



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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|--|--|---|--|
| (51) International Patent Classification <sup>7</sup> :<br><b>A61K 31/00, 31/195, 31/19, 31/165, 31/135, 31/22, 31/35, 31/445, 31/16</b>   |  | <b>A3</b>   | (11) International Publication Number: <b>WO 00/07583</b>        |
|  |  |   | (43) International Publication Date: 17 February 2000 (17.02.00) |
| (21) International Application Number: PCT/US99/17220<br>(22) International Filing Date: 5 August 1999 (05.08.99)<br>(30) Priority Data:<br>09/129,253                      5 August 1998 (05.08.98)                      US<br>09/189,166                      9 November 1998 (09.11.98)                      US<br>09/209,952                      11 December 1998 (11.12.98)                      US<br>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications<br>US    09/129,253 (CIP)<br>Filed on    5 August 1998 (05.08.98)<br>US    09/189,166 (CIP)<br>Filed on    9 November 1998 (09.11.98)<br>US    09/209,952 (CIP)<br>Filed on    11 December 1998 (11.12.98)<br>(71) Applicant (for all designated States except US):<br>BROOKHAVEN SCIENCE ASSOCIATES [US/US];<br>Building 460, 40 Brookhaven Avenue, Upton, NY 11973 (US). |  | (72) Inventors; and<br>(75) Inventors/Applicants (for US only): DEWEY, Stephen, L. [US/US]; 11 Golf Club Circle, Manorville, NY 11949 (US). BRODIE, Jonathan, D. [US/US]; 52 Frontier Road, Cos Cob, CT 06807 (US). ASHBY, Charles, R., Jr. [US/US]; 28 Sea Cliff Avenue, Miller PLace, NY 11764 (US).<br>(74) Agent: SCHMIDT, William, D.; Hoffmann & Baron, LLP, 6900 Jericho Turnpike, Syosset, NY 11791 (US).<br>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).<br><b>Published</b><br><i>With international search report.</i><br>(88) Date of publication of the international search report: 8 September 2000 (08.09.00) |  |
| (54) Title: TREATMENT OF ADDICTION AND ADDICTION-RELATED BEHAVIOR  |  |   |  |
| (57) Abstract  |  |   |  |
| <p>The present invention provides a method for changing addiction-related behavior of a mammal suffering from addiction to abused drugs, such as cocaine, nicotine, methamphetamine, ethanol, morphine, heroin and combinations thereof. The method includes administering to the mammal an effective amount of a compound increasing central nervous system GABA levels, wherein the effective amount is sufficient to diminish, inhibit or eliminate behavior associated with craving or use of abused drugs. Said compound may be gamma vinyl GABA (GVG), a pharmaceutically acceptable salt thereof, or an enantiomer or a racemic mixture thereof, or may be gabapentin, valproic acid, progabide, gamma-hydroxybutyric acid, fengabine, cetyl GABA, topiramate, tiagabine, acamprosate, pharmaceutically acceptable saltsthereof, enantiomers or racemic mixtures thereof.</p>   |  |   |  |

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# INTERNATIONAL SEARCH REPORT

Int. l. Application No  
PCT/US 99/17220

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/00 A61K31/195 A61K31/19 A61K31/165 A61K31/135  
A61K31/22 A61K31/35 A61K31/445 A61K31/16

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No.   |
|------------|---|---|
| X          | <p>WO 89 03211 A (MATRIX TECHNOLOGIES INC.)<br/>20 April 1989 (1989-04-20)</p> <p>, sentence 6<br/>page 8, line 20 - line 28<br/>page 9, line 22 - line 32<br/>page 11<br/>page 32, line 20 - line 35<br/>page 33 -page 35<br/>claims 19,20,23</p> <p>-----<br/>-/-</p> | <p>1,3,14,<br/>16,22,<br/>26,28,<br/>29,34,<br/>38,39,<br/>41,42,<br/>45,53,<br/>54,56,<br/>63,65,<br/>66,74,75</p> |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

