# 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>
<th>FOR FURTHER ACTION</th>
<th>See item 4 below</th>
</tr>
</thead>
<tbody>
<tr>
<td>SENO-00101WO</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>International application No.</th>
<th>International filing date (day/month/year)</th>
<th>Priority date (day/month/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT/US2008/065650</td>
<td>03 June 2008 (03.06.2008)</td>
<td>08 June 2007 (08.06.2007)</td>
</tr>
</tbody>
</table>

International Patent Classification (8th edition unless older edition indicated)

See relevant information in Form PCT/ISA/237

Applicant

SENOHYX, INC.

---

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 20 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:

   - [x] Box No. I  Basis of the report
   - [ ] Box No. II  Priority
   - [x] Box No. III  Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - [x] Box No. IV  Lack of unity of invention
   - [x] 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).

---

Date of issuance of this report

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer

Yoshiko Kuwahara

e-mail: pft07.pct@wipo.int

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

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
YONG LU
COOLEY GODWARD KRONISH LLP
777 6TH STREET, N.W.
SUITE 1100
WASHINGTON, DC 20001

PCT
WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) 20 NOV 2008

FOR FURTHER ACTION
See paragraph 2 below

Applicant’s or agent’s file reference
SENO-001/01WO 014810-2189

International application No.
PCT/US 08/65680

International filing date (day/month/year)
03 June 2008 (03.06.2008)

Priority date (day/month/year)
08 June 2007 (08.06.2007)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - G01N 33/53 (2008.04)
USPC - 435/7.1

Applicant SENOMYX, 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 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/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Date of completion of this opinion
12 Nov 2008 (12.11.2008)

Authorized officer:
Lee W. Young
PCT Helpdesk: 571-272-4300
PCT CSG: 571-272-7774

Form PCT/ISA/237 (cover sheet) (April 2007)
<table>
<thead>
<tr>
<th>Box No. 1</th>
<th>Basis of this opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. With regard to the <strong>language</strong>, this opinion has been established on the basis of:</td>
<td></td>
</tr>
<tr>
<td>☒ the international application in the language in which it was filed.</td>
<td></td>
</tr>
<tr>
<td>☐ 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)).</td>
<td></td>
</tr>
<tr>
<td>2. ☐ This opinion has been established taking into account the <strong>rectification of an obvious mistake</strong> authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))</td>
<td></td>
</tr>
<tr>
<td>3. With regard to any <strong>nucleotide and/or amino acid sequence</strong> disclosed in the international application, this opinion has been established on the basis of:</td>
<td></td>
</tr>
<tr>
<td>a. type of material</td>
<td></td>
</tr>
<tr>
<td>☐ a sequence listing</td>
<td></td>
</tr>
<tr>
<td>☐ table(s) related to the sequence listing</td>
<td></td>
</tr>
<tr>
<td>b. format of material</td>
<td></td>
</tr>
<tr>
<td>☐ on paper</td>
<td></td>
</tr>
<tr>
<td>☐ in electronic form</td>
<td></td>
</tr>
<tr>
<td>c. time of filing/furnishing</td>
<td></td>
</tr>
<tr>
<td>☐ contained in the international application as filed</td>
<td></td>
</tr>
<tr>
<td>☐ filed together with the international application in electronic form</td>
<td></td>
</tr>
<tr>
<td>☐ furnished subsequently to this Authority for the purposes of search</td>
<td></td>
</tr>
<tr>
<td>4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) 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.</td>
<td></td>
</tr>
<tr>
<td>5. Additional comments:</td>
<td></td>
</tr>
</tbody>
</table>
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. 117-118, 213-215, 221-223 & 231-233

because:

- the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search (specify):

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

Claims 117-118, 213-215, 221-223 & 231-233 are considered unsearchable because they are dependent claims not drafted in accordance with the second and third sentences of Rule 6.4(a).

- 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 said claims Nos. 117-118, 213-215, 221-223 & 231-233

- 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 Rule 13ter.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.
WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

<table>
<thead>
<tr>
<th>Box No. IV</th>
<th>Lack of unity of invention</th>
</tr>
</thead>
</table>

1. **X** 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
   - [x] 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
   - [x] not complied with for the following reasons:

   This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

   **Group I:** claims 1-116 and 119-212, having independent claims 1, 14, 27, 38 and 52 are drawn to the method of screening for a candidate of a chemosensory receptor ligand modifier comprising determining whether a test entity is suitable to interact with a chemosensory receptor via first interacting site within the Venus flytrap domain of the Chemo sensory receptor.

   **Group II:** claims 216-220 and 224-230, having independent claims 216 and 224, drawn to the method of enhancing the sweet taste of an ingestible composition comprising contacting the ingestible composition with a ligand modifier to form a modified ingestible composition.

   **Group III:** claims 234-237, having independent claim 234, drawn to the method of preparing substituted hetero-bicyclic compound formed by a diaza six member ring and substituted sulfur containing five member ring.

   **Group IV:** claims 238-241, having independent claims 238 and 240, drawn to the method of preparing substituted fused bicyclic system containing benzene ring and diaza-thia substituted six member ring.

   The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

   The special technical feature of the Group I claims is screening for a candidate of a chemosensory receptor ligand modifier comprising determining whether a test entity is suitable to interact with a chemosensory receptor via first interacting site within the Venus flytrap domain of the Chemos sensory receptor, which is not present in the claims of Groups II-IV.

   The special technical feature of the Group II claims is enhancing the sweet taste of an ingestible composition comprising contacting the ingestible composition with a ligand modifier to form a modified ingestible composition, which is not present in the claims of Groups I or III-IV.

   The special technical feature of the Group III claims is preparing substituted hetero-bicyclic compound formed by a diaza six member ring and substituted sulfur containing five member ring, which is not present in the claims of Groups II or IV.

   The special technical feature of the Group IV claims is preparing substituted fused bicyclic system containing benzene ring and diaza-thia substituted six member ring, which is not present in the claims of Groups I-III.

   None of these special technical features are common to the other groups, nor do they correspond to a special technical feature in the other groups. Therefore, unity of invention is lacking.

   Claims 117-118, 213-215, 221-223 & 231-233 are considered unsearchable because they are dependent claims not drafted in accordance with the second and third sentences of Rule 6.4(a).

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - [ ] all parts
   - [x] the parts relating to claims Nos. 1-116, and 119-212

Form PCT/ISA/237 (Box No. IV) (April 2007)
WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/65650

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

1. Statement

Novelty (N)  
Claims 13, 15, 16, 22-24, 33, 44-46, 52-116, and 119-212 YES
Claims 1-12, 14, 17-21, 25-32, 34-43, and 47-51 NO

Inventive step (IS)  
Claims None YES
Claims 1-116, and 119-212 NO

Industrial applicability (IA)  
Claims 1-116, and 119-212 YES
Claims None NO

2. Citations and explanations:

Claims 1-12, 14, 17-21, 25-32, 34-43, and 47-51 lack novelty under PCT Article 33(2) as being anticipated by US 20070104709 A1 to Li et al. (hereinafter: Li).

As per claim 1, Li teaches a method of screening for a candidate of a chemosensory receptor ligand modifier comprising (para [0090]; [0305]; [0306]) determining whether a test entity is suitable to interact with a chemosensory receptor via a first interacting site within the Venus flytrap domain of the chemosensory receptor (residues 144 and 302; para [0391]; [0392]; [0120]).

As per claim 2, Li teaches the method of claim 1, wherein the first interacting site of the Venus flytrap domain of the chemosensory receptor includes one or more interacting residues of the Venus flytrap domain of the chemosensory receptor (residues 144 and 302; para [0391]; [0392]; [0120]).

As per claim 3, Li teaches the method of claim 1, wherein the first interacting site of the Venus flytrap domain of the chemosensory receptor includes one or more interacting spaces of the Venus flytrap domain of the chemosensory receptor (residues 144 and 302; para [0391]; [0392]; [0120]).

As per claim 4, Li teaches the method of claim 1, wherein the first interacting site of the Venus flytrap domain includes an interacting space identified based on one or more interacting residues (residues 144 and 302; para [0391]; [0392]; [0120]).

As per claim 5, Li teaches the method of claim 1, wherein the first interacting site of the Venus flytrap domain of the chemosensory receptor includes one or more interacting residues, which are identified based on mutagenesis analysis of the Venus flytrap domain (mutation of residues 144 and 302; para [0391]; [0392]; [0120]).

As per claim 6, Li teaches the method of claim 1, wherein the first interacting site of the Venus flytrap domain is identified based on X-ray crystallography (para [0112]).

As per claim 7, Li teaches the method of claim 1, wherein the first interacting site of the Venus flytrap domain is identified based on one or more known chemosensory receptor ligands (known positive controls; para [0316]).

As per claim 8, Li teaches the method of claim 1, wherein the first interacting site of the Venus flytrap domain is identified based on one or more known chemosensory receptor ligand modifiers (sweeteners; para [0391]).

As per claim 9, Li teaches the method of claim 1, wherein the first interacting site of the Venus flytrap domain is identified based on a predetermined chemosensory receptor ligand (sweeteners; para [0391]).

As per claim 10, Li teaches the method of claim 1, wherein the first interacting site of the Venus flytrap domain is predetermined (site was determined using known sweeteners. screening against receptor using positive controls; para [0391]; [0316]).

As per claim 11, Li teaches the method of claim 1, wherein the first interacting site of the Venus flytrap domain is in the T1R2 Venus flytrap domain (residues 144 and 302; para [0391]).

As per claim 12, Li teaches the method of claim 1, wherein the first interacting site of the Venus flytrap domain is in the T1R2 Venus flytrap domain and is identified in the presence of T1R3 Venus flytrap domain (coexpressed with wild type hT1R; para [0391]).

As per claim 14, Li teaches a method of screening for a candidate of a chemosensory receptor ligand modifier (para [0007]) comprising: determining whether a test entity is suitable to interact with a chemosensory receptor (determining a compound-dependent increase in fluorescence: para [0217]) via a first interacting site within the Venus flytrap domain (para [0051]; [0120]; [0204]) of the chemosensory receptor (para [0217]), wherein the first interacting site is identified in light of a second interacting site (allosteric; para [0386]; [0390]; [0391]) identified based on the interaction between a chemosensory receptor ligand (sweetener) and the chemosensory receptor (compound-dependent increase in the response of cells to a sub-maximal level of a sweetener of at least 1.25-fold compared to the response to the sweetener alone; para [0217] claim 20).

