# PATENT COOPERATION TREATY

## PCT

**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**  
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

<table>
<thead>
<tr>
<th>Applicant’s or agent’s file reference</th>
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See relevant information in Form PCT/ISA/237

Applicant  
BRAINCELLS, INC.

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1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).

2. This REPORT consists of a total of 19 sheets, including this cover sheet.
   
   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:
   
   - [ ] Box No. I  
     Basis of the report
   - [ ] 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
   - [ ] Box No. V  
     Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - [ ] Box No. VI  
     Certain documents cited
   - [ ] Box No. VII  
     Certain defects in the international application
   - [ ] Box No. VIII  
     Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis 2).

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**Date of issuance of this report**  
26 February 2008 (26.02.2008)

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Form PCT/IB/373 (January 2004)
PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
see form PCT/ISA/220

Applicant's or agent's file reference
see form PCT/ISA/220

International application No.
PCT/US2006/033299

International filing date (day/month/year) 25.08.2006

Priority date (day/month/year) 26.08.2005

International Patent Classification (IPC) or both national classification and IPC INV. A61K31/00 A61K31/66 A61K31/325 A61K31/473 A61K31/445 A61P25/00

Applicant
BRAINCELLS, INC.

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

☐ 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
☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐ Box No. VI Certain documents cited
☐ Box No. VII Certain defects in the international application
☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually 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 66.1bis(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.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:
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Fax: +31 70 340 - 3016

Date of completion of this opinion
see form PCT/ISA/220

Authorized Officer
Bonzano, Camilla
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Form (PCT/ISA/237) (Cover Sheet) (April 2005)
1. With regard to the language, this opinion has been established on the basis of:
   ☑ 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. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
   
   a. type of material:
      ☐ a sequence listing
      ☐ table(s) related to the sequence listing
   
   b. format of material:
      ☐ on paper
      ☐ in electronic form
   
   c. time of filing/furnishing:
      ☐ contained in the international application as filed.
      ☐ filed together with the international application in electronic form.
      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:
The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☑ the entire international application

☒ claims Nos. 1-11, 13-26 (with regard to industrial applicability); 1-8, 10, 11, 13-26 (partially); 12

because:

☒ the said international application, or the said claims Nos. 1-11, 13-26 (with regard to industrial applicability) relate to the following subject matter which does not require an international search (specify):

see separate sheet

☐ the description, claims or drawings (indicate particular elements below) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (specify):

☒ no international search report has been established for the whole application or for said claims Nos. 1-8, 10, 11, 13-26 (partially); 12

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13 ter.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details
1. ☑ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
   ☑ paid additional fees
   ☐ paid additional fees under protest and, where applicable, the protest fee
   ☐ paid additional fees under protest but the applicable protest fee was not paid
   ☐ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   ☐ complied with
   ☑ not complied with for the following reasons:
      see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:
   ☐ all parts.
   ☑ the parts relating to claims Nos. 1-11, 13-26 (partially)

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

1. Statement

| Novelty (N) | Yes: Claims 17-19,24,25 | No: Claims 1-11,13-16,20-23,26 |
| Inventive step (IS) | Yes: Claims | No: Claims 1-11,13-26 |
| Industrial applicability (IA) | Yes: Claims | No: Claims 1-11,13-26 |

2. Citations and explanations
   see separate sheet
Re Item III

1.1 Claims 1-3,7,10,11,13-26 relate to therapeutic applications which are actually not well defined. The use of the definitions "nervous system disorder related to cellular degeneration", "neural stem cell disorder", "neural progenitor cell disorder", "inducing, stimulating or increasing neurogenesis", "syndromes related to stress", "cognitive disorders", "sleep disorders", "injury of the nervous system" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is not fully possible to determine the diseases for which protection might legitimately be sought. The attention of the applicant is drawn to the fact that, although the influence of a compound on the the neurogenesis is indisputably a pharmacological effect, it cannot in itself be considered a therapeutic application. There are an undefined number of diseases which might be related to this pharmacological effect. In other terms, it still needs to find a practical application in the form of a defined treatment of a specified pathological condition, this being an essential technical feature, in order to render the claims clear. No Opinion will be carried out in respect of subject-matter which is not covered by the search report (Rule 66(1)(e) PCT).

1.2 Claims 1-6,8,10,11,13-26 relate to an extremely wide variety of compounds, namely muscarinic agents with an aminoacridinic, carbamic, phenanthrinic or piperidinic structure. In fact, the number of claimed variants cannot be estimated without undue burden and in any case appears to be fully disproportionate to what actually is disclosed and supported by pharmacological evidence. As a rule, protection conferred by a patent should be commensurate with the range of compounds for which the effect has been properly demonstrated, including obvious variants thereof.

In this respect, the number of claimed variants has to be justified by the extent of the description and drawings and also the contribution to the art in consideration of the nature of the invention claimed. What is or is not reasonable depends on the facts and circumstances of each particular case. In the present case it seems unreasonable to expect that any piperidinic, aminoacridinic, carbamic or phenanthrinic muscarinic agent would fall within the scope of the present inventions.

1.3 The dependencies of the claims are not clear. Based on the description, it has been assumed that claim 11 is not dependent on claim 9 (nowhere in the description is disclosed a coadministration of subcomeline with a AchE inhibitor).

2. The subject matter of claims 1-11,13-26 concerns a method of treatment of the human/animal body which is considered by this Authority to be covered by the provisions
of Rule 67.1 (IV) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims (Article 34(4) (a)(I)PCT).

Re Item IV.
1. The separate inventions/groups of inventions are:

Claims 1,2,7, 13-26 (partially). Use of subcomelin for stimulating or increasing neurogenesis by treating a nervous system disorder related to cellular degeneration, where the disorders are selected from neurodegenerative disorder, a neural stem cell disorder, a neural progenitor cell disorder, a degenerative disease of the retina, an ischemic disorder.

Claims 1,3,6,7, 8,13-26 (partially); 9
Use of subcomelin for stimulating or increasing neurogenesis by treating a nervous system disorder related to a psychiatric condition, where the disorders are selected from a neuropsychiatric disorder, an affective disorder, depression, hypomania, panic attacks, anxiety, excessive elation, bipolar depression, bipolar disorder (manic-depression), seasonal mood (or affective) disorder, schizophrenia and other psychoses, lissencephaly syndrome, anxiety syndromes, anxiety disorders, phobias, stress and related syndromes, cognitive function disorders, aggression, drug and alcohol abuse, obsessive compulsive behavior syndromes, borderline personality disorder, non-senile dementia, post-pain depression, post-partum depression, cerebral palsy, depression.

Claims 1,4,7, 13-26 (partially)
Use of subcomelin for stimulating or increasing neurogenesis by treating a nervous system disorder related to cellular trauma and/or injury, where the disorders are selected from neurological traumas and injuries, surgery related trauma and/or injury, retinal injury and trauma, injury related to epilepsy, spinal cord injury, brain injury, brain surgery, trauma related brain injury, trauma related to spinal cord injury, brain injury related to cancer treatment, spinal cord injury related to cancer treatment, brain injury related to infection, brain injury related to inflammation, spinal cord injury related to infection, spinal cord injury related to inflammation, brain injury related to environmental toxin, spinal cord injury related to environmental toxin, and combinations thereof.

Claims 1,5,7, 13-26 (partially)
Use of subcomelin for stimulating or increasing neurogenesis by treating a neurologically related condition, where the disorders are selected from learning disorders, memory
disorders, autism, attention deficit disorders, narcolepsy, sleep disorders, cognitive disorders, epilepsy, temporal lobe epilepsy, and combinations thereof.

