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

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| <b>(51) International Patent Classification</b> <sup>5</sup> :<br><br><b>A61K 41/00, 47/48</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | <b>A3</b> | <b>(11) International Publication Number:</b> <b>WO 94/09826</b><br><br><b>(43) International Publication Date:</b> 11 May 1994 (11.05.94)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>(21) International Application Number:</b> PCT/CA93/00466<br><b>(22) International Filing Date:</b> 1 November 1993 (01.11.93)<br><br><b>(30) Priority data:</b><br>07/971,996 30 October 1992 (30.10.92) US<br><br><b>(71) Applicant:</b> MEDIPRO SCIENCES LIMITED [CA/CA];<br>716 Gordon Baker Road, Suite 100, Toronto, Ontario<br>M2H 3B4 (CA).<br><br><b>(72) Inventors:</b> GUILLET, James, E. ; 31 Sagebrush Lane, Don<br>Mills, Ontario M3A 1X4 (CA). BAKHTIYARI, Hamid ;<br>29 Rowe Court, Markham, Ontario L3S 2J6 (CA).<br><br><b>(74) Agents:</b> HIRONS, Robert, G. et al. ; Ridout & Maybee, 101<br>Richmond Street West, Suite 2300, Toronto, Ontario<br>M5H 2J7 (CA). |           | <b>(81) Designated States:</b> AT, AU, BB, BG, BR, BY, CA, CH,<br>CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK,<br>LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU,<br>SD, SE, SK, UA, VN, European patent (AT, BE, CH,<br>DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT,<br>SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN,<br>ML, MR, NE, SN, TD, TG).<br><br><b>Published</b><br><i>With international search report.</i><br><i>Before the expiration of the time limit for amending the</i><br><i>claims and to be republished in the event of the receipt of</i><br><i>amendments.</i><br><br><b>(88) Date of publication of the international search report:</b><br>29 September 1994 (29.09.94) |
| <b>(54) Title:</b> DRUG DELIVERY SYSTEMS, CHARACTERISED BY A PHOTOLABILE LINKAGE<br><br><b>(57) Abstract</b><br><br>A photoactivatable drug delivery system is provided, in which a drug is combined eg. by covalent bonding, incorporation in a matrix or encapsuation, with a photosensitive macromolecule. In combination, the drug is inert. The macromolecule is large enough to prevent migration of the combination within the body, so that the combination can be implanted at a location of maximum effectiveness. The drug is released from the combination, in therapeutically active form, upon appropriate irradiation.                                                    |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 93/00466

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 5 A61K41/00 A61K47/48

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 5 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          | COLLECT. CZECH. CHEM. COMMUN., 1987, VOL. 52, PAGE(S) 1352-5<br>Younes, M. E. et al 'Synthesis of elastin-like peptides using the liquid phase method'<br>see page 1353 - page 1354<br>---                                                                                                         | 1-7,<br>10-14         |
| X          | CHEMICAL ABSTRACTS, vol. 107, no. 23, 7 December 1987, Columbus, Ohio, US; abstract no. 214271,<br>YEN, HUNG REN ET AL 'Synthetic water-soluble copolymers for optically-controlled ligand delivery'<br>see abstract<br>& POLYM. MATER. SCI. ENG., 1987, VOL. 57,,<br>PAGE(S) 243-7<br>---<br>-/-- | 1-7,<br>10-14         |

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

## \* Special categories of cited documents :

"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

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"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

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Date of the actual completion of the international search

3 August 1994

Date of mailing of the international search report

19. 08. 94

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

Dullaart, A

## INTERNATIONAL SEARCH REPORT

Inter:      nal Application No

PCT/CA 93/00466

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

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                | Relevant to claim No. |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X          | JOURNAL OF THE AMERICAN CHEMICAL SOCIETY,<br>vol.97, no.6, 19 March 1975, WASHINGTON<br>DC, US<br>pages 1575 - 1579<br>D.H. RICH & S.K.GURWARA 'Preparatin of a<br>new o-notribenzyl resin for solid-phase<br>synthesis of<br>tert-butyloxycarbiny-protected peptide<br>acids'<br>cited in the application<br>see the whole document<br>---                                       | 1-6,<br>10-14         |
| X          | BIOCONJUGATE CHEM., VOL. 3, NO. 2, PAGE(S)<br>104-107, MARCH/APRIL 1992<br>GOLDMACHER V S ET AL 'PHOTOACTIVATION OF<br>TOXIN CONJUGATES'<br>see the whole document<br>---                                                                                                                                                                                                         | 1-5,<br>10-14         |
| X          | BIOLOGICAL ABSTRACTS, vol. 81<br>Philadelphia, PA, US;<br>abstract no. 015704,<br>SETER P D ET AL 'NOVEL PHOTOCLEAVAGE<br>PROTEIN CROSSLINKING REAGENTS AND THEIR<br>USE IN THE PREPARATION OF ANTIBODY-TOXIN<br>CONJUGATES'<br>see abstract<br>& PHOTOCHEMISTRY AND PHOTOBIOLOGY,, VOL.<br>42, NO. 3, PAGE(S) 231-238, 1985.<br>---                                              | 1-5,<br>10-14         |
| X          | CHEMICAL ABSTRACTS, vol. 110, no. 11,<br>13 March 1989, Columbus, Ohio, US;<br>abstract no. 095775,<br>YONEIS, M. E. ET AL 'An improved<br>application of the photosensitive<br>3-nitro-4-bromomethylbenzoyl polyethylene<br>glycol support in the liquid phase method<br>of peptide synthesis'<br>see abstract<br>& J. INDIAN CHEM. SOC., 1988, VOL. 65,<br>PAGE(S) 498-9<br>--- | 1-7,<br>10-14         |
| X          | CHEMICAL ABSTRACTS, vol. 110, no. 22,<br>29 May 1989, Columbus, Ohio, US;<br>abstract no. 193552,<br>YEN, HUNG REN ET AL 'Optically controlled<br>ligand delivery. 1. Synthesis of<br>water-soluble copolymers containing<br>photocleavable bonds'<br>see abstract<br>& MAKROMOL. CHEM., 1989, VOL. 190, PAGE(S)<br>69-82<br>---<br>-/--                                          | 1-7,<br>10-14         |

