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(54) Title: INHIBITING GERMINATION OF CLOSTRIDIUM PERFRINGENS SPORES TO REDUCE NECROTIC ENTERITIS

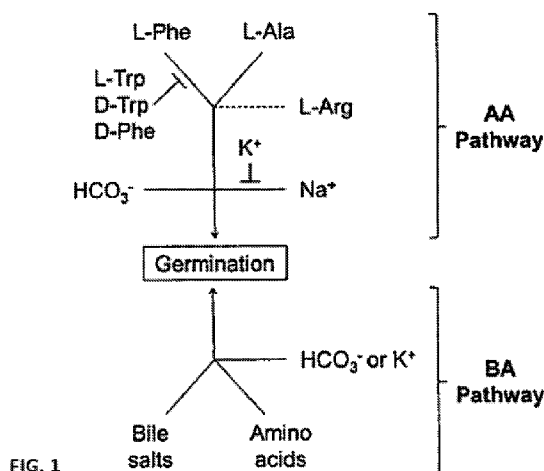


FIG. 1

(57) Abstract: Provided herein are materials and methods useful for reducing, preventing, and/or inhibiting germination of *C. perfringens* spores, including methods for inhibiting *C. perfringens* germination to reduce necrotizing enteritis (NE, also referred to as necrotic enteritis) in animals. This abstract is intended as a scanning tool for purposes of searching in the particular art and is not intended to be limiting of the present invention.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/016848

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A23K 50/75; A23K 20/116; A23K 20/121; A61P 31/04; C07D 263/54 (2016.01)

CPC - A23K 50/75; A23K 20/116; A23K 20/121; C07D 263/54 (2016.05)

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(8) - A23K 20/116; A23K 20/121; A23K 50/75; A61P 31/04; C07D 263/54 (2016.01)

CPC - A23K 20/116; A23K 20/121; A23K 50/75; C07D 263/54 (2016.05)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

USPC - 424/442; 426/2; 514/375; IPC(8) - A23K 20/116; A23K 20/121; A23K 50/75; A61P 31/04; C07D 263/54 (2016.01); CPC - A23K 20/116; A23K 20/121; A23K 50/75; C07D 263/54 (2016.05) (keyword delimited)

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

PatBase, Google Patents, Google Scholar, PubChem

Search terms used: clostridium perfringens, heterocyclic inhibitor, benzoxazole, benzoxazolone, Benzoxazolinone, benzoxazolol, hydroxybenzoxazole, Hydrobenzoxazole, carbamate, hydroxyphenyl, phenylene, necrotizing enteritis, poultry, avian, chicken

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2012/0020950 A1 (DAVIS et al) 26 January 2012 (26.01.2012) entire document	1, 2, 4, 5, 8-13, 15-19
A	US 8,618,100 B2 (GUILLEMONT et al) 31 December 2013 (31.12.2013) entire document	1, 2, 4, 5, 8-13, 15-19
A	US 8,389,516 B2 (HAYDON et al) 05 March 2013 (05.03.2013) entire document	1, 2, 4, 5, 8-13, 15-19
A	US 8,124,623 B2 (HUBSCHWERLEN et al) 28 February 2012 (28.02.2012) entire document	1, 2, 4, 5, 8-13, 15-19
A	US 2010/0168203 A1 (LEVIN et al) 01 July 2010 (01.07.2010) entire document	1, 2, 4, 5, 8-13, 15-19
A	US 6,326,364 B1 (LIN et al) 04 December 2001 (04.12.2001) entire document	1, 2, 4, 5, 8-13, 15-19



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

"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

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/016848

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:

Claims 1, 2, 4, 5, 8-13, and 15-19 have been analyzed subject to the restriction that the claims read on the formula of claim 1 as described in the Lack of Unity of Invention (See extra sheet). The claims are restricted to a method for preventing a disease caused by infection by *Clostridium perfringens* in a subject, the method comprising administering to the subject an effective amount of a compound having a structure represented by a formula: wherein Q is O; wherein Z is O; wherein R1 is hydrogen; wherein each of R2a, R2b, R2c, and R2d is independently hydrogen, thereby preventing the disease caused by infection of *Clostridium perfringens* in a subject; methods thereof; and compositions thereof.