Claims 1-6,8,10,11, 13-26 (partially)
Use of an AchE inhibitor, namely the organophosphates metrifonate or echothiophate for stimulating or increasing neurogenesis by treating:

a. a nervous system disorder related to cellular degeneration, selected from neurodegenerative disorder, a neural stem cell disorder, a neural progenitor cell disorder, a degenerative disease of the retina, an ischemic disorder and combinations thereof;

b. nervous system disorder related to a psychiatric condition selected from a neuropsychiatric disorder, an affective disorder, depression, hypomania, panic attacks, anxiety, excessive elation, bipolar depression, bipolar disorder (manic-depression), seasonal mood (or affective) disorder, schizophrenia and other psychoses, lissencephaly syndrome, anxiety syndromes, anxiety disorders, phobias, stress and related syndromes, cognitive function disorders, aggression, drug and alcohol abuse, obsessive compulsive behavior syndromes, borderline personality disorder, non-senile dementia, post-pain depression, post-partum depression, cerebral palsy, depression and combinations thereof;

c. nervous system disorder related to cellular trauma and/or injury selected from neurological traumas and injuries, surgery related trauma and/or injury, retinal injury and trauma, injury related to epilepsy, spinal cord injury, brain injury, brain surgery, trauma related brain injury, trauma related to spinal cord injury, brain injury related to cancer treatment, spinal cord injury related to cancer treatment, brain injury related to infection, brain injury related to inflammation, spinal cord injury related to infection, spinal cord injury related to inflammation, brain injury related to environmental toxin, spinal cord injury related to environmental toxin, and combinations thereof;

d. neurologically related condition selected from learning disorders, memory disorders, autism, attention deficit disorders, narcolepsy, sleep disorders, cognitive disorders, epilepsy, temporal lobe epilepsy, and combinations thereof.

Claims 1-6,8,10,11, 13-26 (partially)
Use of an AchE inhibitor, namely an aminoacridine derivative or tacrine for stimulating or increasing neurogenesis by treating one or more of the above mentioned disorders a,b,c and d.
Claims 1-6, 8, 10, 11, 13-26 (partially)
Use of an AchE inhibitor, namely a carbamate, phenserine, physostigmine, neostigmine, rivastigmine for stimulating or increasing neurogenesis by treating one or more of the above mentioned disorders a, b, c and d.

Claims 1-6, 8, 10, 13-26 (partially)
Use of an AchE inhibitor, namely a phenanthrine derivative, for stimulating or increasing neurogenesis by treating one or more of the above mentioned disorders a, b, c and d.

Claims 1-6, 8, 10, 11, 13-26 (partially)
Use of an AchE inhibitor, namely itopride, for stimulating or increasing neurogenesis by treating one or more of the above mentioned disorders a, b, c and d.

Claims 1-6, 8, 10, 11, 13-26 (partially)
Use of an AchE inhibitor, namely huperzine A for stimulating or increasing neurogenesis by treating one or more of the above mentioned disorders a, b, c and d.

Claim 1-6, 8, 11, 13-26 (partially)
Use of an AchE inhibitor, namely donepezil for stimulating or increasing neurogenesis by treating one or more of the above mentioned disorders a, b, c and d.

Claim 12
Method of preparing cells or tissue for transplantation to a subject comprising contacting said cells with a muscarinic agent, optionally in combination.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:
2. The problem to be solved by the present invention is:
1. to provide a medicament for stimulating or treating neurogenesis, by treating:
   a. a nervous system disorder related to cellular degeneration, selected from
      neurodegenerative disorder, a neural stem cell disorder, a neural progenitor cell
      disorder, a degenerative disease of the retina, an ischemic disorder;
   b. nervous system disorder related to a psychiatric condition selected from a
      neuropsychiatric disorder, an affective disorder, depression, hypomania, panic
      attacks, anxiety, excessive elation, bipolar depression, bipolar disorder (manic-
      depression), seasonal mood (or affective) disorder, schizophrenia and other
      psychoses, lissencephaly syndrome, anxiety syndromes, anxiety disorders, phobias,
      stress and related syndromes, cognitive function disorders, aggression, drug and
      alcohol abuse, obsessive compulsive behavior syndromes, borderline personality
      disorder, non-serile dementia, post-pain depression, post-partum depression,
      cerebral palsy, depression;
   c. nervous system disorder related to cellular trauma and/or injury selected from
      neurological traumas and injuries, surgery related trauma and/or injury, retinal injury
      and trauma, injury related to epilepsy, spinal cord injury, brain injury, brain surgery,
      trauma related brain injury, trauma related to spinal cord injury, brain injury related
      to cancer treatment, spinal cord injury related to cancer treatment, brain injury related
      to infection, brain injury related to inflammation, spinal cord injury related to infection,
      spinal cord injury related to inflammation, brain injury related to environmental toxin,
      spinal cord injury related to environmental toxin, and combinations thereof;
   d. neurologically related condition is selected from learning disorders, memory
      disorders, autism, attention deficit disorders, narcolepsy, sleep disorders, cognitive
      disorders, epilepsy, temporal lobe epilepsy, and combinations thereof;
2. to provide a method for preparing cells or tissue for transplantation;

