



- (51) International Patent Classification:  
C07K 1/04 (2006.01)
- (21) International Application Number:  
PCT/US2014/017970
- (22) International Filing Date:  
24 February 2014 (24.02.2014)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
13/833,745 15 March 2013 (15.03.2013) US
- (63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:  
US 13/833,745 (CON)  
Filed on 15 March 2013 (15.03.2013)
- (71) Applicant: MASSACHUSETTS INSTITUTE OF TECHNOLOGY [US/US]; 77 Massachusetts Avenue, Cambridge, MA 02139 (US).
- (72) Inventors: SIMON, Mark, David; 10218 SW 13th Pl., Gainesville, FL 32607 (US). PENTELUTE, Bradley, L.; 108 Armory Street, Unit 1, Cambridge, MA 02139 (US). ADAMO, Andrea; 4 Gordon Place, Cambridge, MA

02139 (US). HEIDER, Patrick, Louis; 1819 Eastlawn Drive, Apt. J12, Midland, MI 48642 (US). JENSEN, Klavs, F.; 103 Outlook Drive, Lexington, MA 02421 (US).

(74) Agent: BLACKWELL, Brandon, S.; Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210-2206 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, 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, IR, IS, JP, KE, KG, 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, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,

[Continued on next page]

(54) Title: SOLID PHASE PEPTIDE SYNTHESIS PROCESSES AND ASSOCIATED SYSTEMS

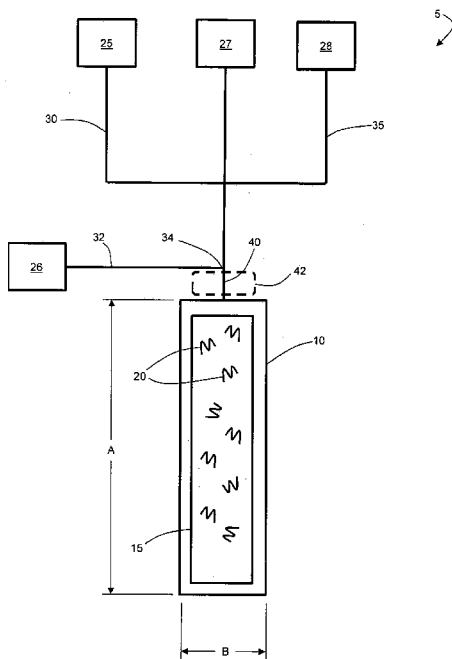


FIG. 1

(57) Abstract: Systems and processes for performing solid phase peptide synthesis are generally described. Solid phase peptide synthesis is a known process in which amino acid residues are added to peptides that have been immobilized on a solid support. In certain embodiments, the inventive systems and methods can be used to perform solid phase peptide synthesis quickly while maintaining high yields. Certain embodiments relate to processes and systems that may be used to heat, transport, and/or mix reagents in ways that reduce the amount of time required to perform solid phase peptide synthesis.

WO 2014/149387 A3



MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,  
SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,  
GW, KM, ML, MR, NE, SN, TD, TG).

— before the expiration of the time limit for amending the  
claims and to be republished in the event of receipt of  
amendments (Rule 48.2(h))

**Published:**

— with international search report (Art. 21(3))

**(88) Date of publication of the international search report:**

27 November 2014

**INTERNATIONAL SEARCH REPORT**

International application No  
PCT/US2014/017970

**A. CLASSIFICATION OF SUBJECT MATTER**  
INV. C07K1/04  
ADD.  
  
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)  
C07K  
  
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 practicable, search terms used)  
EPO-Internal, BIOSIS, EMBASE, 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	EP 1 923 396 A2 (CEM CORP [US]) 21 May 2008 (2008-05-21)	1-11
Y	claims	1-11
Y	----- WO 82/03077 A1 (BIORESEARCH INC [US]) 16 September 1982 (1982-09-16) page 3, line 14 - page 6, line 6	1-11
Y	----- US 4 192 798 A (FULLER WILLIAM D [US] ET AL) 11 March 1980 (1980-03-11) the whole document	1-11
	-----	

