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(72) Inventors; and

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

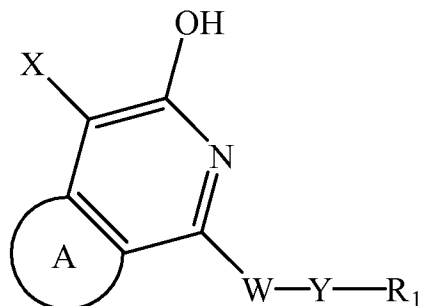
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- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

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20 March 2008

(54) Title: PYRIDONE/HYDROXYPYRIDINE 11-BETA HYDROXYSTEROID DEHYDROGENASE TYPE I INHIBITORS



(I)

(57) Abstract: Novel compounds are provided which are 11-beta-hydroxysteroid dehydrogenase type I inhibitors. 11-beta-hydroxysteroid dehydrogenase type I inhibitors are useful in treating, preventing, or slowing the progression of diseases requiring 11-beta-hydroxysteroid dehydrogenase type I inhibitor therapy. These novel compounds have the structure formula (I) enantiomers, diastereomers, solvates, salts, tautomers or prodrugs thereof wherein, A, W, X, Y and R<sub>1</sub> are defined herein.

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**INTERNATIONAL SEARCH REPORT**

International application No  
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<b>A. CLASSIFICATION OF SUBJECT MATTER</b>					
INV.	C07D217/24	C07D221/04	C07D401/12	C07D405/12	C07D417/12
	C07D453/00	C07D471/04	A61K31/4355	A61P3/00	

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)  
C07D

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)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>SAUTER F ET AL: "SYNTHESIS OF DIHYDROTHIOPYRANO[3,4-C]PYRIDINES AND OF FUSION PRODUCTS THEREOF" MONATSHEFTE FUER CHEMIE, SPRINGER VERLAG, VIENNA, AT, vol. 126, no. 8-9, 1995, pages 945-952, XP008058278 ISSN: 0026-9247 compound 2</p> <p align="center">----- -/--</p>	1-13

Further documents are listed in the continuation of Box C.       See patent family annex.

- |   |  |
|---|--|
| <p>* Special categories of cited documents :</p> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> | <p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*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.</p> <p>* &amp; * document member of the same patent family</p> |
|---|--|

Date of the actual completion of the international search	Date of mailing of the international search report
11 January 2008	29/01/2008

Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer  Bakboord, Joan
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## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/072626

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>PARONIKIAN Y G ET AL: "Synthesis of 3-oxopyrano/3,4-c pyridine's derivatives and investigation of their coronary activity"</p> <p>ARMYANSKII KHIMICHESKII ZHURNAL /AIKAKAN HIMIAKAN AMSAGIR / ARMENIAN CHEMICAL JOURNAL, AKADEMIYA NAUK ARMENII, EREVAN, AI,</p> <p>vol. 42, no. 8, 1989, pages 505-509, XP009093144</p> <p>ISSN: 0515-9628</p> <p>compounds VII-X</p>	1-13
X	<p>KAIHO T ET AL: "CARDIOTONIC AGENTS. 1-METHYL-7-(4-PYRIDYL)-5,6,7,8-TETRAHYDRO-3(2H)-I SOQUINOLINONES AND RELATED COMPOUNDS. SYNTHESIS AND ACTIVITY"</p> <p>JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US,</p> <p>vol. 32, no. 2,</p> <p>1 February 1989 (1989-02-01), pages 351-357, XP000676338</p> <p>ISSN: 0022-2623</p> <p>compounds 13, 14, 16-27, 39-36, 41-44</p>	1-13
X	<p>OUCHI HIDEKAZU ET AL: "Synthesis of Azaphenanthrene Derivatives Using Ring-transformation of 4H-1,3-Oxazin-4-one Derivatives"</p> <p>TOHOKU YAKKA DAIGAKU KENKYUSHI - JOURNAL OF TOHOKU PHARMACEUTICAL UNIVERSITY, TOHOKU YAKKA DAIGAKU, SENDAI, JP,</p> <p>vol. 50, 2003, pages 75-79, XP009093101</p> <p>ISSN: 1345-157X</p> <p>compounds 4A-4F</p>	1-7
X	<p>JOHN W DUCKER AND MAXWEEL J GUNTER: "The reaction of malononitrile with some beta-dicarbonyl compounds"</p> <p>AUSTRALIAN JOURNAL OF CHEMISTRY, XX, XX,</p> <p>vol. 28, no. 3, 1975, pages 581-290, XP009093433</p> <p>ISSN: 0004-9425</p> <p>compounds 3A, 3B</p>	1-13
X	<p>US 4 775 757 A (KANOJIA RAMESH M [US] ET AL) 4 October 1988 (1988-10-04)</p> <p>example 24</p>	1-10
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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2007/072626

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

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>KASTURI AND LALITHA KRISHNAN T R: "A total synthesis of 4-cyano-1,3-dimethoxy-2-azaestra-1,3,5(10)-trien 17beta-ol and its configuration assignment" PROCEEDINGS OF THE INDIAN ACADEMY OF SCIENCES. CHEMICAL SCIENCES, INDIAN ACADEMY OF SCIENCES, BANGALORE, IN, vol. 90, no. 4, 1981, pages 281-290, XP009093104 ISSN: 0253-4134 compound 1A</p>	1-13
X	<p>KASTURI T R ET AL: "Amide-catalysed isomerisation of 5.6-Dihydroisoquinolines: a Novel synthesis of 1.2-Dihydroisoquinolines" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, CHEMICAL SOCIETY. LETCHWORTH, GB, no. 1, 1982, pages 63-68, XP009093112 ISSN: 0300-922X compound 2</p>	1-13
X	<p>ABDOU S ET AL: "Activated nitriles in heterocyclic synthesis: Synthesis of several new coumarin derivatives" MONATSHEFTE FUR CHEMIE, SPRINGER VERLAG. WIEN, AT, vol. 113(8-9), 1982, pages 985-991, XP009093109 ISSN: 0026-9247 compound 13</p>	1-7
X	<p>GEWALD K ET AL: "Reaktion von methylenaktiven Nitrilen und Cyanamid mit acylierten Enaminen Reaction of Methylene Active Nitriles and Cyanamide with Acylated Enamines" JOURNAL FUR PRAKTISCHE CHEMIE, LEIPZIG, DE, vol. 324, no. 6, 1982, pages 933-941, XP009093097 ISSN: 0021-8383 compounds 14A, 14B</p> <p style="text-align: center;">----- -/--</p>	1-13

## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/072626

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>VICTORY P ET AL: "Synthesis of 4-dimethoxymethyl-6-hydroxy-2-methoxynicotinonitrile: A suggested mechanism revision"            JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, CHEMICAL SOCIETY.            LETCHWORTH, GB, no. 12, 1989, pages 2269-2272, XP009093111            ISSN: 0300-922X            compound 4B</p>	1-13
X	<p>VAN DER BAAN J L ET AL: "The knoevenagel condensation of malononitrile with some cyclic beta-keto-esters. A correction"            JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS, CHEMICAL SOCIETY.            LETCHWORTH, GB, no. 6, 1970, pages 326-327, XP009093114            ISSN: 0022-4936            compound VA</p>	1-12
X	<p>YA URITSKAYA M ET AL: "Reactions of 4-chloro-6-oxo-2,3-dihydro-5-azabenzofuran s with amines"            CHEMISTRY OF HETEROCYCLIC COMPOUNDS (A TRANSLATION OF KHIMIYA GETEROTSIKLICHESKIKH SOEDINENII), PLENUM PRESS CO., NEW YORK, NY, US, vol. 10, 1973, pages 1185-1187, XP009093093            ISSN: 0009-3122            compound VIA</p>	1-12
X	<p>ROW T N G ET AL: "Crystal and molecular structure of 8a-bromo-1.2.3.5.6.7.8.8a-octahydro-1.3-dioxoisoquinoline-4-carbonitrile"            JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 2, CHEMICAL SOCIETY.            LETCHWORTH, GB, no. 14, 1975, pages 1597-1600, XP009093113            ISSN: 1472-779X            compounds 3A, 3B</p>	1-13
X	<p>EL-KHAWAGA A M ET AL: "Synthesis and reactions of some isoquinoline derivatives"            PHOSPHORUS, SULFUR AND SILICON AND THE RELATED ELEMENTS, GORDON AND BREACH SCIENCE PUBLISHERS, AMSTERDAM, GB, vol. 44, no. 3-4, 1989, pages 203-207, XP009093095            ISSN: 1042-6507            compounds 6A-6C</p>	1-13