********************************************************************************************continued in supplemental box******************************************************************************************
In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Box V No 2 (citations and explanations)

As per claims 17 and 18, Li teaches the method of claim 1, wherein the first interacting site includes an interacting residue of amino acid S144 of human TIR2 (para [0205]; [0391]).

As per claims 19 and 20, Li teaches the method of claim 1, wherein the first interacting site includes an interacting residue of amino acid E302 human of TIR2 (para [0205]; [0391]).

As per claim 21, Li teaches the method of claim 1, wherein the first interacting site includes an interacting residue selected from the group consisting of amino acid S144 and E302 (para [0205]; [0391]).

As per claim 25, Li teaches the method of claim 1, wherein the test entity is a designed compound structure (structure-based design methods to identify molecules; para [0084]).

As per claim 26, Li teaches the method of claim 1, wherein the chemosensory receptor ligand is the sweet flavor entity sucrose (para [0030]).

As per claim 27, Li teaches a method of screening for a candidate of a chemosensory receptor modifier (para [0007]) comprising determining whether a test entity is suitable to interact with a chemosensory receptor (determining a compound-dependent increase in fluorescence; para [0217]) via an interacting site within the Venus flytrap domain (para [0051]; [0120]; [0204]) of the chemosensory receptor (para [0217]), wherein the interacting site includes an interacting residue selected from the group consisting of S144 and E302, of a human TIR2 and a combination thereof (para [0205]; [0391]) wherein a test entity suitable to interact with the interacting site of the chemosensory receptor is indicative of a candidate of a chemosensory receptor modifier (para [0217]).

As per claims 28 and 29, Li teaches the method of claim 27, wherein the interacting site includes an interacting residue of S144 of a human TIR2 (para [0205]; [0391]).

As per claim 30, Li teaches the method of claim 27, wherein the interacting site includes an interacting residue of E302 of a human TIR2 (para [0205]; [0391]).

As per claim 31, Li teaches the method of claim 27, wherein the interacting site is in the TIR2 Venus flytrap domain (para [0051]; [0120]; [0204]).

As per claim 32, Li teaches the method of claim 27, wherein the interacting site is in the TIR2 Venus flytrap domain and identified in the presence of TIR3 Venus flytrap domain (TIR2 needs to be coexpressed with TIR3 to be functional; para [0051]).

As per claim 34, Li teaches the method of claim 27, wherein the test entity is a designed compound structure (structure-based design methods to identify molecules; para [0084]).

As per claim 35, Li teaches a chemosensory receptor ligand modifier identified by the method of claim 1 (para [0090]).

As per claim 36, Li teaches a chemosensory receptor ligand modifier identified by the method of claim 27 (para [0007]; [0217]).

As per claim 38, Li teaches a method of modulating the activity of a chemosensory receptor ligand comprising contacting a chemosensory receptor ligand modifier with a cell containing TIR2 Venus flytrap domain (para [0051]; [0120]; [0204]) in the presence of a chemosensory receptor ligand (when added to foods, beverages or medicinals modulate the flavor or taste thereof, particularly by enhancing the sweet thereof by modulating the response to naturally occurring and synthetic sweeteners; para [0070]; [0071]; [0219]), wherein the chemosensory receptor ligand modifier interacts with an interacting site of the chemosensory receptor (para [0120]; [0204]).

As per claim 37 and 47, Li teaches the methods of claims 1 and 38, respectively, as discussed above, and further teaches that the ligand enhancer identified or modiﬁer contacted has structural Formula I, wherein:
- G forms a single bond with D and a double bond with E;
- R1 and R2 together with atoms to which they are bonded form a heteroaryl;
- A is hydrogen;
- B is –C(R12);
- R12 is hydrogen
- G is –C
- D is –OR15
- N is 1
- E is –(R18)
- R18 is hydrogen (Compound A35; Table 1 on page 11).

As per claims 39 and 40, Li teaches the method of claim 38, wherein the interacting site includes an interacting residue of S144 of a human TIR2 (para [0205]; [0391]).

As per claims 41 and 42, Li teaches the method of claim 38, wherein the interacting site includes an interacting residue of E302 of a human TIR2 (para [0205]; [0391]).

**********continued in next supplemental box**********
In case the space in any of the preceding boxes is not sufficient.

As per claim 43, Li teaches the method of claim 38, wherein the interacting site includes an interacting residue of S144 and E302 (para [0205]; [0391]).

As per claim 48, Li teaches the method of claim 38, wherein the cell contains T1R2 Venus flytrap domain (para [0051]; [0120]; [0204]) within a GPCR pathway (para [0090]; [0100]; [0102]; [0314]).

As per claim 49, Li teaches the method of claim 38, wherein the chemosensory receptor ligand modifier is provided in a comestible composition (para [0219]; [0144]).

As per claim 50, Li teaches the method of claim 38, wherein the chemosensory receptor ligand modifier is provided in a medicinal composition (para [0144]).

As per claim 51, Li teaches the method of claim 38, wherein the chemosensory receptor ligand modifier is provided in a food or beverage product (para [0382]).

Claims 15-16, 24, 52, 56-59, 173, and 201-212 lack an inventive step under PCT Article 33(3) as being obvious over Li, as above.

As per claim 15, Li teaches the method of claim 14, as discussed above. Li teaches an interacting site is in the T1R2 Venus flytrap domain (para [0091]; [0120]; [0204]; [0205]) and a skilled artisan would have appreciated providing said known sweeteners as the chemosensory receptor ligand (sweetener).

As per claim 16, it is obvious for the reasons discussed in claim 15 and further because Li teaches wherein the site is identified in the presence of T1R3 Venus flytrap domain (T1R3 needs to be coexpressed with T1R2 to be functional; para [0051]).

As per claim 24, Li teaches the method of claim 1, wherein the first interacting site includes an interacting residue of amino acid S144, a human T1R2 (para [0205]; [0391]) wherein a test entity suitable to interact with the first interacting site of the chemosensory receptor is indicative of a candidate of an enhancer for a sweetener (para [0217]). Although Li does not explicitly teach screening for an enhancer of sucrose as the sweetener, such would have been further obvious to obtain the invention as claimed because Li teaches sucrose as a sweetener (para [0212]).

As per claim 52, Li teaches a chemosensory receptor (T1R) ligand modifier (para [0019]; [0286]), wherein in the presence of a chemosensory receptor ligand it interacts with T1R2 Venus flytrap domain via residues S144 and E302 (para [0205]). Li does not explicitly teach that the modifier further interacts with one of residues D142, N143, S303, I306; however, such would have been further obvious to a skilled artisan to obtain the invention as claimed because a skilled artisan would have readily appreciated that the modifier would additionally interact with residues adjacent or near the residues taught by Li.

As per claim 56, Li further teaches wherein the modifier is a compound having structural Formula I, wherein:
- G forms a single bond with D and a double bond with E;
- R1 and R2 together with atoms to which they are bonded form a heteroaryl;
- A is hydrogen;
- B is -C(R12)-;
- R12 is hydrogen
- G is -C-
- D is -OR15
- N is 1
- E is -C(R18)-
- R18 is hydrogen (Compound A35; Table 1 on page 11).

As per claim 57, Li further teaches wherein R1 and R2, together with the atoms to which they are bonded form a heteroaryl (Compound A35; Table 1 on page 11).

As per claim 58, Li further teaches a compound having structural Formula II, wherein:
- Y forms a single bond with W and a double bond with Z
- W is -NR26-
- Y is -C(R26)-
- Z is -C(R27)-
- R26 is hydrogen
- R27 is hydrogen (Compound A35; Table 1 on page 11).

As per claim 59, Li further teaches that (D)n-G is -C(O)- (Compound A35; Table 1 on page 11).