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search  16 September 2014	Date of mailing of the international search report  22/09/2014
------------------------------------------------------------------------------------	----------------------------------------------------------------------

Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer  Bayrak, Sinasi
----------------------------------------------------------------------------------------------------------------------------------------------------------------------	------------------------------------------

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2014/017970

## 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.:  
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:
  
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:

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 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.:

1-11

### 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**

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

## 1. claims: 1-11

a process for adding amino acid residues to peptides, comprising: heating a stream comprising amino acids such that the temperature of the amino acids is increased by at least about 1 °C; and exposing the heated amino acids to a plurality of peptides immobilized on a solid support, wherein the heating step is performed prior to and within about 30 seconds of exposing the heated amino acids to the peptides.

---

## 2. claims: 12-29

a process for adding amino acid residues to peptides, comprising: providing a plurality of peptides comprising protection groups, each peptide immobilized on a solid support; performing a first amino acid addition cycle comprising exposing amino acids to the immobilized peptides such that an amino acid residue is added to at least about 99% of the immobilized peptides; and performing a second amino acid addition cycle comprising exposing amino acids to the immobilized peptides such that an amino acid residue is added to at least about 99% of the immobilized peptides; wherein: the total amount of time between the ends of the first and second amino acid addition cycles is about 10 minutes or less and the protection groups comprise fluorenylmethyloxycarbonyl protection groups and/or the total amount of time between the ends of the first and second amino acid addition cycles is about 5 minutes or less.

---

## 3. claims: 30-44

a process for adding amino acid residues to peptides, comprising: providing a plurality of peptides immobilized on a solid support; and exposing activated amino acids to the immobilized peptides such that at least a portion of the activated amino acids are bonded to the immobilized peptides to form , newly-bonded amino acid residues; wherein an amino acid residue is added to at least about 99% of the immobilized peptides within about 1 minute or less.

---

## 4. claims: 45-59

a process for adding amino acid residues to peptides, comprising: flowing a first stream comprising amino acids; flowing a second stream comprising an amino acid activating agent; merging the first and second streams to form a mixed fluid comprising activated amino acids; and, within about 30 seconds after merging the first and second streams to form

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

the mixed fluid, exposing the mixed fluid to a plurality of peptides immobilized on a solid support.

---

5. claims: 60-77

a process for adding amino acid residues to peptides, comprising: providing a plurality of peptides comprising protection groups, each peptide immobilized on a solid support; exposing a deprotection reagent to the immobilized peptides to remove protection groups from at least a portion of the immobilized peptides; removing at least a portion of the deprotection reagent; exposing activated amino acids to the immobilized peptides such that at least a portion of the activated amino acids are bonded to the immobilized peptides to form newly-bonded amino acid residues; and removing at least a portion of activated amino acids that do not bond to the immobilized peptides; wherein an amino acid residue is added to at least about 99% of the immobilized peptides during the amino acids exposing step; and wherein: the total amount of time taken to perform the combination of all of the deprotection reagent exposing step, the deprotection reagent removal step, the activated amino acid exposing step, and the activated amino acid removal step is about 10 minutes or less and the protection groups comprise fluorenylmethyloxycarbonyl protection groups and/or the total amount of time taken to perform the combination of all of the deprotection reagent exposing step, the deprotection reagent removal step, the activated amino acid exposing step, and the activated amino acid removal step is about 5 minutes or less.

---

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2014/017970

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
EP 1923396	A2	21-05-2008	CA 2604609 A1	24-04-2008
			EP 1923396 A2	21-05-2008
			JP 2008110977 A	15-05-2008
			US 2007090104 A1	26-04-2007
-----				
WO 8203077	A1	16-09-1982	EP 0073828 A1	16-03-1983
			WO 8203077 A1	16-09-1982
			ZA 8201537 A	25-01-1984
-----				
US 4192798	A	11-03-1980	NONE	
-----				