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## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/072626

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>PARONIKYAN E G ET AL: "SYNTHESIS AND SOME CONVERSIONS OF PARTIALLY HYDROGENATED 1-AMINOPYRANO(THIOPYRANO)(4,3-d)-PYRAZOLO(3,4-b)PYRIDINES AND PYRAZOLO(3,4-c)ISOQUINOLINES" CHEMISTRY OF HETEROCYCLIC COMPOUNDS (A TRANSLATION OF KHIMIYA GETEROTSIKLICHESKIKH SOEDINENII), PLENUM PRESS CO., NEW YORK, NY, US, vol. 39, no. 3, March 2003 (2003-03), pages 374-378, XP009093089 ISSN: 0009-3122 compounds 1A-1E</p>	1-13
X	<p>-----</p> <p>PARONIKYAN E G ET AL: "Synthesis and structure of 3-oxopyrano Å3,4-cÜpyridines" CHEMISTRY OF HETEROCYCLIC COMPOUNDS (A TRANSLATION OF KHIMIYA GETEROTSIKLICHESKIKH SOEDINENII), PLENUM PRESS CO., NEW YORK, NY, US, vol. 8, 1989, pages 953-958, XP009093094 ISSN: 0009-3122 compounds IX-XV</p>	1-13
X	<p>-----</p> <p>AZIMOV V A ET AL: "Azaindole derivatives. 59. Synthesis and chemical properties of 1-benzyl-4-dimethylamino-6-chloro-7-cyano-5-azaindoline" CHEMISTRY OF HETEROCYCLIC COMPOUNDS (A TRANSLATION OF KHIMIYA GETEROTSIKLICHESKIKH SOEDINENII), PLENUM PRESS CO., NEW YORK, NY, US, vol. 2, 1981, pages 155-159, XP009093088 ISSN: 0009-3122 compound IV</p>	1-12
X	<p>-----</p> <p>KASTURI T R ET AL: "Nitrile ketenimine tautomerism in substituted alkylidene malononitriles and alkylidene cyanoacetates" TETRAHEDRON, vol. 29, 1973, pages 4103-4109, XP002463919 compound 7C</p> <p>-----</p> <p style="text-align: center;">-/--</p>	1-13

## INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>ROSOWSKY A ET AL:  "pyrimido[4,5-c]isoquinolines.2. synthesis and biological evaluation of some 6-alkyl-6-aralkyl-, and 6-aryl-1,3-diamino-7,8,9,10-tetrahydropyrimido[4,5-c]isoquinolines as potential folate antagonists"  JOURNAL OF MEDICINAL CHEMISTRY,  vol. 17, no. 12, 1974, pages 1272-1276,  XP002463920  compounds 8B-8F</p>	1-13
X	<p>VAN DER BAAN J L ET AL: "The Knoevenagel reaction of malonitrile with some cyclic beta-keto-esters -II"  TETRAHEDRON,  vol. 30, 1974, pages 2447-2453,  XP002463921  compounds 3A, 3B</p>	1-13
X	<p>KASTURI T R ET AL: "Knoevenagel condensation of 2-carbethoxycyclohexanone and malonitrile: synthesis of 4-cyano-3-ethoxy-1-hydroxy-5,6,7,8-tetrahydroisoquinoline, an isomer of the abnormal product"  TETRAHEDRON,  vol. 31, 1975, pages 527-531, XP002463922  compounds 3A, 3C</p>	1-13
X	<p>VAN DER BAAN J L ET AL: "Palladium (0)-catalyzed non-concerted cope rearrangement"  TETRAHEDRON LETTERS,  vol. 33, no. 10, 1992, pages 1377-1378,  XP002463923  compound 4</p>	1-13
X	<p>US 4 180 666 A (CHORVAT ROBERT J [US])  25 December 1979 (1979-12-25)  examples 2-5,12-14</p>	1-13
X	<p>DE 37 25 357 A1 (MITSUI TOATSU CHEMICALS [JP]) 3 March 1988 (1988-03-03)  intermediates of examples 1,2,4,8,11-14</p>	1-13
X	<p>DE 40 29 466 A1 (CIBA GEIGY AG [CH])  28 March 1991 (1991-03-28)  compounds 8-01-8.15</p>	1-13
P,X	<p>WO 2007/017078 A (ALMIRALL PRODESFARMA SA [ES]; TALTAVULL MOLL JOAN [ES]; PAGES SANTACAN) 15 February 2007 (2007-02-15)  preparation 13, 20, 35</p>	1-13

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## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/072626

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2006/034804 A (HOFFMANN LA ROCHE [CH]; AMREIN KURT [CH]; CAI JIANPING [US]; GOODNOW R) 6 April 2006 (2006-04-06) claims 1,30 -----	18-20
A	WO 2006/024628 A (JANSSEN PHARMACEUTICA NV [BE]; JAROSKOVA LIBUSE [BE]; LINDERS JOANNES) 9 March 2006 (2006-03-09) claims 1,6 -----	18-20
A	WO 2006/000371 A (HOFFMANN LA ROCHE [CH]; AMREIN KURT [CH]; HUNZIKER DANIEL [CH]; KUHN B) 5 January 2006 (2006-01-05) claims 1,19 -----	18-20



# INTERNATIONAL SEARCH REPORT

International application No.  
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## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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.: 18-20  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
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 No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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 fees, this Authority did not invite payment of additional fees.
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.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

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

Continuation of Box II.1

Although claims 18-20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2007/072626

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4775757	A	04-10-1988	NONE
US 4180666	A	25-12-1979	NONE
DE 3725357	A1	03-03-1988	CA 1285281 C 25-06-1991 FR 2603282 A1 04-03-1988 GB 2194532 A 09-03-1988 IT 1211684 B 03-11-1989 JP 1918017 C 07-04-1995 JP 6037491 B 18-05-1994 JP 63057585 A 12-03-1988 US 4782154 A 01-11-1988
DE 4029466	A1	28-03-1991	NONE
WO 2007017078	A	15-02-2007	AR 055999 A1 12-09-2007 ES 2281251 A1 16-09-2007
WO 2006034804	A	06-04-2006	AR 050952 A1 06-12-2006 AU 2005289107 A1 06-04-2006 CA 2581865 A1 06-04-2006 CN 101027286 A 29-08-2007 KR 20070047839 A 07-05-2007 US 2006069269 A1 30-03-2006
WO 2006024628	A	09-03-2006	AU 2005279209 A1 09-03-2006 CA 2576850 A1 09-03-2006 NO 20071685 B 30-03-2007
WO 2006000371	A	05-01-2006	AR 049699 A1 30-08-2006 AU 2005256442 A1 05-01-2006 CA 2571361 A1 05-01-2006 CN 1972918 A 30-05-2007 US 2005288308 A1 29-12-2005