



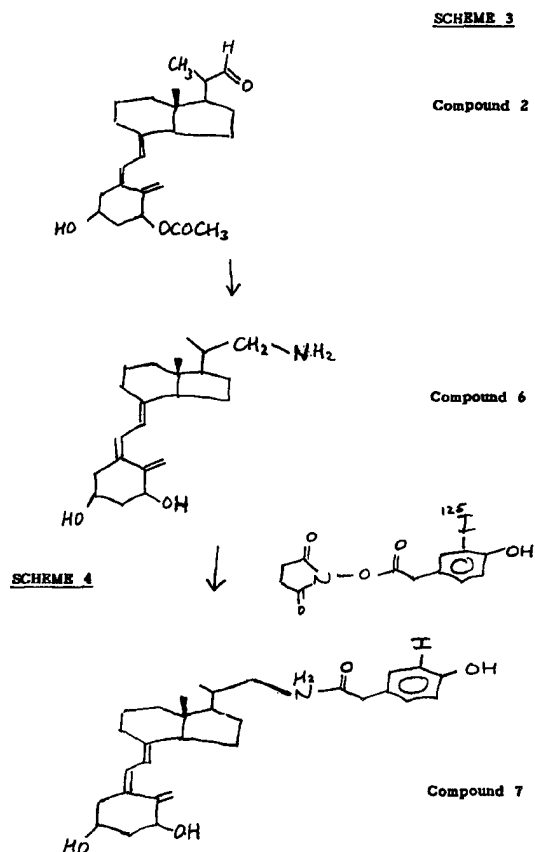
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : C07C 401/00, G01N 33/82</p>	<p>A3</p>	<p>(11) International Publication Number: WO 98/21580 (43) International Publication Date: 22 May 1998 (22.05.98)</p>
<p>(21) International Application Number: PCT/GB97/03097 (22) International Filing Date: 12 November 1997 (12.11.97) (30) Priority Data: 9623569.2 13 November 1996 (13.11.96) GB (71) Applicant (for all designated States except US): IMMUNODI-AGNOSTIC SYSTEMS LIMITED [GB/GB]; Boldon Business Park, Boldon, Tyne & Wear NE35 9PD (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): LAURIE, David [GB/GB]; IDS Limited, 10 Diddcot Way, Boldon Business Park, Boldon, Tyne & Wear NE35 9PD (GB). BARNES, Alexander, Kirkley [GB/GB]; IDS Limited, 10 Diddcot Way, Boldon Business Park, Boldon, Tyne & Wear NE35 9PD (GB). (74) Agent: MARKGRAAF PATENTS LIMITED; The Crescent, 54 Blossom Street, York YO2 2AP (GB).</p>	<p>(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 30 July 1998 (30.07.98)</p>	

(54) Title: VITAMIN D IMMUNOASSAY SYSTEMS

(57) Abstract

Compound comprising an analogue of 1,25-dihydroxy vitamin D, modified at the C²⁰ position, which is adapted to bind to at least an existing or readily produced antibody, wherein the analogue comprises a substituent adapted for quantitative detection, preferably comprises a radioactive substituent, more preferably iodine 125, or comprises a chemiluminescent or fluorescent substituent adapted for luminescent or fluorescent intensity determination, process for the preparation thereof and of intermediates thereof novel intermediates prepared by the process, composition comprising the compound and its use in an immunoassay method, preferably comprising an immunoassay kit, the novel use of an inhibitor comprised in composition and the method for determining the concentration of 1,25-dihydroxy vitamin D.



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INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C401/00 G01N33/82

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 C07C G01N

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.
	-/--	

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *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
- *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
- *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.
- *Z* document member of the same patent family