******************************************************************************continued in next supplemental box******************************************************************************
<table>
<thead>
<tr>
<th>Supplemental Box</th>
</tr>
</thead>
<tbody>
<tr>
<td>In case the space in any of the preceding boxes is not sufficient.</td>
</tr>
<tr>
<td>Continuation of:</td>
</tr>
<tr>
<td>Previous Supplemental Box - Box V No 2 (citations and explanations)</td>
</tr>
<tr>
<td>As per claim 173, Li further teaches wherein the compound has structural Formula IV (Compound A35; Table 1 on page 11) wherein L is ( \mathcal{N}R47- ), M is ( \text{CH}_2\text{R61} ), R is ( \text{CHR62} ), T is absent (p is 0), R61 is hydrogen, R62 is hydrogen, R47 is hydrogen (Compound A35; Table 1 on page 11).</td>
</tr>
<tr>
<td>As per claim 201, Li further teaches an ingestible composition comprising the chemosensory receptor ligand (para [0219]; [0144]).</td>
</tr>
<tr>
<td>As per claim 202, Li teaches wherein the composition is a medicinal composition (para [0144]).</td>
</tr>
<tr>
<td>As per claim 203, Li teaches wherein the composition is a beverage (para [0382]).</td>
</tr>
<tr>
<td>As per claim 204, Li teaches wherein the food or beverage is a sauce (para [0139]).</td>
</tr>
<tr>
<td>As per claim 205, Li teaches wherein the non-edible product is an oral care product (para [0144]).</td>
</tr>
<tr>
<td>As per claim 206, Li teaches wherein the chemosensory receptor ligand modifier is a compound having structural formula I (Compound A35; Table 1 on page 11).</td>
</tr>
<tr>
<td>As per claim 207, Li teaches wherein the composition comprises at least .001 ppm of the chemosensory receptor ligand (para [0406]).</td>
</tr>
<tr>
<td>As per claim 208, Li teaches wherein the composition comprises at least .001 ppm to 10 ppm of the chemosensory receptor ligand (para [0406]).</td>
</tr>
<tr>
<td>As per claim 209, Li teaches wherein the composition comprises at least 0.01 ppm to 100 ppm of the chemosensory receptor ligand (para [0406]).</td>
</tr>
<tr>
<td>As per claim 210, Li teaches wherein the composition comprises at least 10 ppm to 100,000 ppm of the chemosensory receptor ligand (para [0406]).</td>
</tr>
<tr>
<td>As per claim 211, Li teaches wherein the composition comprises one or more sweeteners (para [0067]; [0071]).</td>
</tr>
<tr>
<td>As per claim 212, Li teaches wherein the sweetener is sucrose (para [0067]).</td>
</tr>
<tr>
<td>Claims 13 and 33 lack an inventive step under PCT Article 33(3) as being obvious over Li, as above, in view of US 2005/0032158 A2 to Adler et al. (hereinafter Adler.).</td>
</tr>
<tr>
<td>As per claims 13 and 33, Li teaches the methods of claims 1 and 27, respectively. Li teaches structure-based assays that utilize the x-ray crystalline structure to identify molecules that modulate T1R2 receptor activity (para [0112]) but does not explicitly teach determining the interaction in silico. Adler also teaches screens for candidates against a T1R2 receptor and teaches determining interaction by providing the structure of the T1R receptor in silico (para [0051]). One skilled in the art would have found obvious the method of determining the determination is carried out in silico, as taught by Adler in order to provide a computer-aided method, as taught by Adler since Li recognizes the use of structural design based assays.</td>
</tr>
<tr>
<td>Claims 22, 23, 44, 46, 53, and 54 lack an inventive step under PCT Article 33(3) as being obvious over Li, as above, in view of the article entitled &quot;Delineating a Ca^2+ Binding Pocket Within the Venus Flytrap Module of the Human Calcium Sensing Receptor&quot; by Silve et al. (hereinafter Silve.).</td>
</tr>
<tr>
<td>As per claim 22, Li teaches the method of claim 1, as discussed above, and further teaches that the interacting residues comprise S144 and E302 of T1R2 (para [0391]; [0392]; [0120]) but does not explicitly teach wherein the interacting residues additionally comprise N143 and I167. However, like Li, Silve teaches that ligand interacting residues of the Venus flytrap domain (abstract) of T1R2 comprise S144 and further teaches that the interacting residues further comprise N143 and I167 (pg 11, table 1). One skilled in the art would have found obvious the method of Li wherein the interacting residues further comprise N143 and I167, as taught by Silve, to obtain the invention as claimed in order to screen for compounds that bind known interacting residues.</td>
</tr>
<tr>
<td>As per claims 23 and 44, Li teaches the methods of claim 1 and 38, respectively. Li does not teach wherein the interacting residues comprise K65, D278, L279, D307, R383 and V384. Silve teaches that ligand interacting residues of the Venus flytrap domain (abstract) of T1R2 comprise I67, D278, D307, and E382 (pg 11, table 1). One skilled in the art would have found obvious the methods of Li wherein the interacting residues comprise D278, D307, and E382, as taught by Silve, and K65, L279, R383 and V384, as suggested by Silve to obtain the invention as claimed in order to screen for compounds that bind known interacting residues. Although Silve does not explicitly teach interacting residues K65, L279, R383 and V384, a skilled artisan would readily appreciate screening for interaction with said residues because Silve teaches residues in close proximity (I67, L279, R383 and V384) that are interacting residues.</td>
</tr>
</tbody>
</table>

*continued in next supplemental box*
In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Previous Supplemental Box - Box V No 2 (citations and explanations)

As per claim 46, Li teaches that the interacting residues comprise S144 and E302 of T1R2 (para [0391]; [0392]; [0120]) but does not teach wherein the chemosensory receptor ligand modifier stabilizes a close conformation within T1R2 Venus flytrap domain formed by the interaction between the chemosensory receptor ligand and the chemosensory receptor. However, Silve teaches that S144 and E302 (pg 11, Table 1) are in the Ca2+ binding site of T1R2 and that Ca2+ binding stabilizes the closed conformation with in T1R2 venus flytrap domain (pg 6, col 2, para 1 and the abstract).

One skilled in the art would have found obvious the method of Li wherein the chemosensory receptor ligand modifier stabilizes a close conformation within T1R2 Venus flytrap domain formed by the interaction between the chemosensory receptor ligand and the chemosensory receptor, as suggested by Silve, to obtain the invention as claimed because Li teaches screening for compounds that bind a site (S144 and E302) which is taught by Silve to stabilize the closed conformation when bound.

As per claim 53, Li suggests the chemosensory receptor ligand modifier of claim 52 as discussed above. Li teaches that the interacting residues comprise S144 of T1R2 (para [0391]; [0392]; [0120]) but does not explicitly teach residues S143 and I167. However, like Li, Silve teaches that ligand interacting residues of the Venus flytrap domain (abstract) of T1R2 comprise S144 and further teaches that the interacting residues further comprise N143 and I167 (pg 11, Table 1). One skilled in the art would have found obvious the method of Li wherein the interacting residues further comprise N143 and I167, as taught by Silve, to obtain the invention as claimed in order to provide a compound that binds additional residues known to modulate activity of the receptor (Ca2+ binding stabilizes the closed conformation with in T1R2 venus flytrap domain: pg 6, col 2, para 1 and the abstract).

As per claim 54, Silve teaches that ligand interacting residues of the Venus flytrap domain (abstract) of T1R2 comprise I67, D278, D307, and E382 (pg 11, Table 1). Although Silve does not explicitly teach interacting residues K65, L279, R383 and V384, a skilled artisan would readily appreciate screening for interaction with said residues because Silve teaches residues in close proximity (I67, L279, R383 and V384) that are interacting residues.

Claims 60-75, 77-87, 174-179, 188-200 lack an inventive step under PCT Article 33(3) as being obvious over Li, as above, in view of the article entitled "Purine and Pyrimidine Nucleotides Inhibit a Nonactivating K Current and Depolarize Adrenal Cortical Cells through a G Protein-Coupled Receptor. by Xu et al. (hereinafter ‘Xu’).

As per claim 60, Li teaches the compound of claim 58, as discussed above. Li teaches that the chemosensory receptor (T1R) also binds nucleotides (para [0092]) and is a G Protein-Coupled Receptor (GPCR), a class of receptors known to bind nucleotides (para [0047]; [0050]; [0051]). Although Li teaches a compound similar to Formula I (Compound A35 or A36; Table 1 on page 11), Li does not teach that (D)n = O or that E is N.

Xu teaches that a compound (nucleotide), wherein (D)n = O and E is N (uridine from UTP), exhibits high activity against a GPCR (inhibits current by activating a GPCR pg 367, col 1, para 2 - col 2, para 1 and the abstract).

One skilled in the art at the time the invention was made would have found obvious the compound of Li, wherein (D)n = O and E is N, as taught by Xu to obtain the invention as claimed because Li identifies the chemosensory receptor as a GPCR which are known to bind nucleotides while Xu teaches that a nucleotide, wherein (D)n = O and E is N (uridine), is highly active against a GPCR.

As per claim 61, Li teaches wherein W is C(R24), Y is C(R26) and Z is N(R28) - (Compound A36; Table 1 on page 11) while Xu further teaches wherein B is N- (uridine from UTP; abstract).

As per claims 62, Li further teaches wherein W is C(R24) and Y is C(R26) (Compound A36; Table 1 on page 11)

As per claims 63 and 64, Li further teaches wherein R24 is hydrogen and wherein R26 is hydrogen (Compound A36; Table 1 on page 11).

As per claim 65, Li further teaches wherein A, R17, R24, and R26 are hydrogen (Compound A36; Table 1 on page 11).

As per claim 66-68, Li further teaches wherein R17 is hydrogen, wherein R24 is hydrogen; and wherein R26 hydrogen (Compound A36; Table 1 on page 11). Although neither Li nor Xu explicitly teaches wherein A is -NH2, such a substituent would have been further obvious to obtain the invention as claimed because Li teaches that nucleotides bind the receptor (para [0245]) and because cytosine, a well-known nucleotide, comprises -NH2 at the claimed position.

As per claims 69 and 70, Li further teaches wherein R28 is hydrogen (Compound A36; Table 1 on page 11).

As per claim 71, the fifth recited compound is further obvious for the reasons discussed above and because Li teaches wherein R17 is hydrogen, wherein W is N, wherein Y is C(CH3)-, and wherein Z is O (Compound A23; Table 1 on page 9) and because although neither Li nor Xu explicitly teaches wherein A is -NH2, such a substituent would have been further obvious to obtain the invention as claimed because Li teaches that nucleotides bind the receptor (para [0245]) and because cytosine, a well-known nucleotide, comprises -NH2 at the claimed position.

As per claim 72, Li further teaches wherein the salt is a hydrochloride salt (para [0143]).

As per claim 73, Li further teaches wherein W is -S-, -N(R25)-, or -O-; wherein Y is -C(R26)- or -N-, and wherein Z is -C(R27)- or -N- (Compounds 26, 27, 29, or A35; Table 1 on pages 10-11).

As per claim 74, Li further teaches wherein Y is -C(R26)- and wherein Z is -C(R27)- or (Compound A35; Table 1 on page 11).