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 93/00466

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

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                            | Relevant to claim No.   |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|
| Y          | BIOCHEM INT, APRIL 1992, VOL. 26, NO. 5,<br>PAGE(S) 943-51,<br>Marriott G et al 'Photomodulation of the<br>nucleating activity of a photocleavable<br>crosslinked actin dimer.'<br>see abstract; figure 1<br>---                                                                              | 1-7,<br>10-14           |
| Y          | PROC NATL ACAD SCI U S A, DEC 1980, VOL.<br>77, NO. 12, PAGE(S) 7237-41,<br>McCray JA et al 'A new approach to<br>time-resolved studies of ATP-requiring<br>biological systems;laser flash photolysis<br>of caged ATP.'<br>see page 7237<br>see page 7240<br>---                              | 1-7,<br>10-14           |
| Y          | CHEM. LETT., 1989, NO. 3, PAGE(S) 433-6<br>Kusumi, Akihiro et al 'Liposomes that can<br>be disintegrated by photo-irradiation'<br>---                                                                                                                                                         | 1-7,<br>10-14           |
| Y          | BIOCONJUGATE CHEM., 1990, VOL. 1, NO. 4,<br>PAGE(S) 296-304<br>Koch, Troels et al 'The oxidative<br>cleavability of protein cross-linking<br>reagents containing organoselenium<br>bridges'<br>see page 297 - page 298<br>---                                                                 | 1-7,<br>10-14           |
| Y          | MACROMOLECULES, 1990, VOL. 23, PAGE(S)<br>2704-9<br>Li, Min Yu et al 'Photodecoupling of<br>cross-links in polymeric gels'<br>see the whole document<br>---                                                                                                                                   | 1-7,<br>10-14,<br>19-23 |
| Y          | J. CONTROL. RELEASE (NL), 1990, VOL. 12,<br>NO. 2, PAGE(S) 155-158,<br>Shah S.S. et al 'Zero-order release of<br>pendent substituted active ingredients<br>from swollen hydrogel matrices'<br>see paragraph "RESULTS AND DISCUSSION"<br>---                                                   | 1-7,<br>10-14,<br>19-23 |
| Y          | J. APPL. POLYM. SCI., 1991, VOL. 43,<br>PAGE(S) 1879-84<br>Shah, S. S. et al 'Swellable hydrogel<br>matrixes for the release of the pendent<br>chain-linked active ingredients over<br>extended time periods'<br>see paragraph "RESULTS AND DISCUSSION"<br>see paragraph "CONCLUSIONS"<br>--- | 1-7,<br>10-14,<br>19-23 |
| 3 A        | PHARMAZIE,<br>vol.32, no.11, November 1977, BERLIN DD<br>Pawelczyk E et al 'Kinetics of drug<br>decomposition Part 51: Kinetics of<br>indometacine photodegradation.'<br>-----                                                                                                                |                         |

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA93/00466

**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.:  
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:  
please see attached sheet!
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:

For further information, please 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.:  
1. 1,2,10-14 (in part, 3-7)  
2. 1 (in part) and 19-23
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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

LACK OF UNITY OF INVENTION

The concept of linking a medicament to a polymeric carrier via a photodegradable linkage is already known, as is demonstrated by the documents cited in the search report. In e.g. Bioconjugate Chemistry, Vol. 3, No. 2, pages 104-107, PAP-s is conjugated to either 5E9 antibody or Ricin B-chain, after which the toxicity is shown to take place only in the presence of light.

Therefore, each photodegradable linkage represents, in its own distinct way, a different solution to the problem: to provide further photocleavable linkages for drug delivery.

Consequently, the present application contains the following subject-matters, each characterised by the special technical feature mentioned above, i.e. the photodegradable linkage.

Since searching this plurality of different subjects would have caused major additional searching efforts, a search was performed for the first subject only.

1 Claims 1-2, 10-14 in part, 3-7: The claimed complex, as far as the photolabile bond is derived from a peptide blocker compound.

2 Claims 1-2 in part, 8: The claimed complex, as far as the photolabile bond is of the general formula according to claim 8.

3 Claims 1-2 in part, 9: The claimed complex, as far as the photolabile bond is [4-(2-chloropropionyl)phenyl]acetic acid.

4 Claims 1-2 in part, 15-16: The claimed complex, as far as the photolabile bond is a carbamate linkage from an amino group of the therapeutically active substance.

5 Claims 1-2 in part, 17-18: The claimed complex, as far as the photolabile bond is a keto aromatic group.

6 Claim 1 in part, 19-23: The claimed complex, as far as the the active compound is diffused into a hydrogel.

7 Claim 1 in part, 24-26: The claimed complex, as far as the the active compound is enclosed in a capsule of photodegradable polymeric material.

8 Claims 1-2 in part, 27-29: The claimed complex, as far as the therapeutic substance is a photoactivable porphyrin compound.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

OBSCURITIES, ETC.

In view of the large number of compounds, which are defined by the general definition of the claims, the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned in the claims, and to the general idea underlying the application (see guidelines, Part B, Chapter III, paragraph 3.6).

Partially searched claims: 1-7, 10-14

Partially searchable claims: 1-7, 10-28