Date of the actual completion of the international search

19 May 1998

Date of mailing of the international search report

12.06.98

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INTERNATIONAL SEARCH REPORT

 International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category ^a	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 121, no. 9, 29 August 1994 Columbus, Ohio, US; abstract no. 109401, M. TANABE ET AL: "Preparation of Vitamin D Derivatives Containing a Substituent at the 25-Hydroxy Group" page 1143; column 1; XP002054205 see abstract & DATABASE WPI Section Ch, Week 9411 Derwent Publications Ltd., London, GB; Class B01, AN 94-089316 M. TANABE ET AL: & JP 06 041 058 (ASAHI CHEM IND CO LTD) , 15 February 1994 see abstract & AMERICAN CHEMICAL SOCIETY: "CHEMICAL ABSTRACTS FORMULA INDEX, C25H520-Z, VOLUME 121 (PART 3 OF 3 PARTS)" 1994 , CHEMICAL ABSTRACTS , COLUMBUS OHIO US see formula C40H60IN06 see page 4409F, column 3 ---	1-3, 13-16, 19,20
Y	B. HOLLIS ET AL: "Determination of Vitamin D Status by Radioimmunoassay with an 125-Iodine Labelled Tracer" CLINICAL CHEMISTRY., vol. 39, no. 3, 1993, WINSTON US, pages 529-533, XP002054204 see the whole document ---	1-8, 13-16, 19,20
Y	WO 94 26707 A (HOLMES MICHAEL JOHN ;RES INST MEDICINE CHEM (US); HESSE ROBERT HEN) 24 November 1994 see examples 9,12,15,16 ---	1-8, 13-16, 19,20
X	CHEMICAL ABSTRACTS, vol. 123, no. 15, 9 October 1995 Columbus, Ohio, US; abstract no. 199203, H. WATANABE ET AL: "Synthetic studies of Vitamin D Analogs. 20. Synthesis of Tritiated 1.alpha.,25-Dihydroxy-22-oxavitamin D2" page 1295; column 1; XP002065444 see abstract & J. LABELLED COMPD. RADIOPHARM., vol. 36, no. 7, 1995, pages 645-654, --- -/--	1-3, 13-17, 19,20

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>CHEMICAL ABSTRACTS, vol. 107, no. 25, 21 December 1987 Columbus, Ohio, US; abstract no. 236332, R. SICINSKI ET AL: "Synthesis of 25-Hydroxy-[26,27-3H]-vitamin D₂, 1.alpha.,25-Dihydroxy-[26,27-3H]-vitamin D₂ and their (24R)-epimers" page 751; column 2; XP002065445 see abstract & ANALYTICAL BIOCHEMISTRY., vol. 161, no. 1, 1987, ORLANDO US, pages 96-102,</p>	1-3, 13-17, 19,20
X	<p>--- CHEMICAL ABSTRACTS, vol. 97, no. 9, 30 August 1982 Columbus, Ohio, US; abstract no. 66509, J. CHANDLER ET AL: "Biosynthesis, Purification and Receptor Binding Properties of High Specific Radioactivity 1.alpha.,24(R),25-Trihydroxy-[26,27-methyl -3H]-vitamin D₃" page 76; column 2; XP002065446 see abstract & JOURNAL OF STEROID BIOCHEMISTRY, vol. 16, no. 2, 1982, pages 303-310,</p>	1-3, 13-17, 19,20
X	<p>--- CHEMICAL ABSTRACTS, vol. 91, no. 25, 17 December 1979 Columbus, Ohio, US; abstract no. 211666, K. BANNAI ET AL: "Synthesis of (24S)- and (24R)-1.alpha.-Hydroxy-cholecalciferol" page 711; column 2; XP002065447 see abstract & JOURNAL OF STEROID BIOCHEMISTRY, vol. 10, no. 4, 1979, pages 411-418,</p>	1-3, 13-17, 19,20
X	<p>--- A. CALDAS ET AL: "The Simultaneous Measurement of Vitamin D Metabolites in Plasma: Studies in Healthy Adults and in Patients with Calcium Nephrolithiasis" JOURNAL OF LABORATORY AND CLINICAL MEDICINE , vol. 91, no. 5, 1978, pages 840-849, XP002065441 see the whole document --- -/--</p>	1-3, 13-17, 19,20

