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(54) Title: NOVEL PRODRUGS DERIVED FROM NICOTINIC ACID AND RIBOSE

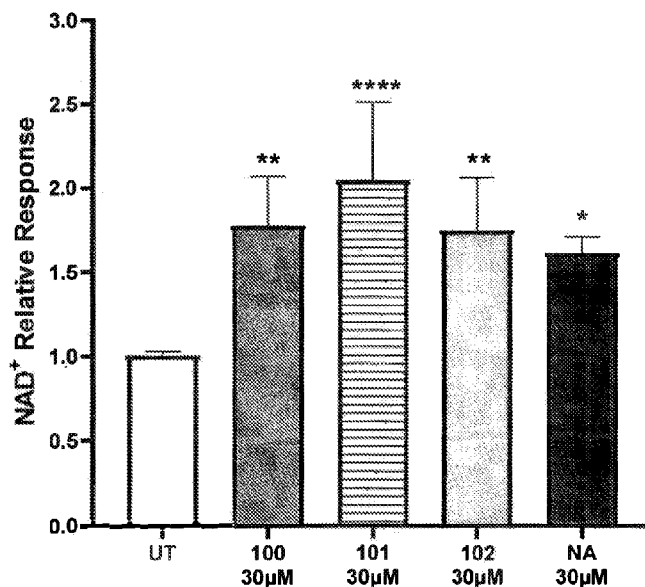


Fig-1

Fig. 1

(57) Abstract: Disclosed are novel prodrugs derived from nicotinic acid and pharmaceutical compositions thereof which may be used to treat or prevent a variety of medical disorders, which may be characterized by mitochondrial dysfunction. The compounds and pharmaceutical compositions thereof may be used to treat or prevent metabolic disorders, cardiovascular disorders, cerebrovascular disorders, liver disorders, a kidney disorders or muscle disorders.



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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US23/63565

A. CLASSIFICATION OF SUBJECT MATTER
 IPC - INV. A61K 31/455; A61K 31/7024; C07D 213/80 (2023.01)
 ADD.
 CPC - INV. A61K 31/455; A61K 31/7024; C07D 213/80
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B. FIELDS SEARCHED
 Minimum documentation searched (classification system followed by classification symbols)
 See Search History document
 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
 See Search History document
 Electronic database consulted during the international search (name of database and, where practicable, search terms used)
 See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---	WO 2018/033639 A1 (THE QUEEN'S UNIVERSITY OF BELFAST) 22 February 2018; paragraphs [0027], [0030], [0034], [00133], [00233], [00235], [00254], [00272], [00274]	1-3, 10, 20, 69, 71-74 ---
Y		75
Y	WO 2020/131578 A2 (MITOPOWER LLC) 25 June 2020; page 98, lines 15-30	75
A	US 5,739,117 A (YOKOYAMA, A et al.) 14 April 1998; 1,3,4-tri-O-acetyl-6-O-nicotinoyl-D-glucose; column 3, lines 10-20; claim 2	1
A	(DEYRUP, M et al.) Improved delivery through biological membranes. Synthesis and antiviral activity of a series of ribavirin chemical delivery systems: 2' and 3' derivatives. Antiviral Chemistry and Chemotherapy, Vol. 2, No. 6, 1991, pages 337-355; entire publication	1
A	(BHAGRATH, M et al.) Improved delivery through biological membranes. Synthesis, characterization and antiviral activity of a series of ribavirin chemical delivery systems: 5' and carboxamide derivatives. Antiviral Chemistry and Chemotherapy, Vol. 2, No. 5, 1991, pages 265-286; entire publication	1
A	WO 2008/106227 A1 (CONCOURSE HEALTH SCIENCES LLC) 4 September 2008; paragraph [0061]	1

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"D" document cited by the applicant in the international application	"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
"E" earlier application or patent but published on or after the international filing date	"&" document member of the same patent family
"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	

Date of the actual completion of the international search 16 October 2023 (16.10.2023)	Date of mailing of the international search report NOV 14 2023
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US23/63565

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:
-***-Please See Supplemental Page-***-

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.:
Group I+, claims 1-75, Formula I, wherein R1 is the third moiety for provided that at least one of R1 or R4 is O-nicotinate; R2 is -H; R3 is -H; R4 is -H; provided that at least one of R1 or R4 is O-nicotinate (first exemplary compound).

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/US23/63565

-***-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 must be paid.

Group I+, claims 1-75, Formula I, wherein R1 is the third moiety for provided that at least one of R1 or R4 is O-nicotinate; R2 is -H; R3 is -H; R4 is -H; provided that at least one of R1 or R4 is O-nicotinate (first exemplary compound), and methods and composition associated therewith.

The compounds and methods of Claims 1-3, 10, 20, 69, 71-75 are believed to encompass the first named invention of Groups I+ and are the claims that will be searched to the extent that they encompass a compound of structural Formula I, wherein R1 is the third moiety for provided that at least one of R1 or R4 is O-nicotinate; R2 is -H; R3 is -H; R4 is -H; provided that at least one of R1 or R4 is O-nicotinate (first exemplary compound), and methods and composition associated therewith. This first named invention of Group I+ has been selected to encompass the first species of the genus found in claim 1 based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines.

Applicant is invited to elect additional compounds, with specified substituents for each Rx, and where available as an option within at least one searchable claim, to be searched. Additional compound(s) will be searched upon the payment of additional fees. Applicants must specify the searchable claims that encompass any additionally elected compound(s). Applicants must further indicate, if applicable, the claims which encompass 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. An exemplary election would be a compound of structural Formula I, wherein R1 is R8C(O)-, R2 is R9C(O)-; R3 is R10C(O)-; R4 is O-nicotinate for provided that at least one of R1 or R4 is O-nicotinate; R8, R9 and R10 are C1 alkyl (second exemplary compound), and methods and composition associated therewith.

Groups I+ share the technical features including the compound of structural Formula I, a pharmaceutical composition comprising the compound and a pharmaceutically acceptable excipient, and a method of preventing or treating a disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound. However, these shared technical features are previously disclosed by WO 2018/033639 A1 (THE QUEEN'S UNIVERSITY OF BELFAST) (hereinafter "UNIVERSITY").

UNIVERSITY discloses the compound of structural Formula I (compound 5, or 1,2,3-trio-O-acetyl-5-O-nicotinoyl-ribose; paragraph [00133]), wherein R1 is the third moiety (the nicotinoyl moiety is attached through the oxygen bridge to the C5 carbon of the ribose moiety; paragraph [00133]); R2 is R9C(O)-; R3 is R10C(O)-; R4 is R10C(O)-; R9, R10 and R11 are C1 alkyl (the O-acetyl moieties are attached to the C1, C2 and C3 carbons of the ribose ring; paragraph [00133]); provided that at least one of R1 or R4 is O-nicotinate (the nicotinoyl moiety is attached through the oxygen bridge to the C5 carbon of the ribose moiety; paragraph [00133]), a pharmaceutical composition comprising the compound and a pharmaceutically acceptable excipient (the compounds can be formulated into pharmaceutical compositions that comprise a pharmaceutically acceptable carriers the include excipients; paragraph [00254]), and a method of preventing or treating a disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound (a method of treating a disease or disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound; paragraphs [0030], [00233]).

Since none of the special technical features of the Group I+ is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the UNIVERSITY reference, unity of invention is lacking.