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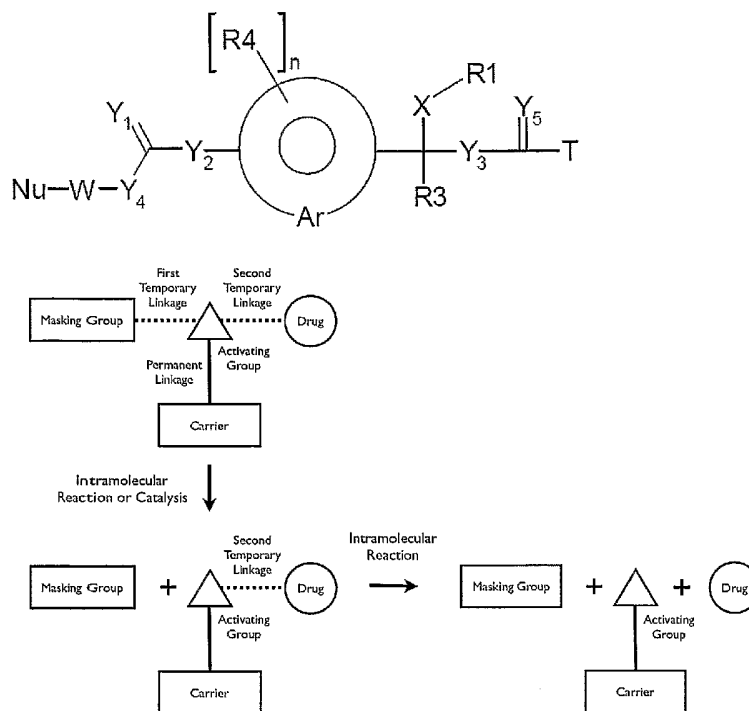
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[Continued on next page]

(54) Title: POLYMERIC PRODRUG WITH A SELF-IMMOLATIVE LINKER



(57) Abstract: A cascade carrier linked prodrug is described which comprises a biologically active moiety and - a masking group having at least one nucleophile and being distinct from the carrier. In one preferred embodiment of the invention, the prodrug has the structure represented by formula (I).



FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO,
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/003061

A. CLASSIFICATION OF SUBJECT MATTER

INV. 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)
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)

EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/057716 A (BOERTH NANCY JOHNSTON ; NEW RIVER PHARMACEUTICALS INC (US); BISHOP BAR) 17 July 2003 (2003-07-17) page 7 - page 8; claims 10,11; figures 3-5 page 5, paragraph 2 -----	1,2,4, 10-13, 21-25, 32, 34-36, 74-88
X	WO 02/083180 A (BEUSKER PATRICK HENRY ; BUSSCHER GUUSKE FREDERIKE (NL); SCHEEREN JOHAN) 24 October 2002 (2002-10-24) cited in the application page 10, lines 25-28; claims 13,14; figures 3,12 ----- -/-	1,2,4, 10-12, 20-25, 32-36, 40-72, 74-88

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

☒ Patent family members are listed in annex.

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"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

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2005/003061

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/019993 A (LIST BENJAMIN ; PESSAH NETA (IL); SHAMIS MARINA (IL); AMIR ROEY JACOB) 11 March 2004 (2004-03-11) cited in the application page 5; figure 3; compound IB page 25, line 12 - page 26, line 10 page 32, lines 6-16; claims 3,7,13,16,24,123,129,161	1,2,4, 10-12, 20-25, 27-36, 40-72, 74-88
X	SHABAT D. ET AL: "Chemical adaptor systems" CHEM. EUR. J., vol. 10, 22 March 2004 (2004-03-22), XP002298470 cited in the application see conclusions abstract; figures 1,2,8	1,2,4, 10-12, 20-25, 27-36, 40-72, 74-88
P,X	WO 2004/043493 A (BEUSKER PATRICK HENRY ; SCHEEREN JOHANNES WILHELM (NL); SYNTARGA B V ()) 27 May 2004 (2004-05-27) cited in the application page 34, lines 18-20; claims 42,49 page 41, line 10 - page 42, line 28 page 50, line 29 - page 51, line 25 page 12, paragraph 3 page 14, paragraphs 1,2	1,2,4, 10-13, 20-25, 27-36, 40-72, 74-88
Y	AMIR R. J. ET AL: "Self immolative dendrimers" ANGEW. CHEM. INT., vol. 42, 2003, pages 4494-4499, XP008035926 abstract; figure 1	1,2,4, 10-13, 20-25, 27-36, 40-72, 74-88
Y	SAUERBREI B. ET AL: "An enzyme labile linker group for organic syntheses on solid supports" ANGEW. CHEM. INT. ED, vol. 37, 1998, pages 1143-1146, XP001120792 page 1144, paragraph 2; figure 1	1,2,4, 10-13, 20-25, 27-36, 40-72, 74-88
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International Application No.