*********************************************************************************************************************continued in next supplemental box*********************************************************************************************************************
<table>
<thead>
<tr>
<th>Supplemental Box</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IN CASE THE SPACE IN ANY OF THE PRECEDING BOXES IS NOT SUFFICIENT.</strong></td>
</tr>
<tr>
<td><strong>CONTINUATION OF:</strong></td>
</tr>
<tr>
<td>Previous Supplemental Box - Box V No 2 (citations and explanations)</td>
</tr>
<tr>
<td>As per claim 75, Li further teaches wherein R26 is hydrogen and wherein R27 is hydrogen (Compound A35; Table 1 on page 11).</td>
</tr>
<tr>
<td>As per claim 77, Li further teaches wherein A is hydrogen and wherein R17 is hydrogen (Compound A35; Table 1 on page 11).</td>
</tr>
<tr>
<td>As per claim 78, Li further teaches wherein A is hydrogen; wherein R17 is hydrogen, wherein R26 is hydrogen, and wherein R27 is hydrogen (Compound A35; Table 1 on page 11).</td>
</tr>
<tr>
<td>As per claim 79, Li further teaches wherein R17 is hydrogen, wherein R26 is hydrogen and wherein R27 is hydrogen (Compound A35; Table 1 on page 11). Although although neither Li nor Xu explicitly teaches wherein A is -NH2, such a substrate would have been further obvious to obtain the invention as claimed because Li teaches that nucleotides bind the receptor (para [0245]) and because cytosine, a well-known nucleotide, comprises -NH2 at the claimed position.</td>
</tr>
<tr>
<td>As per claim 80, the fourth recited compound is obvious for the reasons discussed above and because Li teaches wherein W is S (Compound A22; Table 1 on page 9) and also teaches wherein both Y and Z are -CH- (Compound A35; Table 1 on page 11) and wherein R17 is H (Compounds A22 or A35; Table 1 on pages 9 and 11). Although neither Li nor Xu explicitly teaches wherein A is -NH2, such a substrate would have been further obvious to obtain the invention as claimed because Li teaches that nucleotides bind the receptor (para [0245]) and because cytosine, a well-known nucleotide, comprises -NH2 at the claimed position.</td>
</tr>
<tr>
<td>As per claim 81, Li further teaches wherein the salt is a hydrochloride salt (para [0143]).</td>
</tr>
<tr>
<td>As per claim 82, Li teaches suggests the compound of claim 58, as discussed above. Li further teaches wherein G forms a single bond with E (Compounds 26, 27, or 29; Table 1 on page 10), wherein W is -S-, -N(R25)-, or -O-, wherein Y is -C(R26)- or -N-, and wherein Z is -C(R27)- or -N- (Compounds 26, 27, 29, or A35; Table 1 on pages 10-11). Li further teaches that the chemosensory receptor (T1R) also binds nucleotides (para [0092]) and is a G Protein-Coupled Receptor (GPCR), a class of receptors known to bind nucleotides (para [0047]; [0050]; [0051]); however, Li does not teach wherein G forms a double bond with D, wherein D is =S, wherein E is -NR17, or wherein B is -N-.</td>
</tr>
<tr>
<td>Xu teaches a compound (nucleotide), wherein G forms a double bond with D, wherein D is =O, wherein E is -NR17, and wherein B is -N- (uridine from UTP) that exhibits high activity against a GPCR (inhibit current by activating a GPCR (pg 367, col 1, para 2 - col 2, para 1 and the abstract).</td>
</tr>
<tr>
<td>One skilled in the art at the time the invention was made would have found obvious the compound of Li, wherein G forms a double bond with D, wherein E is -NR17, and wherein B is -N-, as taught by Xu, and wherein D is =S, as suggested by Xu, to obtain the invention as claimed because Li identifies the chemosensory receptor as a GPCR which are known to bind nucleotides while Xu teaches that a nucleotide, wherein G forms a double bond with D, wherein D is =O, wherein E is -NR17, and wherein B is -N- (uridine from UTP), is highly active against a GPCR. Although Xu does not explicitly teach wherein B is =S, it would have been further obvious to provide such a substituent since Xu teaches wherein D is =O and it is well-known that S and O have similar properties.</td>
</tr>
<tr>
<td>As per claim 83, Li teaches the compound of claim 58, as discussed above. Li further teaches wherein G forms a double bond with E and a single bond with D:</td>
</tr>
<tr>
<td>D is OR15</td>
</tr>
<tr>
<td>W is N(R25)-</td>
</tr>
<tr>
<td>Y is C(R26)-; and</td>
</tr>
<tr>
<td>Z is C(R27)-(Compound A35; Table 1 on page 11). Li does not teach that B and E are both -N-.</td>
</tr>
<tr>
<td>Xu teaches a compound (nucleotide), wherein E is -N-, and wherein B is -N- (uridine from UTP) that exhibits high activity against a GPCR (inhibit current by activating a GPCR (pg 367, col 1, para 2 - col 2, para 1 and the abstract).</td>
</tr>
<tr>
<td>One skilled in the art at the time the invention was made would have found obvious the compound of Li, wherein E is -N-, and wherein B is -N-, as taught by Xu, to obtain the invention as claimed because Li identifies the chemosensory receptor as a GPCR which are known to bind nucleotides while Xu teaches that a nucleotide, wherein E is -N-, and wherein B is -N- (uridine from UTP), is highly active against a GPCR.</td>
</tr>
<tr>
<td>As per claim 84, Li further teaches wherein A is hydrogen (Compound A35; Table 1 on page 11).</td>
</tr>
<tr>
<td>As per claim 85, Li further teaches wherein R17 is hydrogen, wherein R26 is hydrogen and wherein R27 is hydrogen (Compound A35; Table 1 on page 11).</td>
</tr>
<tr>
<td>As per claim 86, the second recited compound is obvious for the reasons discussed above and because Li teaches wherein W is S (Compound A22; Table 1 on page 9) and also teaches wherein both Y and Z are -CH- (Compound A35; Table 1 on page 11) and wherein R17 is H (Compounds A22 or A35; Table 1 on pages 9 and 11). Although although neither Li nor Xu explicitly teaches wherein A is -NH2, such a substrate would have been further obvious to obtain the invention as claimed because Li teaches that nucleotides bind the receptor (para [0245]) and because cytosine, a well-known nucleotide, comprises -NH2 at the claimed position. In addition, although neither Li nor Xu does not explicitly teach wherein D is =S, it would have been further obvious to provide such a substituent since Xu teaches wherein D is =O (uridine from UTP; abstract) and it is well-known that S and O have similar properties.</td>
</tr>
<tr>
<td>As per claim 87, Li further teaches wherein the salt is a hydrochloride salt (para [0143]).</td>
</tr>
</tbody>
</table>

---

Form PCT/ISA/237 (Supplemental Box) (April 2007)
In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Previous Supplemental Box - Box V No 2 (citations and explanations)

As per claim 174, Li suggests the compound of claim 173 as discussed above. Although Li does not explicitly teach wherein B is \(N\)- and E is NR17, such limitation would have been further obvious for the reasons discussed in claim 83, specifically because Li identifies the chemosensory receptor as a GPCR which are known to bind nucleotides while Xu teaches that a nucleotide, wherein E is \(N\)-, and wherein B is \(N\)-(uridine from UTP), is highly active against a GPCR.

As per claim 175, Li teaches wherein G is \(C\)- (Compound A35; Table 1 on page 11).

As per claim 176, Xu further teaches wherein D is [a tautomer of] \(OH = O\), and wherein A is [a tautomer of] \(OH = O\) (uridine from UTP; abstract).

As per claim 177, the third recited compound is obvious for the reasons discussed above, specifically because Xu teaches wherein D is [a tautomer of] \(OH = O\), and wherein A is [a tautomer of] \(OH = O\) (uridine from UTP; abstract) and further because Li teaches wherein R17 is hydrogen (Compound A35; Table 1 on page 11) and teaches compounds having carbon atoms in the same positions of the five-membered ring as claimed (Compounds A35 and A36; Table 1 on page 11) and further teaches a compound having an oxygen in the position of the sulfur atom in the claimed compound (compound E71, Table 5 on page 43) and a skilled artisan would have readily appreciated providing a sulfur atom in the position of the claimed compound because it is well-known that S and O have similar properties.

As per claim 178, Li further teaches wherein the salt is a hydrochloride salt (para [0143]).

As per claim 179, Li teaches wherein A is hydrogen (Compounds A35 and A36; Table 1 on page 11) while Xu teaches wherein D = \(O\) (uridine from UTP; abstract).

As per claim 188, Li teaches wherein R17 is hydrogen (Compound A35; Table 1 on page 11). Li does not teach wherein D is \(O\), wherein E is \(N\), or wherein A is \(NH_2\); however, such would have been obvious for the reasons discussed above, specifically because Li identifies the chemosensory receptor as a GPCR which are known to bind nucleotides while Xu teaches that a nucleotide, wherein D is [a tautomer of] \(OH = O\), and wherein E is \(N\) (uridine from UTP; abstract) and is highly active against a GPCR. Although neither Li nor Xu explicitly teaches wherein A is \(NH_2\), such a substituent would have been further obvious to obtain the invention as claimed because Li teaches that nucleotides bind the receptor (para [0245]) and because cytosine, a well-known nucleotide, comprises \(NH_2\) at the claimed position.

As per claim 189, Li further teaches wherein
\[ W = -(C)(R24)-; \]
\[ Y = -(C)(R26)-; \]
\[ Z = -(N)(R28)-; \]
\[ R26 is hydrogen \]
\[ R27 is hydrogen \]

As per claim 190, Li further teaches wherein
\[ Y \text{ forms a single bond with } W \text{ and a double bond with } Z \]
\[ D is -(R15) \]
\[ W is -(N)(R25)-; \]
\[ Y is -(C)(R26)-; \]
\[ Z is -(C)(R27)- (Compound A35; Table 1 on page 11). \]

As per claim 191, Li further teaches wherein B is \(C(R12)-(Compound A35; Table 1 on page 11). \)

As per claim 192, Li further teaches a sulfur in the claimed position (Compound A22; Table 1 on page 9) and teaches C=C in the other two non-fused positions, wherein R26 and R27 are hydrogen (Compound A35; Table 1 on page 11). Although Li does not teach wherein B is \(N\), such would have been obvious for the reasons discussed above, specifically because Li identifies the chemosensory receptor as a GPCR which are known to bind nucleotides while Xu teaches that a nucleotide, wherein B is \(N\) (uridine from UTP; abstract) and is highly active against a GPCR.

As per claim 193, neither Li nor Xu teaches wherein D is methyl, \(-CH_3\), or hydrogen.

As per claim 194, Li teaches a methyl group on the five-membered ring (Compound A23; Table 1 on page 9). Although Li does not explicitly teach that both non-fused carbons are substituted with methyl, such would have been further obvious based on routine experimentation. Although neither Li nor Xu explicitly teaches wherein A is \(NH_2\), such a substituent would have been further obvious to obtain the invention as claimed because Li teaches that nucleotides bind the receptor (para [0245]) and because cytosine, a well-known nucleotide, comprises \(NH_2\) at the claimed position.

As per claim 195, it is further obvious for the reasons discussed above and because Li teaches wherein A is hydrogen (Compounds A23, A35, or A36; Table 1 on pages 9 and 11) while Xu teaches wherein D is [a tautomer of] \(OH = O\) (uridine from UTP; abstract). Although neither Li nor Xu explicitly teaches wherein D is \(SH\), such would have been further obvious because it is well known that S and O have similar properties.

******************************************************************************continued in next supplemental box******************************************************************************

Form PCT/ISA/237 (Supplemental Box) (April 2007)
In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Previous Supplemental Box - Box V No 2 (citations and explanations)

As per claim 196, it is further obvious for the reasons discussed above, and because although neither Li nor Xu explicitly teaches wherein A is LNWR10, such a substituent would have been further obvious to obtain the invention as claimed because Li teaches that nucleotides bind the receptor (para [0245]) and because cytosine, a well-known nucleotide, comprises -NH2 at the claimed position and because a skilled artisan would have readily appreciated substituting the N with a moiety such as a methyl group.

