-Harris

2016 and Carhart-Harris 2017 the person of ordinary skill in the art would not have been motivated to administer both a first serotonergic drug and a purified psilocybin derivative at the time of the invention.

For these reasons, Griffiths, Carhart-Harris 2016, Shirota, and GB '696 in view of US '255 and Carhart-Harris 2017 do not render obvious the claimed invention. Therefore, Applicant respectfully requests that the Office withdraw this rejection.

6. Conclusion

In view of the above amendments and remarks, Applicant respectfully requests further examination of this application and the timely allowance of the pending claims. If the Examiner finds that any issue arises that could be resolved through discussions with Applicant's representative, Applicant invites the Examiner to telephone the undersigned to expedite further prosecution of this application.

Please grant any extensions of time in connection with this response and charge any additional required fees for this submission to our Deposit Account No. 50-5410.

Respectfully submitted,

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