28 April 2000

Date of mailing of the international search report

09.05.00

Name and mailing address of the ISA

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Gac, G

# INTERNATIONAL SEARCH REPORT

Int. l. Application No  
PCT/US 99/17220

**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No.  |
|------------|---|--|
| X          | <p>KUSHNER ET AL.: "Comparison of the effects of vigabatrin on cocaine self-administration and food reinforcement"<br/>SOC. NEUROSCI. ABSTR.,<br/>vol. 23, no. 1-2, 1997, page 1942<br/>XP002127040</p> <p>see abstract 754.4</p> <p style="text-align: center;">---</p>  | <p>1,3-5,7,<br/>14,<br/>16-18,<br/>20,22,<br/>23,26,<br/>28-30,<br/>32,<br/>38-42,<br/>50,51</p>     |
| X          | <p>DEWEY ET AL.: "A new GABAergic strategy for treating cocaine addiction"<br/>J. NUCLEAR MED.,<br/>vol. 39, no. 5suppl., May 1998 (1998-05),<br/>pages 99-100, XP000857227</p> <p>see abstract N 388</p> <p style="text-align: center;">---</p>  | <p>1,3,6,<br/>14,16,<br/>17,19,<br/>22,26,<br/>28,29,<br/>31,34,<br/>38,39,<br/>41-43,<br/>53,54</p> |
| X          | <p>MORGAN ET AL.: "Vigabatrin attenuates cocaine-induced changes in brain dopamine concentrations"<br/>J. NUCLEAR MED.,<br/>vol. 38, no. 5suppl., 1997, page 11p<br/>XP000857224</p> <p>see abstract n 33</p> <p style="text-align: center;">---</p>  | <p>1,3,6,<br/>14,16,<br/>17,19,<br/>22,26,<br/>28,29,<br/>31,34,<br/>38,39,<br/>41-43,<br/>53,54</p> |
| X          | <p>DEWEY ET AL.: "GABAergic attenuation of cocaine-induced dopamine release and locomotor activity"<br/>SYNAPSE,<br/>vol. 25, no. 4, 1997, pages 393-398,<br/>XP000856597<br/>cited in the application<br/>see the whole document, especially<br/>abstract and page 397</p>   | <p>1-5,<br/>14-18,<br/>22-30,<br/>34-42,<br/>53,54</p>   |
| A          |   | <p>7,8,20,<br/>21,32,33</p>  |
| X          | <p>MORGAN ET AL.: "Effects of pharmacologic increases in brain GABA levels on cocaine-induced changes in extracellular dopamine"<br/>SYNAPSE,<br/>vol. 28, no. 1, January 1998 (1998-01),<br/>pages 60-65, XP002127041<br/>cited in the application<br/>the whole document</p> <p style="text-align: center;">---</p> | <p>1,3-5,<br/>14,<br/>16-18,<br/>22,23,<br/>26,<br/>28-30,<br/>34,35</p>                             |

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/17220

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No.  |
|------------|---|--|
| P,X        | DEWEY ET AL.: "A novel strategy for the treatment of cocaine addiction"<br>SYNAPSE,<br>vol. 30, no. 2, October 1998 (1998-10),<br>pages 119-129, XP000856612<br>the whole document  | 1-8,<br>14-43,<br>50-54,<br>61,62                              |
| P,X        | KUSHNER ET AL.: "The irreversible<br>Gamma-aminobutyric acid (GABA)<br>transaminase inhibitor Gamma-vinyl-GABA<br>blocks cocaine self-administration in<br>rats"<br>J. PHARMACOL. EXP. THER.,<br>vol. 290, no. 2,<br>19 July 1999 (1999-07-19), pages 797-802,<br>XP002127042<br>the whole document | 1-6,8,<br>14,<br>16-19,<br>21,26,<br>28-31,<br>38,39,<br>41-43 |
| A          |   | 7,20,32,<br>50-52  |
| A          | KUSHNER ET AL.: "Gamma-vinyl GABA<br>attenuates cocaine-induced lowering of<br>brain stimulation reward thresholds"<br>PSYCHOPHARMACOLOGIA,<br>vol. 133, no. 4,<br>11 November 1997 (1997-11-11), pages<br>383-388, XP000856604<br>cited in the application<br>the whole document                   | 1-3,7,8,<br>14-18,<br>20-30,<br>34,35,<br>37-42,<br>50-54,62   |
| A          | TAKADA ET AL.: "Drug dependence study on<br>Vigabatrin in Rhesus monkeys and rats"<br>ARZNEIMITTEL FORSCHUNG,<br>vol. 47, no. 10, October 1997 (1997-10),<br>pages 1087-1092, XP000857211<br>cited in the application<br>the whole document   | 1-5,7,<br>14-18,<br>20,<br>26-30,<br>32,<br>38-42,<br>50,51    |
| A          | ROBERTS ET AL.: "Baclofen attenuates the<br>reinforcing effects of cocaine in rats"<br>NEUROPSYCHOPHARMACOLOGY,<br>vol. 15, no. 4, 1996, pages 417-423,<br>XP002127043<br>cited in the application<br>the whole document  | 38,<br>40-42,<br>50,53,61                                      |
| A          | TSUJI ET AL.: "Activation of ventral<br>tegmental GABA-B receptors inhibits<br>morphine-induced place preference in rats"<br>EUR. J. PHARMACOL.,<br>vol. 313, no. 3,<br>17 October 1996 (1996-10-17), pages<br>169-173, XP002127044<br>the whole document   | 38,<br>41-43,<br>50,53   |