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2005/003061

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2005/082023 A (GENENTECH, INC; SEATTLE GENETICS, INC; FENG, BAINIAN) 9 September 2005 (2005-09-09) abstract; claims 4,5,34,35; figure 1 -----	1,2,4, 10-13, 20-25, 27-36, 40-72, 74-88

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2005/003061

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

Although claims 76-88 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.
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 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:

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.:
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.:

see annex

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

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1,2, 4, 10-13, 20-25, 27-36, 40-72, 74-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a polymer as recited in claim 13 and T is a biologically active small molecule. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 2-31

2. claims: 1,2, 4-9, 12, 13, 20-25, 27-36, 40-72, 74-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a polymer as recited in claim 13 and T is protein or polypeptide. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1, 3-31

3. claims: 1, 2, 4, 5, 12, 13, 20-25, 27-36, 40-72, 74-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a polymer as recited in claim 13 and T is an oligonucleotide or peptide nucleic acid. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1, 2, 4-31

4. claims: 1, 2, 4, 10-12, 14, 20-25, 27-36, 40-72, 74-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is an hydrogel and T is a biologically active small molecule. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-3, 5-31

5. claims: 1, 2, 4-9, 12, 14, 20-25, 27-36, 40-72, 74-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a hydrogel and T is a protein or peptide. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-4, 6-31

6. claims: 1, 2, 4, 5, 12, 14, 20-25, 27-36, 40-72, 74-88 in part

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is an hydrogel and T is an oligonucleotide or peptide nucleic acid. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-5, 7-31

7. claims: 1, 2, 4, 10-12, 15, 20-25, 27-36, 40-72, 74-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a branched or hyperbranched polymer and T is a biologically active small molecule. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-6, 8-31

8. claims: 1, 2, 4-9, 12, 15, 20-25, 27-36, 40-72, 74-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a branched or hyperbranched polymer and T is a protein or a peptide. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-7, 9-31

9. claims: 1,2, 4, 5, 12, 15, 20-25, 27-36, 40-72, 74-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a branched or hyperbranched polymer and T is an oligonucleotide or peptide nucleic acid. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-8, 10-31

10. claims: 1, 2, 4, 10-12, 16, 20-25, 27-36, 40-72, 74-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a dendrimer or dense star polymer and T is a biologically active small molecule. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-9, 11-31.

11. claims: 1, 2, 4-9, 12, 16, 20-25, 27-36, 40-72, 74-88 in part

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a dendrimer or dense star polymer and T is a protein or a peptide. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-10, 12-31

12. claims: 1, 2, 4, 5, 12, 16, 20-25, 27-36, 40-72, 74-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a dendrimer or dense star polymer and T is an oligonucleotide or peptide nucleic acid. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-11, 13-31

13. claims: 1, 2, 4, 10-12, 17-25, 27-36, 40-72, 74-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a biopolymer or a protein and T is a biologically active small molecule. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-12, 14-31.

14. claims: 1,2, 4-9, 12, 17-25, 27-36, 40-72, 74-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a biopolymer or protein and T is a protein or a peptide. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-13, 15-31

15. claims: 1, 2, 4, 5, 12, 17-25, 27-36, 40-72, 74-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a biopolymer or a protein and T is an oligonucleotide or peptide nucleic acid. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-14, 16-31

16. claims: 1, 3, 4, 10-13, 20-25, 27-36, 40-88 in part

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a polymer as recited in claim 13 and T is a biologically active small molecule. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-15, 17-31

17. claims: 1, 3-9, 12, 13, 20-25, 27-36, 40-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a polymer as recited in claim 13 and T is protein or polypeptide. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-16, 18-31

18. claims: 1, 3-5, 12, 13, 20-25, 27-36, 40-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a polymer as recited in claim 13 and T is an oligonucleotide or peptide nucleic acid. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-17, 19-31

19. claims: 1, 3, 4, 10-12, 14, 20-25, 27-36, 40-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is an hydrogel and T is a biologically active small molecule. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-18, 20-31

20. claims: 1, 3-9, 12, 14, 20-25, 27-36, 40-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a hydrogel and T is a protein or peptide. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-19, 21-31

21. claims: 1, 3-5, 12, 14, 20-25, 27-36, 40-88 in part

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is an hydrogel and T is an oligonucleotide or peptide nucleic acid. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-20, 22-31

22. claims: 1, 3, 4, 10-12, 15, 20-25, 27-36, 40-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a branched or hyperbranched polymer and T is a biologically active small molecule. Excluding the subject matter of inventions 1-21, 23-31

23. claims: 1, 3-9, 12, 15, 20-25, 27-36, 40-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a branched or hyperbranched polymer and T is a protein or a peptide. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-22, 24-31

24. claims: 1, 3-5, 12, 15, 20-25, 27-36, 40-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a branched or hyperbranched polymer and T is an oligonucleotide or peptide nucleic acid. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-23, 25-31

25. claims: 1, 3, 4, 10-12, 16, 20-25, 27-36, 40-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a dendrimer or dense star polymer and T is a biologically active small molecule. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-24, 26-31

26. claims: 1, 3-9, 12, 16, 20-25, 27-36, 40-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a dendrimer or dense star polymer and T is a protein or a peptide. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-25, 27-31

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

27. claims: 1, 3-5, 12, 16, 20-25, 27-36, 40-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a dendrimer or dense star polymer and T is an oligonucleotide or peptide nucleic acid. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-26, 28-31

28. claims: 1, 3, 4, 10-12, 17-25, 27-36, 40-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a biopolymer or a protein and T is a biologically active small molecule. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-27, 29-31

29. claims: 1, 3-9, 12, 17-25, 27-36, 40-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a biopolymer or protein and T is a protein or a peptide. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-28, 30-31

30. claims: 1,3-5, 12, 17-25, 27-36, 40-88 in part

Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a biopolymer or a protein and T is an oligonucleotide or peptide nucleic acid. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-29, 31

31. claims: 26, 37-39 complete; 1-3, 12-25, 27-36, 40-52, 54, 55, 60-62, 64-71 in part

Molecule having the structure as depicted by claims 2 or 3 wherein R1 is a polymer and T is leaving group A. Excluding the subject matter of inventions 1-30

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2005/003061

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
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