As per claim 197, it is further obvious for the reasons discussed in claim 195 and because although neither Li nor Xu explicitly teaches wherein A is -NH2, such a substituent would have been further obvious to obtain the invention as claimed because Li teaches that nucleotides bind the receptor (para [0245]) and because cytosine, a well-known nucleotide, comprises -NH2 at the claimed position.

As per claim 198, it is obvious for the reasons discussed in claim 194 and further because Xu teaches wherein D is [a tautomer of] LOH (uridine from UTP; abstract).

As per claim 199, the twenty-ninth recited compound is further obvious because Li teaches wherein W is LO-, Y is -C(CH3)-, and Z is N (Compound A24; Table 1 on page 9) while Xu teaches wherein E and B are each N and wherein D is [a tautomer of] LOH (=O on uridine from UTP; abstract).

As per claim 200, Li further teaches wherein the salt is a hydrochloride salt (para [0143]).

Claims 45 and 55 lack an inventive step under PCT Article 33(3) as being obvious over Li in view of Silve, and further in view of the article entitled "Distinct Contributions of T1R2 and T1R3 Taste Receptor Subunits to the Detection of Sweet Stimuli" by Nie et al. (hereinafter LNLe). As per claims 45 and 55, Li teaches the method of claim 38 and suggests the modifier of claim 52, as discussed above. Li teaches that the interacting residues comprise S144 of T1R2 (para [0391]; [0392]; [0120]) but does not explicitly teach residues S40, Y103, D142, S143, or P277. Silve teaches that ligand interacting residues of the Venus flytrap domain (abstract) of T1R2 comprise Y103, S143, or P277 (pg 11, table 1). However, neither Li nor Silve teaches residues S40 or D142. Nie teaches that a ligand binding site of T1R2 lies in the N-terminal domain (pg 1948, col 2, para 2 and the abstract).

One skilled in the art at the time the invention was made would have found obvious the method and modifier of Li, wherein the interacting residues further comprise Y103, S143, or P277, as taught by Silve, and wherein the interacting residues further comprise D142, as suggested by Silve, and further comprise S40 as suggested by Nie, to obtain the invention as claimed to provide a compound that binds additional residues known to modulate activity of the receptor (Ca2+ binding stabilizes the closed conformation with in T1R2 venus flytrap domain; pg 6, col 2, para 1 and the abstract). Although D142 and S40 are not specifically taught, D142 would have been further obvious since Silve teaches an adjacent residue in close proximity (S143) that is an interacting residue and S40 would have been further obvious since Nie teaches that a ligand binding site of T1R2 lies in the N-terminal domain.

Claims 97 and 98 lack an inventive step under PCT Article 33(3) as being obvious over Li as above, in view of US 2006/0045953 A1 to Tachdjian et al. (hereinafter 'Tachdjian'). As per claim 97, Li suggests the compound of claim 56, as discussed above. Li teaches that the compound binds T1R1/T1R3 or T1R2/T1R3 (para [0005]) but does not explicitly teach atoms H, I, J, and K in the claimed orientation.

Tachdjian also teaches compounds that bind the T1R1/T1R3 or T1R2/T1R3 receptors (para [0009]; [0012]) and further teaches compounds of similar structure to formula I, comprising atoms H, I, J, and K wherein H is LC(R35), I is LC(R36), J is LC(R37), and K is LC(R38), and wherein R35-R38 are each hydrogen (para [0166], pg 15 top of right column).

One skilled in the art at the time the invention was made would have found obvious the compound of Li, further comprising the claimed H, I, J, and K atoms, as taught by Tachdjian to obtain the invention as claimed because Li teaches that the compounds bind T1R1/T1R3 and T1R2/T1R3, while Tachdjian teaches similar compounds that also bind T1R1/T1R3 or T1R2/T1R3 receptors and may comprise the claimed H, I, J, and K atoms.

As per claim 98, Li further teaches that (D)npG is -C(O) (Compound A35; Table 1 on page 11).

Claim 76 lacks an inventive step under PCT Article 33(3) as being obvious over Li in view of Xu, as above, and further in view of US 2006/0135552 A1 to Malherbe et al. (hereinafter 'Malherbe'). As per claim 76, the combined teachings of Li and Xu produce the compound of claim 74, as discussed above; however, neither teaches wherein R26 and R27 together with the atom to which they are bonded form a cycloalkyl or heterocycloalkyl ring.

Malherbe also teaches a receptor ligand enhancer (agonist) that binds a venus flytrap domain (venus flytrap module) (para [0003]) and also teaches a similar compound, also of Formula I (Formula I; para [0008]). Malherbe further teaches that, together with the atom to which they are bonded, the two available non-heterocyclic atoms (R4 and R5) form a cycloalkyl or heterocycloalkyl ring (para [0008]).

One skilled in the art at the time the invention was made would have found obvious the compound produced by the combined teachings of Li and Xu wherein R26 and R27 together with the atom to which they are bonded form a cycloalkyl or heterocycloalkyl ring, as taught by Malherbe to obtain the invention as claimed because both references teach similar structures (Formula I) that are receptor ligand enhancers and bind a venus flytrap domain.

***************continued in next supplemental box***************
In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Previous Supplemental Box - Box V No 2 (citations and explanations)

Claims 85-96, 99-116, 119-165, 168-171, 180-187 lack an inventive step under PCT Article 33(3) as being obvious over Li as above, in view of Xu and further in view of Tachdjian.

As per claim 88, Li suggests the compound of claim 58, as discussed above. Li teaches that the chemosensory receptor (T1R1/T1R3 or T1R2/T1R3; para [008]) also binds nucleotides (para [0092]) and is a G Protein-Coupled Receptor (GPCR), a class of receptors known to bind nucleotides (para [0047]; [0050]; [0051]). Although Li teaches a compound similar to Formula I (Compound A35 or A36; Table 1 on page 11), Li does not teach that the receptor X or B is N or that G-(D)n is S(O)2.

Xu teaches that a compound (nucleotide), wherein (D)n is =O and E and B are each N (uridine from UTP), exhibits high activity against a GPCR (inhibits current by activating a GPCR (pg 367, col 1, para 2 - col 2, para 1 and the abstract). However, neither Xu nor Li teaches wherein G is S and wherein G is substituted with an additional = O to form S(O)2.

Tachdjian also teaches compounds that bind the T1R1/T1R3 or T1R2/T1R3 receptors (para [0089]; [0012]) and further teaches compounds similar to structure (para [0170]), wherein G-(D)n is S(O)2 (note the various positions R2 may be provided; para [0170] and that the phenyl ring of the R2 group can by modified to comprise a heteroatom; para [0171]) and that the heteroatom may be a S(O)2 group; para [0121]). One skilled in the art at the time the invention was made would have found obvious the compound of Li, wherein (D)n is =O and E and B are each N, as taught by Xu, and further wherein G is substituted with an additional =O to form S(O)2, as taught by Tachdjian, to obtain the invention as claimed because Li identifies the chemosensory receptors, T1R1/T1R3 and T1R2/T1R3, as GPCRs which are known to bind nucleotides while Xu teaches that a nucleotide, wherein (D)n is =O and E and B are each N (uridine), is highly active against a GPCR and because Tachdjian teaches compounds similar to Formula II that also bind T1R1/T1R3 or T1R2/T1R3 receptors and may comprise S(O)2 in the claimed position.

As per claim 89, Li further teaches wherein W is -S-, -N(R25), or -O-, wherein Y is -C(R26)- or -N-, and wherein Z is -C(R27)- or -N-. (Compounds 26, 27, 29, or A35; Table 1 on pages 10-11) and wherein W and Y forms a single bond and Z forms a double bond (Compound A35; Table 1 on page 11).

As per claim 90, Li further teaches wherein W is -C(R24)- wherein Y is -C(R26)- and wherein Z is -N(R28)- and wherein W and Y forms a double bond and Z forms a single bond (Compound A36; Table 1 on page 11).

As per claims 91 and 92, Li further teaches wherein W is -N(R25)- wherein Z is -C(R27)- and wherein W and Y forms a single bond and Z forms a double bond (Compound A35; Table 1 on page 11) while Tachdjian teaches wherein Y is -N-(para [0175], pg 18, third to last compound listed in left column).

As per claim 93, Li teaches wherein A is hydrogen (Compound A35; Table 1 on page 11).

As per claim 94, Li teaches wherein R17 is hydrogen (Compound A35; Table 1 on page 11).

As per claim 95, Li teaches wherein R26 and R27 are each hydrogen (Compound A35; Table 1 on page 11).

As per claim 96, the ninth recited compound is further obvious because Li teaches wherein W is -NH- (Compound A35; Table 1 on page 11) while Tachdjian teaches wherein Y is -N-(para [0175], pg 18, third to last compound listed in left column).

As per claim 99, the combined teachings of Li and Tachdjian produce the compound of claim 97, as discussed above. Although Li teaches that the chemosensory receptor (T1R1/T1R3 or T1R2/T1R3; para [008]) also binds nucleotides (para [0092]) and is a G Protein-Coupled Receptor (GPCR), a class of receptors known to bind nucleotides (para [0047]; [0050]; [0051]), neither Li nor Tachdjian teaches wherein E is N(R17) or wherein -(D)n is =O.

Xu teaches a compound (nucleotide), wherein -(D)n is =O and wherein E is -NR17 (uridine from UTP), that exhibits high activity against a GPCR (inhibit current by activating a GPCR (pg 367, col 1, para 1-2, col 2, para 1 and the abstract). One skilled in the art at the time the invention was made would have found obvious the compound produced by the combined teachings of Li and Tachdjian wherein -(D)n is =O and wherein E is -NR17, as taught by Xu, to obtain the invention as claimed because Li identifies the chemosensory receptor as a GPCR which are known to bind nucleotides while Xu teaches that a nucleotide, wherein D is =O and wherein E is -NR17 (uridine from UTP), is highly active against a GPCR.

As per claim 100, Li teaches wherein A is hydrogen (Compound A35; Table 1 on page 11).

As per claim 101, although neither Li, Tachdjian, nor Xu explicitly teaches wherein A is -NH2, such a substituent would have been further obvious to obtain the invention as claimed because Li teaches that nucleotides bind the receptor (para [0245]) and because cytosine, a well-known nucleotide, comprises -NH2 at the claimed position.

As per claims 102 and 103, Li teaches wherein R17 is hydrogen (Compound A35; Table 1 on page 11).

