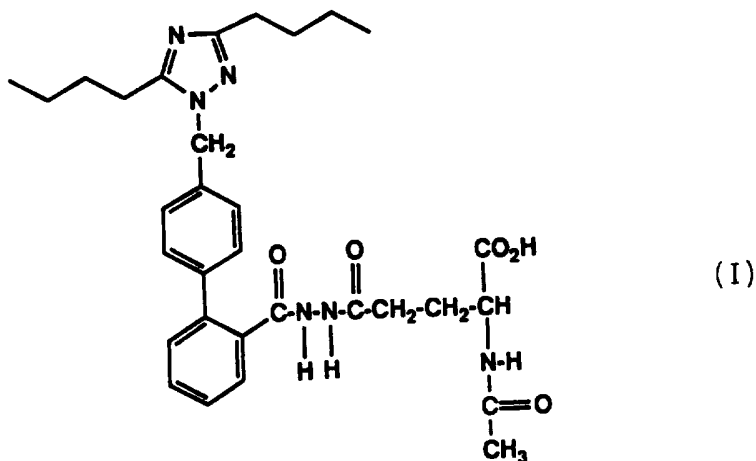




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07D 249/08, 403/10 A61K 31/41	A3	(11) International Publication Number: WO 92/04335 (43) International Publication Date: 19 March 1992 (19.03.92)
(21) International Application Number: PCT/US91/05897 (22) International Filing Date: 26 August 1991 (26.08.91) (30) Priority data: 574,314 28 August 1990 (28.08.90) US (60) Parent Application or Grant (63) Related by Continuation US 574,314 (CIP) Filed on 28 August 1990 (28.08.90) (71) Applicant (for all designated States except US): G.D. SEARLE & CO. [US/US]; Corporate Patent Department, P.O. Box 5110, Chicago, IL 60680-5110 (US). (72) Inventors; and (75) Inventors/Applicants (for US only) : REITZ, David, B. [US/US]; 14814 Pleasant Ridge Court, Chesterfield, MO 63017 (US). MANNING, Robert, E. [US/US]; 1298 South Mason Road, St. Louis, MO 63131 (US).		(74) Agents: KEANE, J., Timothy et al.; G.D. Searle & Co., Corporate Patent Department, P.O. Box 5110, Chicago, IL 60680-5110 (US). (81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, SD, SE, SE (European patent), SN (OAPI patent), SU ⁺ , TD (OAPI patent), TG (OAPI patent), US. 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: 16 April 1992 (16.04.92)

(54) Title: RENAL-SELECTIVE BIPHENYLALKYL 1H-SUBSTITUTED-1,2,4-TRIAZOLE ANGIOTENSIN II ANTAGONISTS FOR TREATMENT OF HYPERTENSION

**(57) Abstract**

Renal-selective compounds are described which, in one embodiment, are prodrugs preferentially converted in the kidney to compounds capable of blocking angiotensin II (AII) receptors. These prodrugs are conjugates formed from two components, namely, a first component provided by an AII antagonist compound and a second component which is capable of being cleaved from the first component when both components are chemically linked within the conjugate. The two components are chemically linked by a bond which is cleaved selectively in the kidney, for example, by an enzyme. The liberated AII antagonist compound is then available to block AII receptors within the kidney. Conjugates of particular interest are glutamyl derivatives of biphenylmethyl 1H-substituted-1,2,4-triazole compounds, of which N-acetylglutamic acid, 5-[[4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]]carbonylhydrazide is an example.

+ DESIGNATIONS OF "SU"

Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

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INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/05897

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC5: C 07 D 249/08, 403/10, A 61 K 31/41											
II. FIELDS SEARCHED Minimum Documentation Searched⁷ <table style="width: 100%; border: none;"> <tr> <td style="width: 25%; border: 1px solid black; padding: 5px;">Classification System</td> <td style="border: 1px solid black; padding: 5px;">Classification Symbols</td> </tr> <tr> <td style="border: 1px solid black; padding: 5px;">IPC5</td> <td style="border: 1px solid black; padding: 5px;">C 07 D</td> </tr> </table> Documentation Searched other than Minimum Documentation to the extent that such Documents are included in Fields Searched⁸			Classification System	Classification Symbols	IPC5	C 07 D					
Classification System	Classification Symbols										
IPC5	C 07 D										
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; font-size: x-small;">Category¹⁰</th> <th style="width: 70%; font-size: x-small;">Citation of Document,¹¹ with indication, where appropriate, of the relevant passages¹²</th> <th style="width: 20%; font-size: x-small;">Relevant to Claim No.¹³</th> </tr> </thead> <tbody> <tr> <td style="vertical-align: top; padding: 5px;">P,X</td> <td style="padding: 5px;">WO, A1, 9117148 (G.D. SEARLE & CO.) 14 November 1991, see especially example 41 --</td> <td style="vertical-align: top; padding: 5px;">13,17- 18,31, 65</td> </tr> <tr> <td style="vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;">EP, A2, 0323841 (E.I. DU PONT DE NEMOURS AND COMPANY) 12 July 1989, see pages 44-79 -- -----</td> <td style="vertical-align: top; padding: 5px;">13</td> </tr> </tbody> </table>			Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	P,X	WO, A1, 9117148 (G.D. SEARLE & CO.) 14 November 1991, see especially example 41 --	13,17- 18,31, 65	A	EP, A2, 0323841 (E.I. DU PONT DE NEMOURS AND COMPANY) 12 July 1989, see pages 44-79 -- -----	13
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* Special categories of cited documents: 10 "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "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) "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 "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. "&" document member of the same patent family											
IV. CERTIFICATION <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; padding: 5px;"> Date of the Actual Completion of the International Search 19th February 1992 </td> <td style="width: 50%; border: none; padding: 5px;"> Date of Mailing of this International Search Report 1 1. 03. 92 </td> </tr> <tr> <td style="border: none; padding: 5px;"> International Searching Authority EUROPEAN PATENT OFFICE </td> <td style="border: none; padding: 5px;"> Signature Authorized Officer Mma. M. van der Drift </td> </tr> </table>			Date of the Actual Completion of the International Search 19th February 1992	Date of Mailing of this International Search Report 1 1. 03. 92	International Searching Authority EUROPEAN PATENT OFFICE	Signature Authorized Officer Mma. M. van der Drift					
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International Searching Authority EUROPEAN PATENT OFFICE	Signature Authorized Officer Mma. M. van der Drift										

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹

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

1. ☒ Claim numbers ~~69-108~~ because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy,
see rule 39.1.

2. ☒ Claim numbers ~~1-30~~ ³⁵⁻⁶⁴ 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:

Claims 1-12, 35-46 are too broadly formulated to permit a meaningful search, see Article 6. The search of claims 13-30 and 47-64 has been limited to the compounds considered to be most relevant.

3. ☐ Claim numbers..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

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 of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ 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 the claims. It is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

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

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. PCT/US 91/05897**

SA 53059

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 30/12/91
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 9117148	14/11/91	NONE	
EP-A2- 0323841	12/07/89	AU-D- 2777089	13/07/89
		JP-A- 1287071	17/11/89
		US-A- 5015651	14/05/91
		US-A- 5043349	27/08/91

For more details about this annex : see Official Journal of the European patent Office, No. 12/82