3. The proposed solution to problem 1 is to use a muscarinic agent, namely:
1. sabcomeline
2. or an AchE inhibitor, such as:
   2a. an organophosphate, metrifonate, echothiophate
   2b. an aminoacridine, tacrine
   2c. a carbamate, pheneserine, physostigmine, neostigmine, rivastigmine,
2d a phenanthrine derivative,
2e a piperidine derivative
2f itopride
2g huperzine A
2h galantamine,
2i donepezil
alone or in combination with other neurogenic agents.

3.1 The use of a muscarinic agent for treating a nervous system disorder related to cellular degeneration, a psychiatric condition, cellular trauma or injury or a neurologically related condition represents the technical feature common to the uses of the compounds 1. and 2. claimed.

Document WO9847900 discloses the use of derivatives having a muscarinic cholinergic activity for treating Alzheimer's disease, pain, glaucoma, epilepsy or anxiety.

WO9904778 discloses the use of specific muscarinic receptor agonists in treating psychoses, schizophrenia, glaucoma, depression, Alzheimer's disease (a neurodegenerative disorder).

3.2 The use of an acetylcholinesterase inhibitor for treating a nervous system disorder related to cellular degeneration, a psychiatric condition, cellular trauma or injury or a neurologically related condition represents the technical feature common to the uses of the compounds 2a to 2i claimed.

US4067971 discloses the treatment tissue or organ damage in a human or lower animal caused by ischemia of that tissue or organ (falling under the definition of a nervous system disorder ischemic disorder), comprising administering organophosphonate compound characterized by more than one phosphonate moiety.

WO2005041979 discloses the treatment of a subject afflicted with a neurodegenerative disorder, the neurodegenerative disorder being HIV-associated dementia (HAD) or Alzheimer's disease (AD) with a cholinergic agonist and a acetylcholinesterase inhibitor such as galantamine.

Consequently, because muscarinic agents, as claimed, and more particularly acetyl cholinesterase inhibitors have already been used in the treatment of nervous system disorders, the use of an muscarinic agent, more particularly an acetylcholinesterase inhibitor, can no longer serve as a single general inventive concept linking the compounds 1, 2a to 2h, which have no other technical feature in common.

Therefore the uses of the muscarinic agents 1, 2a to 2i in the treatment of a nervous
system disorder represent each a distinct invention, characterised by its own special technical features, i.e. the structural features of the compounds.

4. Concerning invention 1, the use of sabcomelin for treating a nervous system disorder represents the technical feature common to the uses a. to d. claimed. WO0176571 discloses the use of sabcomeline as an anxiolytic. US20010036949 discloses a method of enhancing cognition or treating a disorder involving cognitive dysfunction in a mammal comprising administering to said mammal, an amount of a nicotine receptor partial agonist together with an acetylcholinesterase inhibitor such as sabcomelin. Consequently, because sabcomelin, as claimed, has already been used in the treatment of nervous system disorders, the use of of sabcomelin for treating a nervous system disorder can no longer serve as a single general inventive concept linking the uses a. to d. which have no other technical feature in common. Therefore the uses a,b,c and d represent each a distinct invention, characterised by its own special technical features, i.e. the structural features of the compounds.

5. The documents cited above do not represent a comprehensive search for the defined inventions and are to be considered in the present context only as part of the prior art pertaining to the general idea underlying the present application. Searching these different subjects would have caused a major additional searching effort. This objection of lack of unity was raised by the search division with an invitation to pay for additional search fees. The applicant replied to the invitation and requested ten additional searches. Therefore, inventions 1-4,6-11 and 13 have been searched as requested. The present opinion refers to inventions 1-4,6-11 and 13, namely to claims 1-11,13-26 (partially), in other words to the uses a,b,c and d of sabcomeline and of the AchE inhibitors aminoacidine, tacrine, carbamate, phenserine, physostigmine, neostigmine, rivastigmine, phenanthrine, piperidine derivative, itopride, huperzine A, donepezil.