As per claim 104, Tachdjian teaches wherein H is -C(R35)-, J is -C(R36)-, K is -C(R37)-, and L is -C(R38)- (para [0166], pg 15 top of right column).

As per claim 105, Li teaches wherein A is hydrogen and wherein R17 is hydrogen (Compound A35; Table 1 on page 11).
In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Previous Supplemental Box - Box V No 2 (citations and explanations)

As per claim 106, Li teaches wherein R17 is hydrogen (Compound A35; Table 1 on page 11). Although neither Li, Tachdjian, nor Xu explicitly teaches wherein A is -NH2, such a substituent would have been further obvious to obtain the invention as claimed because Li teaches that nucleotides bind the receptor (para [0245]) and because cytosine, a well-known nucleotide, comprises -NH2 at the claimed position.

As per claim 107, Tachdjian teaches wherein R35-R38 are each hydrogen (para [0166], pg 15 top of right column).

As per claim 108, Tachdjian teaches wherein R38 is hydrogen (para [0166], pg 15 top of right column).

As per claim 109, Li teaches wherein R17 is hydrogen (Compound A35; Table 1 on page 11) while Tachdjian teaches wherein R35-R38 are each hydrogen (para [0166], pg 15 top of right column). Although neither Li, Tachdjian, nor Xu explicitly teaches wherein A is -NH2, such a substituent would have been further obvious to obtain the invention as claimed because Li teaches that nucleotides bind the receptor (para [0245]) and because cytosine, a well-known nucleotide, comprises -NH2 at the claimed position.

As per claim 110, the second recited compound would have been further obvious because Xu teaches wherein B is N (uridine from UTP; abstract) while Tachdjian teaches wherein H is =C(R35), I is =C(R36), J is =C(R37), and K is =C(R38), and wherein R35-R38 are each hydrogen (para [0166], pg 15 top of right column). Although neither Li, Tachdjian, nor Xu explicitly teaches wherein A is -NH2, such a substituent would have been further obvious to obtain the invention as claimed because Li teaches that nucleotides bind the receptor (para [0245]) and because cytosine, a well-known nucleotide, comprises -NH2 at the claimed position.

As per claim 111, Li further teaches wherein the salt is a hydrochloride salt (para [0143]).

As per claim 112, Li teaches wherein A and R17 are each hydrogen (Compound A35; Table 1 on page 11) while Xu teaches wherein B is N (uridine from UTP; abstract) while Tachdjian teaches wherein X1 is =NR9. X2 is absent (m is 0), Y1 is the –X3-C(X4)-X5-Ry moiety, X3 and X5 are covalent bonds, X4 is O, Ry (A) is aryl or heteroaryl, R9 is hydrogen (para [0311]), and wherein Rx is absent (n is 0; para [0315]; [0316]; [0318]).

As per claim 113, Tachdjian teaches wherein Y1 is the –X3-C(X4)-X5-Ry moiety (para [0311]). Although Tachdjian does not explicitly teach wherein X1 is –CH2, such would have been further obvious since Tachdjian teaches that the ring may be substituted with a methyl group (para [0098]) and a skilled artisan would have readily appreciated using said methyl group as the point of attachment.

As per claim 114, Tachdjian teaches wherein X1 is =NR9- and m is 0 (para [0311]) while both Li (GTP; para [0085]) and Xu (ATP, ADP, abstract) teach cycloheptenyl (ribose group on the respective purines) substituted at the first position non-fused position on the second (middle) ring and a skilled artisan would readily appreciate providing such a cyclohexenyl as the Y groups since it provides substituent similar to the purines taught by Li and Xu with the addition short spacer (i.e. =NR9-).

As per claim 115, Tachdjian teaches wherein X1 is =NR9- and wherein Y1 is the –X3-C(X4)-X5-Ry moiety (para [0311]). Although Tachdjian does not explicitly teach wherein m is 1, i.e. does not explicitly teach wherein X1 is –CH2- or –O-, such would have been further obvious since Tachdjian teaches that the ring may be substituted with a methyl group (para [0098]) and a skilled artisan would have readily appreciated using said methyl group as the point of attachment and further because Tachdjian teaches that an oxygen may be inserted to form ethers (para [0157]).

As per claim 116, although Tachdjian does not explicitly teach wherein X2 is methylene, ethylene, or propylene, such would have been further obvious since Tachdjian teaches that R2 may comprise an alkenyl group (para [0138]).

As per claim 117, it is obvious for the reasons discussed in claim 114, specifically because both Li (GTP; para [0085]) and Xu (ATP, ADP, abstract) teach cyclohexenyl (ribose group on the respective purines) substituted at the first position non-fused position on the second (middle) ring and a skilled artisan would readily appreciate providing such a cyclohexenyl as the Y groups since it provides substituent similar to the purines taught by Li and Xu with the addition of a shorter spacer.

As per claim 120, both Li (GTP; para [0085]) and Xu (ATP, ADP; abstract) teach wherein the cyclohexenyl is a substituted dihydrofuran (ribose group).

As per claim 121, both Li (GTP; para [0085]) and Xu (ATP, ADP; abstract) teach wherein the substituted cyclohexenyl comprises an –OR9 (-OH) substituent.

**continues in next supplemental box**
In case the space in any of the preceding boxes is not sufficient.
Continuation of:
Previous Supplemental Box - Box V No 2 (citations and explanations)

As per claim 122, Tachdjia teaches wherein X4 is O (para [0311]).

As per claim 123, Tachdjia teaches wherein –X3-C(X4)-X5—is –NHC(O)– (para [0311]).

As per claim 124, it is obvious for the reasons discussed in claim 114, specifically because both Li (GTP; para [0085]) and Xu (ATP, ADP; abstract) teach cycloheptenylkyl (ribose group on the respective purines) substituted at the first position non-fused position on the second (middle) ring and a skilled artisan would readily appreciate providing such a cycloheptenylkyl as the Y groups since it provides substituent similar to the purines taught by Li and Xu with the addition of a short spacer, and further because Li teaches wherein A and R17 are each hydrogen (Compound A35; Table 1 on page 11).

As per claim 125, Li teaches wherein A and R17 are each hydrogen (Compound A35; Table 1 on page 11) while Tachdjia teaches wherein –X3-C(X4)-X5—is –NHC(O)– (para [0311]).

As per claim 126, the fourth to last compound is obvious for the reasons discussed above, specifically because Li teaches wherein A and R17 are each hydrogen (Compound A35; Table 1 on page 11) while Tachdjia teaches wherein –X3-C(X4)-X5—is –NHC(O)– (para [0311]) and because Tachdjia teaches the use of a phenyl-propyl group (para [0101]) and a skilled artisan would have appreciated providing the phenyl ring of the compound produce by the combined teachings of Li, Xu, and Tachdjia as the phenyl of said phenyl-propyl group and because although Tachdjia teaches providing an aryl ring as RY in the instant embodiment (para [0311]) Tachdjia teaches that Y1 (referred to as ‘A’ or ‘R1) may alternatively be a hydrocarbon (para [0139]) a skilled artisan would have readily providing a methyl group as such.

As per claim 127, Li further teaches wherein the salt is a hydrochloride salt (para [0143]).

As per claim 128, the combined teachings of Li and Tachdjia produce the compound of claim 97, as discussed above. Tachdjian further teaches wherein G(-O) is S(O)2 (note the various positions R2 may be provided; para [0170])—and that the phenyl ring of the R2 group can by modified to comprise a heteroatom; para [0171]—and that the heteroatom may be a S(O)2 group; para [0121]). Li teaches that the chemoreceptor (T1R1/T1R3 or T1R2/T1R3; para [0008]) also binds nucleotides (para [0092]) and is a G Protein-Coupled Receptor (GPCR), a class of receptors known to bind nucleotides (para [0047]; [0050]; [0051]). However, neither Li nor Tachdjia teaches wherein B and E are each N.

Xu teaches that a compound (nucleotide), wherein E and B are each N (uridine from UTP), exhibits high activity against a GPCR (inhibits current by activating a GPCR pg 367, col 1, para 2 - col 2, para 1 and the abstract).

One skilled in the art at the time the invention was made would have found obvious the compound produced by the combined teachings of Li and Tachdjia, wherein E and B are each N, as taught by Xu, to obtain the invention as claimed because Li identifies the chemoreceptors, T1R1/T1R3 and T1R2/T1R3, as GPCRs which are known to bind nucleotides while Xu teaches that a nucleotide, wherein E and B are each N (uridine), is highly active against a GPCR.

As per claim 129, Li teaches wherein A is hydrogen (Compound A35; Table 1 on page 11).

As per claim 130, Li teaches wherein R17 is hydrogen (Compound A35; Table 1 on page 11).

As per claim 131, Li teaches wherein A and R17 are each hydrogen (Compound A35; Table 1 on page 11).

As per claims 132 and 133, Tachdjia teaches wherein H is –C(R35), I is –C(R36), J is –C(R37), and K is –C(R38) (para [0166], pg 15 top of right column).

As per claim 134, Tachdjia teaches wherein R35-R38 are each hydrogen (para [0166], pg 15 top of right column).

As per claim 135, Li teaches wherein R17 is hydrogen (Compound A35; Table 1 on page 11) while Tachdjia teaches wherein R35-R38 are each hydrogen (para [0166], pg 15 top of right column). Although neither Li, Tachdjian, nor Xu explicitly teaches wherein A is -NH2, such a substituent would have been further obvious to obtain the invention as claimed because Li teaches that nucleotides bind the receptor (para [0245]) and because cytosine, a well-known nucleotide, comprises -NH2 at the claimed position.

As per claim 136, the first recited compound is obvious for the reasons discussed above, specifically because Li teaches wherein R17 is hydrogen (Compound A35; Table 1 on page 11) while Tachdjia teaches wherein H is –C(R35), I is –C(R36), J is –C(R37), and K is –C(R38), and wherein R35-R38 are each hydrogen (para [0166], pg 15 top of right column) and because although neither Li, Tachdjian, nor Xu explicitly teaches wherein A is -NH2, such a substituent would have been further obvious to obtain the invention as claimed because Li teaches that nucleotides bind the receptor (para [0245]) and because cytosine, a well-known nucleotide, comprises -NH2 at the claimed position.

As per claim 137, Li further teaches wherein the salt is a hydrochloride salt (para [0143]).
Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
Previous Supplemental Box - Box V No 2 (citations and explanations)

As per claim 138, Li teaches wherein A and R17 are each hydrogen (Compound A35; Table 1 on page 11) while Xu teaches wherein B is N (uridine from UTP; abstract) while Tachdjia teaches wherein
X1 is –NR9;
X2 is absent (m is 0)
Y1 is the –X3-C(X4)-X5-Ry moiety
X3 and X5 are covalent bonds
X4 is O
Ry (A) is aryl or heteroaryl
R9 is hydrogen (para [0311]), and wherein
Rx is absent (n is 0; para [0315]; [0316]; [0318]).

As per claim 139, Tachdjia teaches wherein Y1 is the –X3-C(X4)-X5-Ry moiety (para [0311]). Although Tachdjia does not explicitly teach wherein X1 is –CH2–, such would have been further obvious since Tachdjia teaches that the ring may be substituted with a methyl group (para [0098]) and a skilled artisan would have readily appreciated using said methyl group as the point of attachment.

As per claim 140, Tachdjia teaches wherein X1 is –NR9– and m is 0 (para [0311]) while both Li (GTP; para [0085]) and Xu (ATP, ADP; abstract) teach cyclohexaeryl (ribose group on the respective purines) substituted at the first position non-fused position on the second (middle) ring and a skilled artisan would readily appreciate providing such a cyclohexaeryl as the Y groups since it provides substituent similar to the purines taught by Li and Xu with the addition short spacer (i.e. –NR9–).

As per claim 141, Tachdjia teaches wherein X1 is –NR9– and wherein Y1 is the –X3-C(X4)-X5-Ry moiety (para [0311]). Although Tachdjia does not explicitly teach wherein m is 1, i.e. does not explicitly teach wherein X1 is –CH2– or –O–, such would have been further obvious since Tachdjia teaches that the ring may be substituted with a methyl group (para [0098]) and a skilled artisan would have readily appreciated using said methyl group as the point of attachment and further because Tachdjia teaches that an oxygen may be inserted to form ethers (para [0157]).

As per claim 142, Tachdjia teaches alkylene groups (para [0068]; [0095]; [0120]). Although Tachdjia does not explicitly teach such as X2, a skilled artisan would have readily appreciated providing such in order to reduce flexibility of the Y1 moiety.

As per claim 143, although Tachdjia does not explicitly teach wherein X2 is methylene, ethylene, or propylene, such would have been further obvious since Tachdjia teaches that R2 may comprise an alkylene group (para [0138]).

As per claim 144, Li teaches wherein A is hydrogen (Compound A35; Table 1 on page 11).

As per claim 145, Li teaches wherein R17 is hydrogen (Compound A35; Table 1 on page 11).

As per claim 146, both Li (GTP; para [0085]) and Xu (ATP, ADP; abstract) teach cyclohexaeryl (ribose group on the respective purines) substituted at the first position non-fused position on the second (middle) ring and a skilled artisan would readily appreciate providing such a cyclohexaeryl as the Y groups since it provides substituent similar to the purines taught by Li and Xu with the addition short spacer, and further because Li teaches wherein A and R17 are each hydrogen (Compound A35; Table 1 on page 11).

As per claim 147, both Li (GTP; para [0085]) and Xu (ATP, ADP; abstract) teach wherein the cyclohexaeryl is a substituted dihydrofuranyl (ribose group).

As per claim 148, it is obvious for the reasons discussed in claim 146, specifically because both Li and Xu suggest providing a cyclohexaeryl as Y1, and further because Tachdjia teaches a heteroaryl in a similar position (a heteroaryl as A, linked through a spacer; para [0311]; [0311]).

As per claim 149, a skilled artisan would have readily appreciated providing a substituted furanyl as said heteroaryl since both Li (GTP; para [0085]) and Xu (ATP, ADP; abstract) teach providing said group as a dihydrofuranyl (ribose group).

As per claim 150, both Li (GTP; para [0085]) and Xu (ATP, ADP; abstract) teach wherein the substituted cyclohexaeryl comprises an –OR9 (–OH) substituent.

As per claim 151, Tachdjia teaches wherein Y1 is the –X3-C(X4)-X5-Ry moiety (para [0311]).

As per claim 152, Tachdjia teaches wherein X4 is O (para [0311]).

As per claim 153, Tachdjia teaches wherein –X3-C(X4)-X5- is –NHC(O)– (para [0311]).

*******************************************************************************continued in next supplemental box*******************************************************************************
Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Previous Supplemental Box - Box V No 2 (citations and explanations)

As per claim 154, both Li (GTP; para [0085]) and Xu (ATP, ADP; abstract) teach a substituted dihydrofuranyl (ribose group on the respective purines) substituted at the first position non-fused position on the second (middle) ring and a skilled artisan would readily appreciate providing such a substituted dihydrofuranyl as the Y groups since it provides a substituent similar to the purines taught by Li and Xu with the addition of a short spacer, and further because Li teaches wherein A and R17 are each hydrogen (Compound A35; Table 1 on page 11).

As per claim 155, Li teaches wherein A and R17 are each hydrogen (Compound A35; Table 1 on page 11) while Tachdjia teaches wherein Y1 is the —X3-C-(X4)-X5-Ry moiety (para [0311]), wherein —X3-C-(X4)-X5- is —NHC(O)— (para [0311]).

As per claim 156, the sixty-ninth recited compound (second to last compound on pg 450 of the instant application) is obvious for the reasons discussed above, specifically because Li teaches that R17 may be hydrogen (Compound A35; Table 1 on page 11) while Li teaches that nucleotides bind the receptor (para [0245]) and because cytosine, a well-known nucleotide, comprises —NH2 at the claimed position and because both Li (GTP; para [0085]) and Xu (ATP, ADP; abstract) teach a substituted dihydrofuranyl (ribose group on the respective purines) substituted at the first position non-fused position on the second (middle) ring and because Tachdjia teaches that an oxygen may be inserted to form ethers (para [0157]). Although neither Li nor Xu explicitly teach the additional hydroxyl group present on the ribose, a skilled artisan would have readily added such a group in order to provide an electrophilic substituent since the purines taught by Li and Xu have a phosphate substituted on the ribose.

As per claim 157, Li further teaches wherein the salt is a hydrochloride salt (para [0143]).

As per claim 158, the combined teachings of Li and Tachdjia produce the compound of claim 97, as discussed above. Li further teaches wherein D is —OR15 (Compound A35; Table 1 on page 11). Li teaches that the chemosensory receptor (T1R1/T1R3 or T1R2/T1R3; para [0008]) also binds nucleotides (para [0092]) and is a G Protein-Coupled Receptor (GPCR), a class of receptors known to bind nucleotides (para [0047]; [0050]; [0051]). However, neither Li nor Tachdjia teaches wherein B and E are each N.

Xu teaches that a compound (nucleotide), wherein E and B are each N (uridine from UTP), exhibits high activity against a GPCR (inhibits current by activating a GPCR; pg 367, col 1, para 2 - col 2, para 1 and the abstract).

One skilled in the art at the time the invention was made would have found obvious the compound produced by the combined teachings of Li and Tachdjia, wherein B and E are each N, as taught by Xu, to obtain the invention as claimed because Li identifies the chemosensory receptors, T1R1/T1R3 and T1R2/T1R3, as GPCRs which are known to bind nucleotides while Xu teaches that a nucleotide, wherein E and B are each N (uridine), is highly active against a GPCR.

As per claims 159 and 160, Tachdjia teaches wherein H is —C(R35), I is —C(R36), J is —C(R37), and K is —C(R38)— and wherein R35-R38 are each hydrogen (para [0166], pg 15 top of right column).

As per claim 161, a tautomer of the first recited compound is obvious for the reasons discussed above and because Xu further teaches that D is —O (uridine from UTP; abstract), a tautomer of the claimed compound wherein D is —OH. Although neither Li, Tachdjia, nor Xu explicitly teaches wherein A is —NH2, such a substituent would have been obvious to provide the invention as claimed because Li teaches that nucleotides bind the receptor (para [0245]) and because cytosine, a well-known nucleotide, comprises —NH2 at the claimed position.

As per claim 162, Li further teaches wherein the salt is a hydrochloride salt (para [0143]).

As per claim 163, Li further teaches wherein R12 is hydrogen (Compound A35; Table 1 on page 11) while Tachdjia teaches wherein H is —C(R35), I is —C(R36), J is —C(R37), and K is —C(R38)— wherein R35-R38 are each hydrogen (para [0166], pg 15 top of right column) and wherein R12 is not hydrogen (ring may be substituted with hydroxyl; para [0149]) or wherein R35-R38 are not hydrogen (R22 is selected from a list of substituents para [0166], pg 15 top of right column)—R2 may have additional substituents; para [0161]). Li teaches that the chemosensory receptor (T1R1/T1R3 or T1R2/T1R3; para [0008]) also binds nucleotides (para [0062]) and is a G Protein-Coupled Receptor (GPCR), a class of receptors known to bind nucleotides (para [0047]; [0050]; [0051]). However, neither Li nor Tachdjia teaches wherein E is N, wherein D is —OH, or wherein A is —OH.

Xu teaches that a compound (nucleotide), wherein E is N, D is [a tautomer of] —OH (=O), and wherein A is [a tautomer of] —OH (=O) (uridine from UTP), exhibits high activity against a GPCR (inhibits current by activating a GPCR; pg 367, col 1, para 2 - col 2, para 1 and the abstract).

One skilled in the art at the time the invention was made would have found obvious the compound produced by the combined teachings of Li and Tachdjia, wherein E is N, D is [a tautomer of] —OH and wherein A is [a tautomer of] —OH, as taught by Xu, to obtain the invention as claimed because Li identifies the chemosensory receptors, T1R1/T1R3 and T1R2/T1R3, as GPCRs which are known to bind nucleotides while Xu teaches that a nucleotide, wherein E is each N (uridine), is highly active against a GPCR.

As per claim 164, Tachdjia teaches that the ring may be substituted with —OH (hydroxyl; para [0149]). Although neither Li, Tachdjia, nor Xu explicitly teaches wherein A is —NH2, such a substituent would have been obvious to provide the invention as claimed because Li teaches that nucleotides bind the receptor (para [0245]) and because cytosine, a well-known nucleotide, comprises —NH2 at the claimed position.