INTERNATIONAL SEARCH REPORT

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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	CHEMICAL ABSTRACTS, vol. 89, no. 5, 31 July 1978 Columbus, Ohio, US; abstract no. 38985, S. YAMADA ET AL: "Synthesis of 25-Hydroxy[23,24-3H]-vitamin D3" page 259; column 2; XP002065448 see abstract & ANALYTICAL BIOCHEMISTRY., vol. 85, no. 1, 1978, pages 34-41,	1-3, 13-17, 19,20
X	--- B. HALLORAN ET AL: "Isotopic Labeling Affects 1,25-Dihydroxyvitamin D Metabolism" BIOCHEMISTRY., vol. 28, no. 3, 7 February 1989, EASTON, PA US, pages 1278-1281, XP002065442 see page 1278, column 1, paragraph 1 see page 1279; table I	1-3, 13-17, 19,20
X	--- J. NAPOLI ET AL: "Direct Chemical Synthesis of 1.alpha.,25-Dihydroxy[26,27-3H]vitamin D3 with High Specific Activity: Its Use in Receptor Studies" BIOCHEMISTRY., vol. 19, no. 11, 27 May 1980, EASTON, PA US, pages 2515-2521, XP002065443 see page 2517, compound 11 and page 2520, Figures 6 and 7	1-3, 13-17, 19,20
X	--- EP 0 092 004 A (TEIJIN LTD) 26 October 1983 see pages 5-6, compounds 2, 4, 8, 9 and 13 see page 13, last paragraph - page 14, paragraph 1	1,2, 13-17, 19,20
X	--- WO 80 02562 A (WISCONSIN ALUMNI RES FOUND) 27 November 1980 see page 4, formula IV see example 2A	1-3, 13-17, 19,20
X	--- US 4 585 741 A (CLEVINGER BRIAN L ET AL) 29 April 1986 see column 5, last paragraph; example 1 -----	1-3, 13-17, 19,20

INTERNATIONAL SEARCH REPORT

International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

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

2. Claims Nos.: 17,18
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
1-8, 12-17, 19, 20

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 97/03097

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: 17,18

The subject matter of claims 17 and 18 refers purely to an inhibitor which is defined in claim 16 as "adapted to isolate substantially all of the material to be analysed in a sample to be subjected to immunoassay". The subject matter of claims 16-18 is consequently defined in terms of a result to be achieved which is not considered appropriate in the present case, in particular since the term "inhibitor" does not appear to be appropriate to describe the action of the agent in question and it is not at all clear how the inhibitor brings about the isolation of analytes in the sample, which information might give the skilled person a pointer as to how to interpret this functional definition. Consequently these claims are deemed to be so unclear according to Article 6 PCT and the PCT examination Guidelines III 4.7, that they cannot be searched in respect of this subject matter. Since this is only an optional feature of claim 16, this claim has been searched in as far as it relates to the first claimed invention and in as far as it does not refer to this "inhibitor" but since claims 17 and 18 refer to this product as an essential feature, these claims have not been searched at all. In the case of claim 18, this claim has additionally not been searched since it does not relate to the main claimed invention.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-3, 12-17, 19, 20(partly), 4-8
Labelled Vitamin D derivatives of formula (I) with an I-125 label, the processes for their production and uses and compositions thereof.
2. Claims: 1-3, 12-17, 19, 20(partly)
Labelled Vitamin D derivatives of formula (I) with a label other than I-125, the processes for their production and uses and compositions thereof.
3. Claims: 9; 11(partly)
Unlabelled intermediates of formula (II) and the processes for their production.
4. Claims: 10; 11(partly)
Unlabelled intermediates of formula (IV) and the processes for their production.
5. Claim : 11(partly)
Non-Vitamin D intermediates of formula (III).
6. Claim : 11(partly)
Non-Vitamin D intermediates of formula (V)
7. Claim : 11(partly)
Unlabelled intermediates of formula (VI).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No PCT/GB 97/03097

Patent document cited in search report	A	Publication date	Patent family member(s)	Publication date
WO 9426707	A	24-11-1994	AU 678246 B AU 6683294 A CN 1125436 A CZ 9502903 A EP 0696275 A FI 955316 A HU 74165 A JP 8509971 T NO 954426 A NZ 265665 A ZA 9403162 A	22-05-1997 12-12-1994 26-06-1996 12-06-1996 14-02-1996 22-12-1995 28-11-1996 22-10-1996 08-01-1996 26-05-1997 13-04-1995

EP 0092004	A	26-10-1983	NONE	

WO 8002562	A	27-11-1980	US 4269777 A CA 1152488 A DE 3045287 C DE 3051094 C FR 2457283 A FR 2479214 A FR 2485022 A GB 2052509 A,B GB 2077736 A,B GB 2083043 A,B GB 2082587 A,B JP 56500538 T	26-05-1981 23-08-1983 10-11-1988 18-05-1989 19-12-1980 02-10-1981 24-12-1981 28-01-1981 23-12-1981 17-03-1982 10-03-1982 23-04-1981

US 4585741	A	29-04-1986	CA 1211391 A JP 60049264 A	16-09-1986 18-03-1985