Re Item V
1. The applicant's attention is drawn to the fact that the present opinion expressed as to novelty, inventive step and industrial applicability refers only to matter for which an international search report has been drawn up (the specific compounds of inventions 1-4,6-11 and 13 for treating the clear disorders of groups a,b,c and d).

2. Reference is made to the following documents:
   D1: WO 99/04778 A (LILLY CO ELI [US]; HOLLINSHEAD SEAN PATRICK [US]);


D5: WO 01/76571 A (SMITHKLINE BEECHAM PLC [GB]; BRIGHT JOANNE [GB]; HARRINGTON NICK [GB];) 18 October 2001


D7: WO 2004/101603 A (BOEHRINGER INGELHEIM INT [DE]; BOEHRINGER INGELHEIM PHARMA [DE]; DORNE) 25 November 2004


D10 WO 2006/067494 A (MINSTER RES LTD [GB]; ROUTLEDGE CAROL [GB]; HAGAN JAMES JOSEPH [GB]; C) 29 June 2006

D11 WO 2006/067496 A (MINSTER RES LTD [GB]; ROUTLEDGE CAROL [GB]; HAGAN JAMES JOSEPH [GB]; C) 29 June 2006

D12 WO 98/46226 A (LILLY CO ELI [US]; MITCH CHARLES HOWARD [US]; SAUERBERG PER [DK]; SHAN) 22 October 1998

D13 WO 2005/072713 A (LONG ISLAND JEWISH RES INST [US]; TRACEY KEVIN J [US]; PAVLOV VALENTIN) 11 August 2005

D14 WO 02/078629 A (UNIV EMORY [US]; DAVIS MICHAEL [US]; LU KWOK-TUNG [US]; RESSLER KERRY) 10 October 2002


D16 WO 03/031412 A (SCHERING CORP [US]) 17 April 2003 (2003-04-17)

D17 WO 03/059882 A (MERCK PATENT GMBH [DE]; HOELZEMANN GUENTER [DE]; PRUECHER HELMUT

D18 WO 03/091220 A (SCHERING CORP [US]) 6 November 2003


D20 YAMATO SHIGERU ET AL: "Itopride enhances distention-induced colonic peristalsis in guinea-pig: Simultaneous measurement of wall movement and


Novelty

3.1 Muscarinic agents are already known for treating the disorders of present inventions. D1 discloses the use of specific muscarinic receptor agonists, in treating glaucoma, Parkinson's and Alzheimer's disease (neurodegenerative and cognitive disorders according
to the definition of claims 2 and 5, groups a and d of disorders). Document D2 discloses the use of derivatives having a muscarinic cholinergic activity for treating Alzheimer's disease, cognitive disorders and glaucoma (a,d). The subject-matter of claims 1-2,5,13-16,23 is therefore not new (Article 33(2) PCT).

3.2 D3 discloses the treatment of a subject afflicted with a neurodegenerative disorder, the neurodegenerative disorder being HIV-associated dementia or Alzheimer's disease (disorders according to the definition of claims 5 and 2 respectively, groups of disorders d and a) with a cholinergic agonist (falling under the definition of non-opioid neurogenic agent) and an acetylcholinesterase inhibitor such as galantamine. The subject-matter of claims 1-2,5,13-16,23 is therefore not new (Article 33(2) PCT).

3.3 D4 discloses the treatment tissue or organ damage in a human or lower animal caused by ischemia of that tissue or organ (falling under the definition of claim 2 of ischemic disorder, group a of disorders), comprising administering organophosphonate compound characterized by more than one phosphonate moiety. The subject-matter of claims 1-2,13-15 is therefore not new (Article 33(2) PCT).

3.4 D9 discloses the activity of the muscarinic agent xamomelin for treating schizophrenia (neuropsychiatric disorder according to claim 3, group b of disorders). The subject-matter of claims 1,3,13-15 is therefore not new (Article 33(2) PCT).