# INTERNATIONAL SEARCH REPORT

Int. l. Application No  
PCT/US 99/17220

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No.   |
|------------|---|---|
| A          | EP 0 024 965 A (MERRELL TORAUDE ET CO.)<br>11 March 1981 (1981-03-11)<br>page 8, line 13 - line 24<br>page 10<br>----   | 38,41,<br>42,50,53  |
| A          | EP 0 509 180 A (MERRELL DOW<br>PHARMACEUTICALS INC.)<br>21 October 1992 (1992-10-21)<br><br>the whole document<br>-----   | 1,14,16,<br>17,22,<br>23,26,<br>28,30,<br>34,35,<br>38,39,<br>41,44,<br>50,51,<br>53-55 |
| P,X        | DEWEY ET AL.: "A pharmacologic strategy<br>for the treatment of nicotine addiction"<br>SYNAPSE,<br>vol. 31, no. 1, January 1999 (1999-01),<br>pages 76-86, XP000856613<br>the whole document<br>----- | 1-43,<br>50-54,<br>61,62  |

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 17220

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
See FURTHER INFORMATION SHEET PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:  
1-43, 50-54, 61-66, 68-71, 73-75, 77-79
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 99/17220

### FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-8,14-43,50-54,61-66,  
68-79 (all partially) and 67 completely

Use of GVG in the manufacture of a medicament useful for changing addiction-related behavior associated with craving or use of cocaine alone or in combination with other drugs of abuse.

2. Claims: 1-8,14-43,50-54,61-66,68-71,73-75,  
77-79 (all partially)

Use of GVG in the manufacture of a medicament useful for changing addiction-related behavior associated with craving or use of morphine alone or in combination with other drugs of abuse, except cocaine.

3. Claims: 1-43,50-54,61-66,68-71,73-75,77-79 (all partially)

Use of GVG in the manufacture of a medicament useful for changing addiction-related behavior associated with craving or use of nicotine alone or in combination with other drugs of abuse, except cocaine.

4. Claims: 1,2,4-8,14-43,50-54,61-66,68-71,73-75,  
77-79 (all partially)

Use of GVG in the manufacture of a medicament useful for changing addiction-related behavior associated with craving or use of methamphetamine alone or in combination with other drugs of abuse, except cocaine.

5. Claims: 1,2,4-8,14-43,50-54,61-66,68-71,73-75,  
77-79 (all partially)

Use of GVG in the manufacture of a medicament useful for changing addiction-related behavior associated with craving or use of alcohol alone or in combination with other drugs of abuse, except cocaine.

6. Claims: 1,2,4-8,14-43,50-54,61-66,68-71,73-75,  
77-79 (all partially)



## INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 99/17220

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Use of GVG in the manufacture of a medicament useful for changing addiction-related behavior associated with craving or use of heroin alone.

7. Claims: 38-43,50-54,  
63-  
79 (all partially) and 44 and 50 (both completely)

Use of gabapentine in the manufacture of a medicament useful for changing addiction-related behavior associated with craving or use of (combinations of) drugs of abuse.

8. Claims: 38-43,50-54,  
63-  
79 (all partially) and 45 and 56 (both completely)

Use of valproic acid in the manufacture of a medicament useful for changing addiction-related behavior associated with craving or use of (combinations of) drugs of abuse.

9. Claims: 38-43,50-54,  
63-  
79 (all partially) and 46 and 57 (both completely)

Use of topiramate in the manufacture of a medicament useful for changing addiction-related behavior associated with craving or use of (combinations of) drugs of abuse.

10. Claims: 38-43,50-54,  
63-  
79 (all partially) and 47 and 58 (both completely)

Use of progabide in the manufacture of a medicament useful for changing addiction-related behavior associated with craving or use of (combinations of) drugs of abuse.

