PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	22 Mar 2016
Applicant's or agent's file reference 64401	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL2015/051194	09 Dec 2015	09 Dec 2014

International Patent Classification (IPC) or both national classification and IPC
IPC (2016.01) C07C 211/42 C07C 309/66 C07D 295/096 C07D 317/70 C07D 319/18 C12G 3/08 A23L 2/00

Applicant
GOLAN Ezekiel

1. This opinion contains indications relating to the following items:

- [x] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [x] Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [x] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized officer
Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel Facsimile No. 972-2-5651616	17 Mar 2016	VOLKOV Karina Telephone No. 972-2-5651777

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   [X] the international application in the language in which it was filed.

   [ ] a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. [ ] This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. [ ] forming part of the international application as filed:

      [ ] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

      [ ] in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      [ ] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-48	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-48	NO
Industrial applicability (IA)	Claims	1-48	YES
	Claims		NO

2. Citations and explanations:

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Reference is made to the following documents:

D1 US 5708018(A) UPJOHN CO [US] 1998-01-13

D2 BOYCE, Janel M.; RISINGER, Fred O. Enhancement of ethanol reward by dopamine D3 receptor blockade. Brain research, 2000, 880.1: 202-206.

D3 HEIDBREDER, Christian A., et al. Role of dopamine D3 receptors in the addictive properties of ethanol. Drugs Today, 2004, 40.4: 355-65.

D4 VENGELIENE, Valentina, et al. The dopamine D3 receptor plays an essential role in alcohol-seeking and relapse. The FASEB journal, 2006, 20.13: 2223-2233.

D5 WO2009125923 KOREA RESERACH INST OF CHEMICA [KR]; SEONG CHURLMIN [KR]; PARK CHUL MIN [KR]; KIM SOYOUNG [KR]; PARK WOOKYU [KR]; PARK NOSANG [KR] 2009-10-15

2.1 Novelty:

The present claims meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-48 is novel in the sense of Article 33(2) PCT.

D1 discloses 2-aminoindan analogs that selectively bind to dopamine D3 receptor. The dopamine D3 receptor is of importance for the action of anti-psychotics and shows a high abundance in brain regions associated with emotional and cognitive functions. In addition D1 mentions that 2-aminoindan analogs may be useful in treating CNS disorders, e.g.

schizophrenia, mania, depression, geriatric disorders, drug abuse and addiction, Parkinson's disease, anxiety disorders, sleep disorders, circadian rhythm disorders and dementia. Although D1 describes 2-aminoindan analogs as described in claim 1 it does not describe an alcoholic beverage- substitute comprising a base liquid and said compound or the use of the compound in the preparation of these beverages, as claimed in claims 1-48.
Therefore, claims 1-48 of present application meet the criteria of Article 33(2) PCT.

2.2 Inventive Step:

The present claims do not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-48 does not fulfill the requirements of Article 33(3) PCT.

D1 discloses 2-aminoindan analogs that selectively bind to the dopamine D3 receptor. The dopamine D3 receptor is of importance for the action of anti-psychotics and shows a high abundance in brain regions associated with emotional and cognitive functions.

2-aminoindan analogs may be useful in treating CNS disorders, e.g. schizophrenia, mania, depression, geriatric disorders, drug abuse and addiction, Parkinson's disease, anxiety disorders, sleep disorders, circadian rhythm disorders and dementia.

It is known from D1 that these compounds can be given orally, as liquid dosage forms such as elixirs, syrups or suspensions (column 3 lines 52-55).

D2 refers to a compound which is a specific dopamine D3 receptor antagonist (U- [11] 99194A), D3 teaches that D3 dopamine systems have an important role in the response to ethanol when D3 receptor blockade increases ethanol's rewarding effects.

D3 discloses associations between the dopamine D3 receptor and alcoholism.
Administration of dopamine agonists or antagonists into the ventral tegmental area or into the nucleus accumbens (NAc) can alter ethanol-reinforced responding. The administration of rewarding doses of alcohol preferentially increases dopamine levels in the NAc compared with the dorsal striatum. D3 demonstrates that when the dopamine D3 receptor is expressed in brain regions, it (dopamine) plays a key role in the rewarding effects of drugs of abuse.
D3 shows that repeated exposure to drugs of abuse such as cocaine or nicotine is associated with adaptive changes in the dopamine D3 receptor in the NAc and that there is a relationship between polymorphism at the dopamine D3 receptor gene, novelty seeking, impulsiveness and dopamine release in the NAc in response to ethanol.

D4 discloses the blockade of dopamine D3Rs receptor subtype can reduce alcohol-seeking and relapse behavior. D4 mentions that the increase in dopamine release was seen in the dorsal striatum during alcohol-seeking behavior and blockade of dopamine receptors within the dorsal striatum decreased alcohol seeking.
D4 indicates that the effect of the dopamine D3R ligands was selective for alcohol. It appears to be that the crucial receptor in mediating dopamine dependent processes related to alcohol craving and relapse in the dopamine D3R .

Claims 1,37,40,44 lack an inventive step under Article 33(3) PCT as being obvious over D1 in view of D2-D4. D1 discloses 2-aminoindan derivatives for treating central nervous system (CNS) disorders associated with the dopamine D3 receptor activity, such as drug abuse. Documents D2-D4 mention modulatory role of D3 receptor in ethanol reward by administration of rewarding doses of alcohol preferentially increases dopamine levels and D3 receptor blockade increases ethanol's rewarding effects . In view of this teaching, it would have been obvious to one of ordinary skill in the art to provide an alcoholic beverage substitute comprising a base liquid and a compound associated with the dopamine D3 receptor activity such as 2-aminoindan analogs.

2.2.1 Regarding claims 2-36,38-39,41-43,45-48

None of the features of dependent claims 2-36,38-39,41-43,45-48 based on the prior art cited (see D1-D4) seem to have any surprising technical effect as regards an inventive step. Therefore the subject matter of claims 2-36, 38-39,41-43,45-48 is not considered inventive (Article 33(3)PCT).

2.3 Industrial applicability

The subject-matter of claims 1-48 is considered to be industrially applicable in the sense of Article 33(4) PCT.

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International application No.
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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The wording "All publication … incorporated by reference" on page 39 lines 16-19 seeks to extend the scope of protection sought in some vague and indefinite manner and, therefore should be amended.