

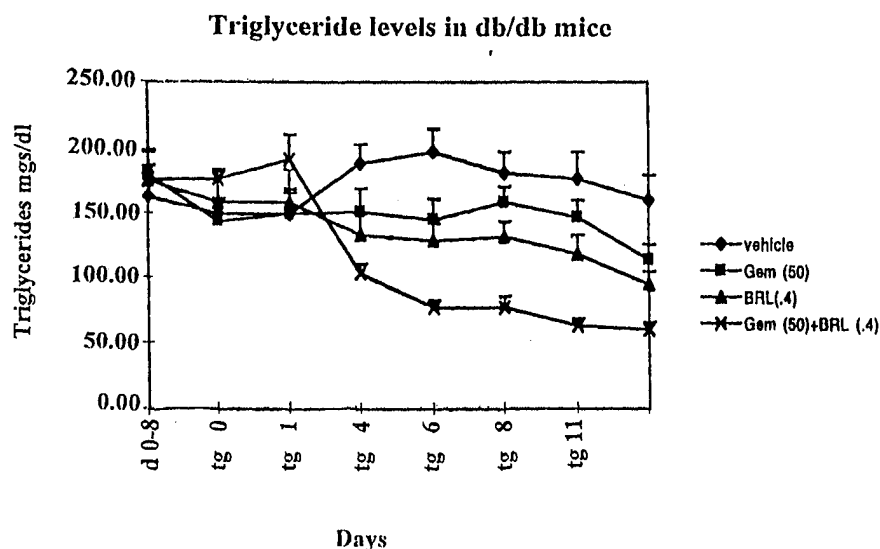


## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61K 31/425, 31/19 //</b> <b>(A61K 31/425, 31:19)</b>	<b>A3</b>	(11) International Publication Number: <b>WO 98/05331</b>  (43) International Publication Date: 12 February 1998 (12.02.98)
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<p>(21) International Application Number: PCT/US97/13605</p> <p>(22) International Filing Date: 1 August 1997 (01.08.97)</p> <p>(30) Priority Data: 60/022,949 2 August 1996 (02.08.96) US</p> <p>(71) Applicant: LIGAND PHARMACEUTICALS INCORPORATED [US/US]; 9393 Towne Centre Drive, San Diego, CA 92121 (US).</p> <p>(72) Inventors: PATERNITI, James, R.; 10833 Birch Bluff Avenue, San Diego, CA 92131 (US). BRIGGS, Michael, R.; 12156 Charbono Street, San Diego, CA 92131 (US). MUKHERJEE, Ranjan; 11341 Avenida De Los Lobos, San Diego, CA 92127 (US). AUWERX, Johan; 60, route de Hasnon, F-59178 Millionfosse (FR). STAEL, Bart; 155, D'Huartlaan, B-1500 Kraainem (BE).</p> <p>(74) Agents: CHEN, Anthony, C. et al.; Lyon &amp; Lyon LLP, Suite 4700, 633 West Fifth Street, Los Angeles, CA 90071-2066 (US).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report.</i></p> <p>(88) Date of publication of the international search report: 7 May 1998 (07.05.98)</p>
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(54) Title: PREVENTION OR TREATMENT OF TYPE 2 DIABETES OR CARDIOVASCULAR DISEASE WITH PPAR MODULATORS



## (57) Abstract

This invention relates to methods and compositions for the prevention and treatment of Type 2 diabetes and cardiovascular disease with diabetic or pre-diabetic conditions or symptoms associated therewith using both a PPAR $\gamma$  agonist and a PPAR $\alpha$  agonist or a compound which activates both PPAR $\gamma$  and PPAR $\alpha$ . A preferred PPAR $\gamma$  agonist is a thiazolidinedione compound, including BRL 49653, troglitazone, pioglitazone, ciglitazone, WAY-120,744, englitazone, AD 5075, darglitazone, and congeners, analogs, derivatives and pharmaceutically acceptable salts thereof. A preferred PPAR $\alpha$  agonist is a fibrate compound including gemfibrozil, fenofibrate, bezofibrate, clofibrate, ciprofibrate, and analogs, derivatives and pharmaceutically acceptable salts thereof.

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**INTERNATIONAL SEARCH REPORT**

International Application No  
PCT/US 97/13605

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K31/425 A61K31/19

//(A61K31/425,31:19)

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

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

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

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WILLSON T M ET AL: "THE STRUCTURE-ACTIVITY RELATIONSHIP BETWEEN PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA AGONISM AND THE ANTIHYPERGLYCEMIC ACTIVITY OF THIAZOLIDINEDIONES" JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, no. 3, 2 February 1996, pages 665-668, XP000613613 cited in the application see page 665, right-hand column, "Discussion", lines 2-3, and page 666, Table I, compounds 1b and 2</p> <p align="center">---</p> <p align="center">-/--</p>	1-4,31

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

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- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
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Date of the actual completion of the international search