11. Claims: 38-43, 50-54,  
63-  
79 (all partially) and 48 and 59 (both completely)

Use of fengabine in the manufacture of a medicament useful for changing addiction-related behavior associated with craving or use of (combinations of) drugs of abuse.

## INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 99/17220

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

12. Claims: 38-43, 50-54,  
63-  
79 (all partially) and 49 and 60 (both completely)

Use of gamma hydroxybutyric acid in the manufacture of a medicament useful for changing addiction-related behavior associated with craving or use of (combinations of) drugs of abuse.

13. Claims: 38-43,50-54,63-79 (all partially)

Use of cetyl GABA in the manufacture of a medicament useful for changing addiction-related behavior associated with craving or use of (combinations of) drugs of abuse.

14. Claims: 38-43, 50-54, 63-79 (all partially)

Use of thiagabine in the manufacture of a medicament useful for changing addiction-related behavior associated with craving or use of (combinations of) drugs of abuse.

15. Claims: 38-43,50-54,63-79 (all partially)

Use of acamprosate in the manufacture of a medicament useful for changing addiction-related behavior associated with craving or use of (combinations of) drugs of abuse.

## INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 99/17220

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims

1,2,4-8,14-16,18-28,30-38,40-41,50,52-53,63-65,68-70,73-74,77-79 relate to compounds and compositions defined by reference to a (un)desirable characteristics or properties, namely : 1) "drug of abuse" (among which different or broad pharmacological and chemical types of drugs: see for example claims 16-17) or 2) "compositions increasing central nervous system GABA levels" (claim 38).

The claims cover all compounds/compositions having the one or the other characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds/compositions.

In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds/compositions as defined in claim 17 concerning "drug of abuse" and as defined in claim 39 concerning "compositions increasing central nervous system GABA levels".

Please note that due to the lack of unity of invention, only GVG for use in treating cocaine addiction has been searched as the first subject.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No  
PCT/US 99/17220

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s)  | Publication<br>date  |
|---|---------------------|---|--|
| WO 8903211 A                              | 20-04-1989          | AT 91891 T<br>DE 3882712 A<br>EP 0381696 A<br>JP 3500411 T<br>US 5189064 A  | 15-08-1993<br>02-09-1993<br>16-08-1990<br>31-01-1991<br>23-02-1993   |
| EP 24965 A                                | 11-03-1981          | AT 3280 T<br>AT 3144 T<br>AU 536371 B<br>AU 6047680 A<br>AU 537901 B<br>AU 6047780 A<br>CA 1161450 A<br>CA 1158657 A<br>DE 3062893 D<br>DE 3063127 D<br>DK 320680 A,B,<br>DK 320780 A,B,<br>EP 0025370 A<br>ES 493555 D<br>ES 8105969 A<br>ES 493556 D<br>ES 8105970 A<br>GB 2055823 A,B<br>GB 2058052 A,B<br>IE 50072 B<br>IE 50025 B<br>IL 60591 A<br>JP 1008613 B<br>JP 1522047 C<br>JP 56020557 A<br>JP 1501207 C<br>JP 56020551 A<br>JP 63052619 B<br>NO 802217 A,B,<br>NO 802218 A,B,<br>NZ 194347 A<br>NZ 194348 A<br>PH 15684 A<br>PH 16349 A<br>US 4353828 A<br>US 4375477 A<br>ZA 8004202 A<br>ZA 8004244 A | 15-05-1983<br>15-05-1983<br>03-05-1984<br>05-02-1981<br>19-07-1984<br>29-01-1981<br>31-01-1984<br>13-12-1983<br>01-06-1983<br>16-06-1983<br>27-01-1981<br>27-01-1981<br>18-03-1981<br>01-07-1981<br>16-09-1981<br>01-07-1981<br>16-09-1981<br>11-03-1981<br>08-04-1981<br>05-02-1986<br>05-02-1986<br>28-02-1985<br>14-02-1989<br>12-10-1989<br>26-02-1981<br>28-06-1989<br>26-02-1981<br>19-10-1988<br>27-01-1981<br>27-01-1981<br>23-11-1982<br>14-09-1982<br>11-03-1983<br>05-09-1983<br>12-10-1982<br>01-03-1983<br>29-07-1981<br>29-07-1981 |
| EP 509180 A                               | 21-10-1992          | NONE  |  |