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[Continued on next page]

(54) Title: NHE3-BINDING COMPOUNDS AND METHODS FOR INHIBITING PHOSPHATE TRANSPORT

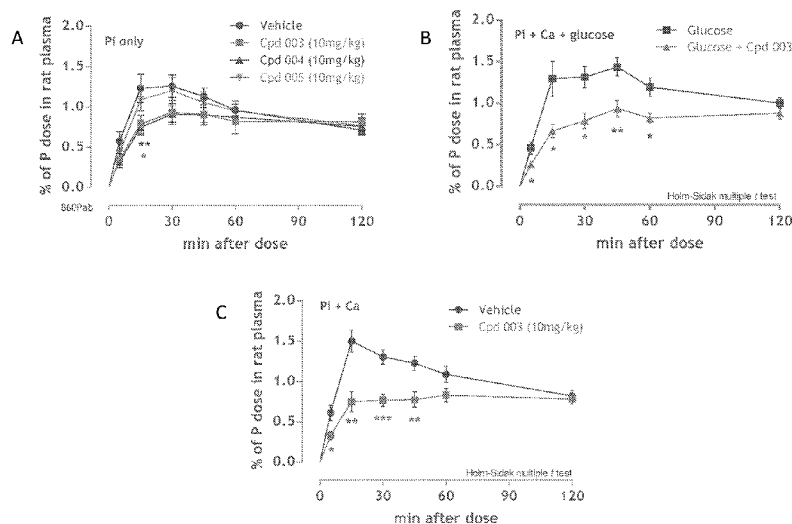


Figure 1

(57) Abstract: Provided are NHE3-binding and/or NHE3-modulating agents having activity as phosphate transport inhibitors, including inhibitors of phosphate transport in the gastrointestinal tract and the kidneys, and methods for their use as therapeutic or prophylactic agent.. Embodiments of the present invention include methods for inhibiting phosphate uptake in the gastrointestinal tract or kidneys of a patient in need of phosphate lowering, comprising administering to the patient a compound that binds to NHE3 and is substantially active in the gastrointestinal tract or kidneys to inhibit transport of phosphate ions (Pi) therein upon administration to the patient in need thereof.



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

29 October 2015

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2014/033603

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/472 (2014.01)

USPC - 424/78.01

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) - A61K 31/405, 31/472, 31/74; A01N 43/38; A61P 1/00 (2014.01)

USPC - 424/78.01; 514/89; 546/23 (keyword delimited)

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

CPC - A61K 31/765, 31/785, 45/06 (2014.10) (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

Search terms used: phosphate uptake inhibitor NHE3

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2012/0263670 A1 (CHARMOT et al) 18 October 2012 (18.10.2012) entire document	1-3
Y	WO 2012/006477 A1 (LEWIS et al) 12 January 2012 (12.01.2012) entire document	1-3
A	US 2003/0216449 A1 (WEINSTOCK et al) 20 November 2003 (20.11.2003) entire document	1-3

☐ 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

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INTERNATIONAL SEARCH REPORT

International application No. .
PCT/US2014/033603

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.: 7, 8, 11-18
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 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.:
1-3

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.

INTERNATIONAL SEARCH REPORT

International application No. .

PCT/US2014/033603

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 1-6, 9, and 10 are drawn to a method of inhibiting phosphate uptake or treating hyperphosphatemia comprising administering a compound that binds to NHE3.

The first invention of Group I+ is restricted to a method of inhibiting phosphate uptake in the gastrointestinal tract of a patient in need of phosphate lowering, comprising enterally administering to the patient a substantially systemically non-bioavailable compound that binds to NHE3 and is substantially active in the gastrointestinal tract to inhibit transport of phosphate ions (Pi) therein upon administration to the patient in need thereof, wherein the compound has the structure of Formula (X): Core-(L-NHE)_n wherein NHE is the first formula with sulfonamide in the meta position, as shown; L is a polyethylene glycol linker; n is 2; and Core is selected as the first urea formula, as shown; or a pharmaceutically acceptable salt thereof; and methods of treating hyperphosphatemia thereof. It is believed that claims 1-3 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) to be searched in a specific combination by paying an additional fee for each set of election. An exemplary election would be a method of inhibiting phosphate uptake in the gastrointestinal tract of a patient in need of phosphate lowering, comprising enterally administering to the patient a substantially systemically non-bioavailable compound that binds to NHE3 and is substantially active in the gastrointestinal tract to inhibit transport of phosphate ions (Pi) therein upon administration to the patient in need thereof, wherein the compound has the structure of Formula (X): Core-(L-NHE)_n wherein NHE is the second formula with sulfonamide in the para position, as shown; L is a polyethylene glycol linker; n is 2; and Core is selected as the first urea formula, as shown; or a pharmaceutically acceptable salt thereof; and methods of treating hyperphosphatemia thereof. 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+ compounds do not share a significant structural element that is responsible for the represented effect of inhibiting phosphate uptake requiring the selection of alternatives for the compound variables Core, L, NHE, and n.

The Groups I+ share the technical features of a method of inhibiting phosphate uptake or treating hyperphosphatemia comprising administering a substantially systemically non-bioavailable compound that binds to NHE3 and is substantially active in the gastrointestinal tract to inhibit transport of phosphate ions (Pi) therein; and species thereof. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2012/0263670 to Charmot et al. teach a substantially systemically non-bioavailable compound that binds to NHE3 and is substantially active in the gastrointestinal tract (Para. [0003], The present disclosure is directed to compounds that are substantially active in the gastrointestinal tract to inhibit NHE-mediated antiport of sodium ions and hydrogen ions...; Para. [0121], ...substantially systemically non-bioavailable compounds exhibiting NHE-3...inhibition are of particular interest); and a compound with the core structure of the species thereof (Para. [1154], Compound 236, N,N'-(10,17-dioxo-3,6,21,24-tetraoxa-9,11,16,18-tetraazahexacosane-1,26-diyl)bis(3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzenesulfonamide).

Additionally, US 2003/0216449 to Weinstock et al. teach a method of inhibiting phosphate uptake comprising administering a benzene sulfonamide compound to inhibit transport of phosphate ions (Pi) therein (Para. [0012], The present invention involves novel methods of using of N-aryl-2-sulfonamidobenzamides as phosphate transport inhibitors for the selective inhibition of Pi transport in ... the intestine; Para. [0013], inhibitors ... selectively inhibit Na-dependent Pi transport in ... intestinal tissue ... including human); and method for treating hyperphosphatemia thereof (Para. [0013], ... inhibitors of phosphate transport, for the treatment of ... hyperphosphatemia).

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