7 November 1997

Date of mailing of the international search report

13. 02.98

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Engl, B

## INTERNATIONAL SEARCH REPORT

Inte. onal Application No

PCT/US 97/13605

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	LENHARD J M ET AL: "ANALYSIS OF THIAZOLIDINEDIONE, BIGUANIDE AND RETINOID EFFECTS ON ADIPOGENESIS AND THE NUCLEAR RECEPTORS PPARG $\gamma$ AND RXR" DIABETOLOGIA, SUPPLEMENT, vol. 39, 5 September 1996, page A234 XP000613679 see abstract	1-4,6,8,17
P,X	--- WO 97 10819 A (LIGAND PHARM INC) 27 March 1997 see page 13, line 1 - page 16, line 19; claims 2-10,14	11,19
P,X	--- WO 97 25042 A (SMITHKLINE BEECHAM PLC; SMITH STEPHEN ALISTAIR (GB)) 17 July 1997 see page 2, line 6-13 see page 3, line 22-26 see page 12, line 8-23 see page 12, line 32 - page 14, line 21; claims 1-4	1-4,13,14
P,X	see claim 13	43
X	--- WO 95 07694 A (SANKYO CO; GOODMAN HERBERT H (US)) 23 March 1995 see the whole document	1-4,6,13-16
X	--- WO 95 07697 A (WARNER LAMBERT CO) 23 March 1995 see page 8, line 9 - page 27, line 12 see page 27, line 13-20	1-4,6,13-16
X	--- LEHMANN J M ET AL: "AN ANTIDIABETIC THIAZOLIDINEDIONE IS A HIGH AFFINITY LIGAND FOR PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA (PPARG $\gamma$ )" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 270, no. 22, 2 June 1995, pages 12953-12956, XP000577082 cited in the application see the whole document	1-4,6,14-16,43
X	--- KARAM J H: "TYPE II DIABETES AND SYNDROME X PATHOGENESIS AND GLYCEMIC MANAGEMENT" ENDOCRINOLOGY AND METABOLISM CLINICS OF NORTH AMERICA, vol. 21, no. 2, 1 June 1992, pages 329-350, XP000605976 see the whole document	1-4,6-10,14-18,31
X	--- EP 0 305 890 A (BOEHRINGER MANNHEIM GMBH) 8 March 1989 see the whole document	10,18
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INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 97/13605

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BARNETT ET AL.: "Effect of Clofibrate on Glucose Tolerance in Maturity Onset Diabetes" BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, vol. 4, 1977, pages 455-458, XP002045778 see the whole document ---	10,18
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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/ 13605

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

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

1.  Claims Nos.: 1 - 13, 31  
because they relate to subject matter not required to be searched by this Authority, namely:  
see attached sheet
2.  Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

see attached sheet

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

1 - 20, 31, 43

Remark on Protest

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

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/ US 97/13605

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/

1. Claims: 1-20, 31, 43 (partially)

Method for treating or preventing Type 2 diabetes and compositions adapted for use in the said methods and method of preparing a compound for treating Type 2 diabetes

2. Claims: 1-20, 31, 43 (partially)

Method for treating cardiovascular disease with diabetic or pre-diabetic conditions, method of preparing a compound for treating cardiovascular disease with diabetic or pre-diabetic conditions

3. Claims: 21, 28, 35, 37, 44

Method for treating or preventing hypertriglyceridemia, for lowering the level of plasma triglyceride or for increasing the level of HDL cholesterol, method of preparing a compound for treating hypertriglyceridemia

4. Claims: 22, 30, 33, 38, 45

Method for treating or preventing hyperglycemia, for lowering the level of plasma glucose or for increasing glucose uptake, method of preparing a compound for treating hyperglycemia

5. Claims: 23, 29, 32, 34, 39, 46

Method for treating or preventing hyperinsulinemia, for lowering the level of plasma insulin or for increasing insulin sensitivity or for preventing insulin resistance, method of preparing a compound for treating hyperinsulinemia

6. Claims: 24, 36, 42, 47

Method for treating or preventing hyperfibrinogenemia or for lowering the level of plasma fibrinogen, method of preparing a compound for treating hyperfibrinogenemia

7. Claims: 25, 41, 48

Method for treating hypertension or for lowering the blood pressure, method of preparing a compound for treating hypertension

8. Claims: 26, 40, 49

Method for treating obesity or for lowering the body weight,

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

method of preparing a compound for treating obesity

9. Claim : 27

Method for treating syndrome X

The problem underlying the application is seen as the provision of compositions for treating or preventing symptoms associated with type 2 diabetes, see specification pages 1 to 3. The conditions other than type 2 diabetes which are recited in the claims are not necessarily related to type 2 diabetes. This would warrant an a priori objection to lack of unity.

The solution claimed is the administration of a PPARGamma agonist and a PPARalpha agonist, wherein both agonists can be the same compound, see claim 4.

The document J. Med. Chem. 1996, 39, 665-668 discloses the antihyperglycemic compounds clofibric acid 1b and 4-[4-(4-chlorphenoxy)phenyl]-4-oxobutyric acid 2 which show agonistic activity both on PPARalpha and PPARGamma. Therefore, the principle of administering a PPARalpha and PPARGamma agonist for treating type 2 diabetes and related diabetic conditions is neither new nor inventive and hence is not capable of providing a single general inventive concept unifying the above-captioned groups of inventions.

The search has been carried out for the first invention mentioned in the claims, i.e. treatment of type 2 diabetes comprising administering a PPARGamma agonist and a PPARalpha agonist. A comprehensive search for the other inventions would have caused major additional searching efforts.

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/ US 97/13605

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 1, 14, 31, 43

because they relate to subject matter not required to be searched by this Authority, namely:

Claims Nos.: 1, 14, 31, 43

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

A compound is not sufficiently characterized by its mechanism of action, as is the case for the expressions "PPARalpha agonist" and "PPARGamma agonist". The said expressions would encompass well-known substances which are conventionally being used in the treatment envisaged but whose mode of action has not as yet been described, thus being directed to a discovery. On the other hand, the said expressions would be directed also to substances to be prepared in the future and fitting the claimed mechanism. Therefore, the number of compounds comprised within these terms is infinite (Article 6 PCT), and the search had to be restricted to the classes of compounds specifically referred to in claims 5, 6 and 10.

### Remark :

Although claims 1-13 and 31 are directed to a method of treatment of the human or animal body by therapy, the search has been carried out and based on the alleged effects of the composition.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/13605

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