As per claim 165, Tachdjia teaches wherein R35-R38 are each hydrogen (para [0166], pg 15 top of right column) while Xu teaches wherein D is [a tautomer of] —OH (uridine from UTP; abstract) while Tachdjia teaches wherein R12 is not —CO2 or CN (ring may be substituted with hydroxyl; para [0149]) and Li suggests that A may be NH2, as discussed above.

*continued in next supplemental box*
In case the space in any of the preceding boxes is not sufficient.

Continuation of:

As per claim 168, Li teaches wherein R17 is hydrogen (Compound A35; Table 1 on page 11) while Tachdjian teaches wherein H is –C
(r35)–, J is –C(r36)–, K is –C(r37)–, and L is –C(r38)– (para [0166], pg 15 top of right column). Li teaches that the chemosensory receptor
(T1R1/T1R3 or T1R2/T1R3; para [0069]) also binds nucleotides (para [0092]) and is a G Protein-Coupled Receptor (GPCR), a class of
receptors known to bind nucleotides (para [0047], [0050], [0051]). However, neither Li nor Tachdjian teaches wherein E or B are each N,
wherein D is =O, or wherein A is =OH.

Xu teach nucleotides, wherein E and B are each N, D is [a tautomer of] –OH (=O), and wherein A is [a tautomer of] –OH (=O)
(uridine from UTP), exhibits high activity against a GPCR (inhibits current by activating a GPCR (pg 367, col 1, para 2 - col 2, page 1
and the abstract).

One skilled in the art at the time the invention was made would have found obvious the compound produced by the combined teachings
of Li and Tachdjian, wherein E and B are each N, D is [a tautomer of] –OH, and wherein A is [a tautomer of] –OH, as taught by Xu, to obtain
the invention as claimed because Li identifies the chemosensory receptors, T1R1/T1R3 and T1R2/T1R3, as GPCRs which are known to
bind nucleotides while Xu teaches that a nucleotide, wherein E and B are each N, D is [a tautomer of] –OH, and wherein A is [a tautomer of]
–OH, (uridine), is highly active against a GPCR.

As per claim 169, Xu teaches that A is not –NH2 (uridine; abstract).

As per claim 170, the first recited compound is obvious for the reasons discussed above and because Tachdjian teaches wherein R35-R38
are each hydrogen (para [0166], pg 15 top of right column) and although Xu does not explicitly teach wherein D is =S, it would have been
further obvious to provide such a substituent since Xu teaches wherein D is =O and it is well-known that S and O have similar properties.

Although neither Li, Tachdjian, nor Xu explicitly teaches wherein A is –NH2, such a substituent would have been further obvious to obtain the
invention as claimed because Li teaches that nucleotides bind the receptor (para [0245]) and because uridine, a well-known nucleotide,
comprises –NH2 at the claimed position.

As per claim 171, Li further teaches wherein the salt is a hydrochloride salt (para [0143]).

As per claim 170, the combined teachings of Li and Xu produce the compound of claim 174. Li suggests the compound of claim 56, as
discussed above. Xu teaches wherein G-D is a double bond (uridine from UTP; abstract). Li teaches that the compound binds
T1R1/T1R3 or T1R2/T1R3 (para [0069]) but does not explicitly teach wherein L is =CHR60, M is CHR61, R is CHR62, and T is CHR63.

Tachdjian also teaches compounds that bind the T1R1/T1R3 or T1R2/T1R3 receptors (para [0099],[0012]) and further teaches
compounds of similar structure, wherein L is =CHR60, M is CHR61, R is CHR62, and T is CHR63 (para [0166], pg 15 top of right column).

One skilled in the art at the time the invention was made would have found obvious the compound produced by the combined teachings
of Li and Xu, wherein L is =CHR60, M is CHR61, R is CHR62, and T is CHR63, as taught by Tachdjian, and wherein A is NH2 to obtain
the invention as claimed because Li teaches that the compounds bind T1R1/T1R3 and T1R2/T1R3, while Tachdjian teaches similar
compounds that also bind T1R1/T1R3 or T1R2/T1R3, wherein L is =CHR60, M is CHR61, R is CHR62, and T is CHR63. Although neither
Li, Tachdjian, nor Xu explicitly teaches wherein A is –NH2, such a substituent would have been further obvious to obtain the invention as claimed
because Li teaches that nucleotides bind the receptor (para [0245]) and because uridine, a well-known nucleotide, comprises
–NH2 at the claimed position.

As per claim 171, it is obvious for the reasons discussed above, and further because Tachdjian teaches wherein R60-R63 are each
hydrogen (para [0166], pg 15 top of right column) while Xu teaches wherein D is O (uridine from UTP; abstract).

As per claim 182, Li further teaches wherein the salt is a hydrochloride salt (para [0143]).

As per claim 183, Li suggests the compound of claim 173, as discussed above. Li teaches that the chemosensory receptor (T1R1/T1R3 or
T1R2/T1R3; para [0069]) also binds nucleotides (para [0092]) and is a G Protein-Coupled Receptor (GPCR), a class of receptors known to
bind nucleotides (para [0047], [0050], [0051]). Although Li teaches a compound similar to Formula IVa (Compound A35 or A36; Table 1 on
page 11), Li does not teach that E or B is N or that (D)n is S(O)2.

Xu teaches that a compound (nucleoside), wherein (D)n is =O and E and B are each N (uridine from UTP), exhibits high activity against a
GPCR (inhibits current by activating a GPCR (pg 367, col 1, para 2 - col 2, page 1 and the abstract).

However, neither Xu nor Li teaches wherein G is S and wherein G is substituted with an additional =O to form S(O)2.

Tachdjian also teaches compounds that bind the T1R1/T1R3 or T1R2/T1R3 receptors (para [0099],[0012]) and further teaches
compounds of similar structure to formula II (para [0170]), wherein (D)n is S(O)2 (note the various positions R2 may be provided; para
[0170])—and that the phenyl ring of the R2 group can be modified to comprise a heterocarom; para [0171]—and that the heterocarom may be
a S(O)2 group; para [0121].

One skilled in the art at the time the invention was made would have found obvious the compound of Li, wherein (D)n is =O and E and B
are each N, as taught by Xu, and further wherein G is substituted with an additional =O to form S(O)2, as taught by Tachdjian, to obtain
the invention as claimed because Li identifies the chemosensory receptors, T1R1/T1R3 and T1R2/T1R3, as GPCRs which are known to
bind nucleotides while Xu teaches that a nucleotide, wherein (D)n is =O and E and B are each N (uridine), is highly active against a GPCR
and because Tachdjian teaches compounds similar to Formula IV that also bind T1R1/T1R3 or T1R2/T1R3 receptors and may comprise S
(O)2 in the claimed position.

=================================================================================

Form PCT/ISA/237 (Supplemental Box) (April 2007)
Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
Previous Supplemental Box - Box V No 2 (citations and explanations)

As per claim 184, Tachdjian teaches wherein L is -CHR60, M is CHR61, R is CHR62, and T is CHR63 (para [0166], pg 15 top of right column).

As per claim 185, Li teaches wherein A is hydrogen (Compound A35; Table 1 on page 11).

As per claim 186, the second recited compound is obvious for the reasons discussed above and because Li teaches wherein R17 is hydrogen (Compound A35; Table 1 on page 11) while Tachdjian teaches wherein R60-R63 are each hydrogen (para [0166], pg 15 top of right column). Although neither Li, Tachdjian, nor Xu explicitly teaches wherein A is -NH2, such a substituent would have been further obvious to obtain the invention as claimed because Li teaches that nucleotides bind the receptor (para [0248]) and because cytosine, a well-known nucleotide, comprises -NH2 at the claimed position.

As per claim 187, Li further teaches wherein the salt is a hydrochloride salt (para [0143]).

Claims 166, 167, and 172 lack an inventive step under PCT Article 33(3) as being obvious over Li in view of Xu, as above and further in view of Tachdjian and US 2004/0127435 A1 to Carson et al. (hereinafter 'Carson').

As per claim 166, the combined teachings of Li and Tachdjian produce the compound of claim 97, as discussed above. Li further teaches wherein B and G are each -C- (Compound A35 or A36; Table 1 on page 11) while Tachdjian teaches wherein I and J are C(R36) and C (R37), respectively (para [0166], pg 15 top of right column). Although Li teaches that the chemosensory receptor (T1R1/T1R3 or T1R2/T1R5), para [0008]) also binds nucleotides (para [0092]) and is a G Protein-Coupled Receptor (GPCR), a class of receptors known to bind nucleotides (para [0047]; [0050]; [0051]), neither Li nor Tachdjian teaches wherein E is -N- or wherein -Dn is -OH or wherein H and I are -N-.

Xu teaches a compound (nucleotide), wherein -Dn is [a tautomer of] -OH (c=O) and wherein E is -N- (uridine from UTP), that exhibits high activity against a GPCR (inhibit current by activating a GPCR pg 367, col 1, para 2 - col 2, para 1 and the abstract).

Carson also teaches compounds such as nucleotides and nucleotide analogs that a GPCR (para [0019]; [0155]) and teach that the second heterocyclic ring compound may have -N- at both positions adjacent to the fused positions (Formula III, para [0191]).

Carson also teaches compounds such as nucleotides and nucleotide analogs that a GPCR (para [0019]; [0155]) and teach that the second heterocyclic ring compound may have -N- at both positions adjacent to the fused positions (Formula III, para [0191]).

One skilled in the art at the time the invention was made would have found obvious the compound produced by the combined teachings of Li and Tachdjian wherein -Dn is [a tautomer of] -OH and wherein E is -N-, as taught by Xu, and wherein H and I are each -N-, as taught by Carson, to obtain the invention as claimed because Li identifies the chemosensory receptor as a GPCR which are known to bind nucleotides while Xu teaches that a nucleotide, wherein D is [a tautomer of] -OH and wherein E is -N- (uridine from UTP), is highly active against a GPCR and because Carson also teaches nucleotide analogs that bind a GPCR and comprise a second heterocyclic ring comprising -N- at both positions adjacent to the fused positions.

As per claim 167, Carson further teaches wherein R12 is [a tautomer of] -OH (=O; para [0190]).

As per claim 172, it is obvious for the reasons discussed in claim 166, and because Xu teaches wherein D is double bonded to -C- as G (uridine from UTP; abstract) and because Li teaches that nucleotides bind the receptor (para [0245]) and because cytosine, a well-known nucleotide, comprises -NH2 at the claimed A position and comprises an allyl as R17 (ribose group of cytosine).

Claims 1-116 and 119-212 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.