See 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.:
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, 2, 4, 5, 8-13, 15-19

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.

Continued from Box No. III Observations where unity of invention is lacking

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 need to be paid.

Group I+: claims 1-20 are drawn to methods for preventing a disease, methods thereof, and feed compositions thereof.

The first invention of Group I+ is restricted based on the proviso provided that if Q is NR3 then R1 is not CRaR5b(C=O)R5 and is restricted to a method for preventing a disease caused by infection by Clostridium perfringens in a subject, the method comprising administering to the subject an effective amount of a compound having a structure represented by a formula: wherein Q is O; wherein Z is O; wherein R1 is hydrogen; wherein each of R2a, R2b, R2c, and R2d is independently hydrogen, thereby preventing the disease caused by infection of Clostridium perfringens in a subject; methods thereof; and compositions thereof. It is believed that claims 1, 2, 4, 5, 8-13, and 15-19 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a method for preventing a disease caused by infection by Clostridium perfringens in a subject, the method comprising administering to the subject an effective amount of a compound having a structure represented by a formula: wherein Q is NR3; wherein R3 is present and is C8 alkyl; wherein Z is NR4; wherein R4 is present and is C8 alkyl; wherein R1 is C8 alkyl; wherein each of R2a, R2b, R2c, and R2d is independently -NO2, thereby preventing the disease caused by infection of Clostridium perfringens in a subject; methods thereof; and compositions thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ 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 I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables Q, Z, R1, R2a, R2b, R2c, and R2d.

The Groups I+ share the technical features of a method for preventing a disease caused by infection by Clostridium perfringens in a subject, the method comprising administering to the subject an effective amount of a compound having a structure represented by a formula, thereby preventing the disease caused by infection of Clostridium perfringens in a subject; a method for inhibiting germination of at least one Clostridium perfringens spore, the method comprising contacting the spore with a compound having a structure represented by a formula: thereby inhibiting germination of at least one Clostridium perfringens spore; and a feed composition comprising a feed component and a compound having a structure represented by a formula. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2010/0168203 A1 to Levin et al. teach a method for preventing a disease caused by infection by Clostridium perfringens in a subject (See Para. [0016]. The invention also provides a method for the treatment of a subject with a disease caused by infection by bacteria, by administering to the subject a therapeutic amount of a modulator of a bacterial adenylyl cyclase, wherein the disease is caused by infection by bacteria selected from the group consisting of... Clostridium perfringens...), the method comprising administering to the subject an effective amount of a compound a structure represented by a formula: wherein Q is NR3; wherein R3 is C1 alkyl; Z is S; wherein R1 is -CR5aR5b(C=O)NHN=CR6Ar1; each Ra and Rb is independently hydrogen; R6 is hydrogen; Ar1 is heteroaryl; each R2a, R2b, R2c, and R2d is independently hydrogen, thereby preventing the disease caused by infection of Clostridium perfringens in a subject (See Para. [0016]; Para. [0167], Pg. 24 Table 1; Compound KH7.140;...see shown structure...; Para. [0025]...a modulator of a bacterial adenylyl cyclase, wherein the modulator of bacterial adenylyl cyclase is selected from the compounds listed in Table 1...); a method for inhibiting germination of at least one Clostridium perfringens spore (See Para. [0016]; Para. [0010]; Claim 5), the method comprising contacting the spore with a compound (See Paras. [0089] through [0092]) thereby inhibiting germination of at least one Clostridium perfringens spore (See Para. [0016]; Para. [0167], Pg. 24 Table 1; Compound KH7.140;...see shown structure...; Para. [0025]); and a feed composition (See Para. [0130]. In one embodiment of the invention, the modulator of bacterial adenylyl cyclase may be added to animal feed, for the prevention and/or treatment of bacterial disease in livestock and pets.) comprising a feed component and a compound (Para. [0130]. This may be accomplished by preparing an appropriate feed premix containing the modulator of bacterial adenylyl cyclase in an effective amount and incorporating the premix into the complete ration.; Para. [0025]).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.