4.1 D5 describes the activity of sabcomelin as anxyolitic (group of disorders b, according to claim 3). D8 discloses the use of sabcomelin for treating Alzheimer's disorder. The subject-matter of claims 1,3,6,7,13-15,23 is therefore not new (Article 33(2) PCT) in view of D5. The subject-matter of claims 1,2,5,7,13-15,23 is therefore not new (Article 33(2) PCT) in view of D8.

4.2 D6 discloses a method of enhancing cognition or treating a disorder involving cognitive dysfunction in a mammal comprising administering to said mammal an amount of a nicotine receptor partial agonist (falling under the definition of non-opioid neurogenic agent see page 36, line 1 of the application) together with the acetylcholinesterase inhibitor selected from sabcomelin (inventions 1-4), donepezil (invention 13), tacrine (invention 6), rivastigmine (Exelon(TM)), physostigmine (Synaptone), neostigmine (invention 7), huperzine A (invention 11). The disorders treated in D6 are: Alzheimer's Disease, vascular dementia, Parkinson's d.
dementia (d), Huntington's disease, stroke (a), traumatic brain injury (c), AIDS associated
dementia and schizophrenia (b) and to enhance memory (d) (see in particular D6,
paragraph 6 for physostigmine and amnesticide).
The subject-matter of claims 1-5,7,10,11,13-16,23 is therefore not new (Article 33(2) PCT).

4.3 D7 discloses the use of sabcomeline (inventions 1-4), tacrine (invention 6), donepezil
(invention 13), rivastagmin or phenserin (inventions 7) together with a statin (a neurogenic
compound according to the present application) of formula (I) for treating stroke (a),
Parkinson (a,d), Alzheimer (d), traumatic brain injury (c), which is an injury of the central
nervous system according to claim 15 of the present application, or dementia (d).
The subject-matter of claims 1-5,7,10,11,13-16,23 is therefore not new (Article 33(2) PCT).

4.4 D12 describes the use of a compound having a formula (II), in particular the compound
of claim 8 of D12 corresponding to sabcomeline, for treating schizophrenia (group of
disorders b) and other disorders such as Alzheimer (a and d), dementia (d), anxiety,
obsessive compulsive disorder (inventions 2 and 4, groups of disorders b and d), dementia
induced by alcohol, amphetamines, cannabis delusional disorder, cocaine delirium,
halocinogen hallucinosis, phenylcyclidine intoxication (all falling under the definition of
depression due to drug use, or alcohol by the subject). No mention is made in D12 of
opioids intoxication.
The subject-matter of claims 1-3,5-9,13-15,23,26 is therefore not new (Article 33(2) PCT).

4.5 D14 discloses the use of tacrine (invention 6) or donepezil (invention 13) for treating
psychiatric disorders such as anxiety, mood disorder (b), addictive disorder (d).
The subject-matter of claims 1-3,5,10,11 is therefore not new (Article 33(2) PCT).

4.6 D15 describes the use of tacrine (invention 6), donepezil (invention 13), phenserine,
neostigmine, rivastagmin, physostigmine (invention 7), huperzine A (invention 11) for
treating macular degeneration (a) obsessive-compulsive disorder, post-traumatic stress
disorder (b), anxiety, panic attack, schizophrenia, depression, mania, manic-depression
(b), autism, attention deficit hyperactivity disorder (d). Also the use of these
acetylcholinesterase inhibitors with a statin, caffeine, NMDA blocker (all neurogenic agents
according to the present invention) against Alzheimer, Parkinson, vascular dementia (a,c) is disclosed in D15. The subject-matter of claims 1-3,5,6,10,11,13-16,23 is therefore not new (Article 33(2) PCT).

4.7 D16 discloses piperidine derivatives (invention 9), as being useful for treating cognitive and neurodegenerative disorders e.g. Alzheimer's disease and senile dementia (a,d), which are muscarinic receptor antagonists. D17 describes the activity of N-(4-(piperidin-4-yloxy)-phenyl) -sulfonamide compounds (piperidinic derivatives according to claim 10), muscarinic acetylcholine receptor effectors, for treating schizophrenia, depression, dementia (b) and Parkinson's disease (a). D18 discloses 1,4-di-substituted piperidine derivatives as muscarinic antagonists useful for the treatment of cognitive or neurodegenerative disorders e.g. Alzheimer's disease and senile dementia (a,d). Muscarinig agents with a piperidinic astructure are therefore already known for treating the presently claimed disorders.

The subject-matter of claims 1-3,5,6,10,13-15,23 is therefore not new (Article 33(2) PCT).

4.8 D19 discloses Amino-alkyl:amino-substuted 3,4-,di aza-phenanthrene and fluorene compounds (invention 8) as agonists of M1 cholinergic receptors, for treating Alzheimer type dementia (d).

The subject-matter of claims 1,2,5,10,13-15 is therefore not new (Article 33(2) PCT).

4.9 Concerning the coadministration of acetylcholinesterase inhibitors together with opioids or other neurogenic agents, it is also not novel. According to D21, physostigmine antagonizes sleep induced by the benzodiazepine midazolam (falling under the definition of neurogenic agent), and reduces sleep duration. D24 discloses the synergy between physostigmine and ketamine (µ and σ opioid receptor binder).

The subject-matter of claims 13-15, 23 is therefore not new (Article 33(2) PCT).

4.10 D22 discloses how morphine induced memory impairment is reversed by acetylcholinesterase inhibitors such as physostigmine, thanks to the increased concentration of acetylcholine induced.

The subject-matter of claims 13-15, 20,21,23-26 is therefore not new (Article 33(2) PCT).

4.11 D23 discloses the coadministration of physostigmine with opioid antagonists such as
naloxone, nor-binaltorphimine to induce analgesia (antinociceptive effect, falling under the definition of increasing neurogenesis).
D25 describes how opioid antagonists increase cholinergic activity, opiates ineract with cholinergic processes: for instance, naloxone (μ, k and δ opioid antagonist) augments physostigmine induced tremors.
D26 discloses that naloxone (opioid receptor antagonist with affinity also for the k subtype) enhances analgesia induced by physostigmine.
The subject-matter of claims 13-16, 20-23 is therefore not new (Article 33(2) PCT).

4.12 The uses a-d of the compound itopride seem to be novel.
D20 discloses that itopride is an inhibitor of the acetylcholinesterase used in therapy for enhancing the peristalsis. As Moreover, the coadministration of the presently claimed compounds together with dopamine according to present claim 17 seems also to be novel in view of the prior art.

Inventive step
5. Should the applicant overcome the above raised objections of lack of novelty, an inventive step has to be demonstrated, because the present subject matter, as far as novel, lacks an inventive step under Article 33(3) PCT.
In particular, the use of itopride, a well known muscarinig agent for treating the presently claimed disorders seems to be obvious in view of the prior art.
Acetylcholinesterase inhibitors are already well known for treating the present disorders. See D1-D19.
The present invention 10 differs from the prior art in that the compound used for treating the claimed disorders is itopride.
Itopride is a well known acetylcholinesterase inhibitor.
D20 discloses that itopride is an inhibitor of the acetylcholinesterase used in therapy.
As acetylcholinesterase inhibitors are already known for treating the presently claimed disorders, and itopride is a well known acetylcholinesterase inhibitor, it would be obvious for the man skilled in the art to expect also from itopride the same activity as other acetylcholinesterase inhibitors.

Re Item VI
6. The attention of the Applicant is drawn to the fact that some documents are mentioned in the search report which might become relevant for novelty in some member states (see D10,D11, indicated in the search report as a P document). Moreover, these documents will anyway be novelty destroying, if the priority of the present application, which has not been
checked, appears not to be valid.
D10 discloses the use of sabcomeline for treating bipolar disorders, as mood stabiliser,
against mania, which includes phases of depression (group of disorders b, invention 2)
alone or together with another antimanic agents, hence neurogenic agents such as
lamotrigine, valproate, carbamazepine, risperidole, lithium etc.
D11 discloses the use of sabcomeline for treating psychotic disorders and other mood
disorders (group of disorders b, invention 2) together with olanzapine, risperidone,
ariiprazole, clozapine (atypical antipsychotics which have a similar action to dopamine).