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(71) Applicant (for all designated States except US): **ANCHOR THERAPEUTICS, INC.** [US/US]; 67 Rogers Street, Cambridge, MA 02142 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **MCBRIDE, Edward** [US/US]; 2 Blueberry Lane, Lexington, MA 02421 (US). **KULIOPULOS, Athan** [US/US]; 134 Mount Vernon Street, Winchester, MA 01890 (US). **MCMURRY, Thomas, J.** [US/US]; 4 Bonad Road, Winchester, MA 01890 (US).

(74) Agents: **ABELLEIRA, Susan, M.** et al.; Hamilton, Brook, Smith & Reynolds, P.C., 530 Virginia Road, P.O. Box 9133, Concord, MA 01742-9133 (US).

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- with international search report (Art. 21(3))
- 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))
- with information concerning refusal to authorize the rectification of an obvious mistake under Rule 91.1 (Rule 91.3(d))

(88) Date of publication of the international search report:
15 July 2010

(54) Title: CRF1 RECEPTOR COMPOUNDS

(57) Abstract: The invention relates generally to compounds which are allosteric modulators (e.g., negative and positive allosteric modulators, allosteric agonists, and ago-allosteric modulators) of the G protein coupled receptor for corticotrophin releasing hormone (or factor) receptor 1, also known as the CRF1, CRHR1, CRFR1, CRHR, CRF-R. The CRF1 receptor compounds are derived from the intracellular loops and domains of CRF1 receptor. The invention also relates to the use of these CRF1 receptor compounds and pharmaceutical compositions comprising the CRF1 receptor compounds in the treatment of diseases and conditions associated with CRF1 receptor modulation, such as inflammatory bowel disease (peripherally acting), irritable bowel syndrome (IBS), stress response (colonic motor activity), anxiety, sleep disorder, addictive behavior, acute and chronic neurodegeneration, preterm labor and pain.



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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07K 1/00; C07K 17/00; C07K 17/00 (2010.01)

USPC - 530/359

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)

USPC: 530/359

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/2, 12; 530/300, 350, 359 (keyword limited; terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PubWEST (USPT, PGPB, EPAB, JPAB), Google Patents/Scholar

Search Terms Used: corticotropin, intracellular domain, peptide conjugate, translocation, internalization, hydrophobic, lipophilic

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- Y	US 2008/0214451 A1 (Kuliopulos et al.) 04 September 2008 (04.09.2008) para [0006], [0009], [0010], [0078], [0083], [0108]	1, 2, 11 ----- 3-10, 12-22, 24-43, 117, 118
Y	US 7,071,161 B2 (Pisarchik et al.) 04 July 2006 (04.07.2006) col 2, ln 47-56, SEQ ID Nos: 12 and 14	3-10, 12-22, 24-43
Y	US 2008/0167231 A1 (Ulich et al.) 10 July 2008 (10.07.2008) para [0003], [0005], [0028]	117, 118
Y	US 6,864,229 B2 (Kuliopulos et al.) 08 March 2005 (08.03.2005) col 2, ln 19-40, col 3, ln 3-17, col 7, ln 50 to col 8, ln 6	14-22, 24-43
Y	Qi et al. Extracellular Cysteines of the Corticotropin-Releasing Factor Receptor Are Critical for Ligand Interaction. Biochemistry. 1997, Vol 36, pages 12442-12448, especially pg 12442, para 2; pg 12443, Fig 1; pg 12446, col 2 and table 3	8, 10, and 13

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

* 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 application or patent 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 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

"&" document member of the same patent family

Date of the actual completion of the international search

30 April 2010 (30.04.2010)

Date of mailing of the international search report

26 MAY 2010

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Authorized officer:

Lee W. Young

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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.
A	Rijkers et al. "Synthesis and biological activity of N-terminal lipidated and/or fluorescently labeled conjugates of astressin as corticotropin relasing factor antagonists' Bioorganic & Medicinal Cehmistry vol 12 pg 5099-5106; 11 August 2004 (11.08.2004)	1

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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.: 23, 109-116, and 119
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:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+: Claims 1-13, 117, and 118 are drawn to a compound having an i1 loop as P, and a method of use, where the first named invention will be searched and includes a search for SEQ ID NO 22 (e.g. the first compound listed in claim 10). Applicant may have additional sequences searched for an additional search fee per sequence.

Group II+: Claims 1, 14-22, 24-43, 117, and 118 are drawn to a compound having an i2 loop as P, and a method of use, where the first named invention will be searched and includes a search for SEQ ID NO 24.

Group III+: Claims 1, 44-75, 117, and 118 are drawn to a compound having an i3 loop as P, and a method of use, where the first named invention will be searched and includes a search for SEQ ID NO 71
.....continued on extra 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 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.: 1-13, 14-22, 24-43, 117, and 118, wherein claims 10 and 13 are limited to SEQ ID NO: 22 and claims 40 and 43 are limited to SEQ ID NO: 48.
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 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.

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Continued from Box III - Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

Group IV+: Claims 1, 76-108, 117, and 118 are drawn to a compound having an i4 domain as P, and a method of use, where the first named invention will be searched and includes a search for SEQ ID NO 100.

The groups listed above do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons.

The groups share the technical feature of a compound of formula T-L-P, where P is a peptide of an intracellular loop or domain of the corticotrophin releasing hormone receptor CRF1, L is a linking moiety represented by C(O) and bonded to P at an N terminal nitrogen of an N-terminal amino-acid residue, and T is a lipophilic tether moiety bonded to L. However, this does not represent an improvement over the prior art of US 20080214451 A1 (Kuliopulos et al; published Sep 2008) which teaches a compound of formula T-L-P, where P is a peptide of an intracellular loop (e.g. i1 loop) or domain of a corticotrophin releasing hormone receptor (para [0005]-[0007]; [0108]), L is a linking moiety represented by C(O) (fatty acid) and bonded to P at an N terminal nitrogen of an N-terminal amino-acid residue, and T is a lipophilic tether moiety bonded to L (para [0006]; [0009]).

In addition, the inventions of Group I+ do not relate to a single general inventive concept because they are drawn to distinct sequences with different structure and function. Although the sequences of Group I+ are all derived from the i1 loop, SEQ ID NO: 1, this shared feature does not represent an improvement over the prior art of US 2003/0113799 A1 (Pisarchik et al) which teaches SEQ ID NO: 12 (SEQ ID NO: 13).

Due to the number of sequences in this application, Groups II+, III+, and IV+ will be defined as necessary depending on Applicant's ultimate payment of additional fees. The additional sequences will be searched if applicant pays for each additional sequence or shows that the sequences share a special technical feature, i.e. a common structure or feature that defines a contribution over the prior art. Note that each additional sequence to be searched must be specified by the Applicant in the response to this invitation and must either (1) have an additional invention fee paid or (2) have a showing that the sequences share a common structure or feature that defines a contribution over the prior art

Accordingly, unity of invention is lacking.

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Box No. I **Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)**

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing filed or furnished:

a. (means)

☐

on paper

☒

in electronic form

b. (time)

☐

in the international application as filed

☒

together with the international application in electronic form

☐

subsequently to this Authority for the purposes of search

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments: