Title: SMALL MOLECULE INHIBITORS OF VIRAL PROTEIN INTERACTIONS WITH HUMAN tRNA3Lys

Abstract: Disclosed herein are compounds, compositions and methods of their use to treat HrV/AIDS disease in a subject in need thereof, wherein the compositions comprise small molecule inhibitors that inhibit viral preparation or viral recruitment of human tRNA3Lys.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/165 (2014.01)
USPC - 514/622

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 31/165 (2014.01)
USPC - 514/622

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

CPC - A61K 31/165 (2013.01)

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

PatBase, Orbit, STN, PubChem, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category* Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No.

| A | GB 2 265 373 A (HINO et al) 29 September 1993 (29.09.1993) entire document | 1-4 |
| A | US 2011/018300 A1 (HARRIS et al) 19 May 2011 (19.05.2011) entire document | 1-4 |

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

"A" 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: 27 January 2014

Date of mailing of the international search report: 07 FEB 2014

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### Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

**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).

### Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

**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.:

1-4

**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.
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 1-4 are drawn to methods of treating HIV/AIDS disease by inhibiting interaction of viral proteins with human tRNA in a patient in need thereof, said method comprising administration of a therapeutically effective amount of a compound that has a preferential specificity and/or binding affinity to human tRNA3Lys selected from the compounds of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX).

The first invention of Group I is restricted to a method of treating HIV/AIDS disease in a patient in need thereof, said method comprising administering a therapeutically effective amount of a compound of formula (II) (see applicants' Paras. [00058]); wherein X is S; Y is O; R1 and R are independently and individually H; R2 and R3 are independently and individually H; R6 is independently and individually halo; and pharmaceutically acceptable salts, solvates, prodrugs, polymorphs, stereoisomers, and tautomers thereof. It is believed that claims 1-4 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 method 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 treating HIV/AIDS disease in a patient in need thereof, said method comprising administering a therapeutically effective amount of a compound of formula (II) (see applicants' Para. [00058]); wherein X is S; Y is O; R1 and R are independently and individually H; R2 and R3 are independently and individually H; R6 is independently and individually halo; and pharmaceutically acceptable salts, solvates, prodrugs, polymorphs, stereoisomers, and tautomers 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 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 responsible for treating HIV/AIDS disease and inhibiting interaction of viral proteins with human tRNA comprising administering a therapeutically effective amount of "one or more compounds selected from the group consisting of formula (I), (II), (III), (IV), (V) (VI), (VII), (VIII) or (IX)."

The Groups I share the technical features of a method of treating HIV disease by inhibiting interaction of viral proteins with human tRNA in a subject in need thereof said method comprising administration of a therapeutically effective amount of a compound that has a preferential specificity and/or binding affinity to human tRNA3Lys; and a method comprising administering a therapeutically effective amount of one or more compounds selected from the group consisting of formula (I), (II), (III), (IV), (V) (VI), (VII), (VIII) or (IX). However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 5,827,935 A to Rossi et al. teach a method of treating HIV disease by inhibiting interaction of viral proteins with human tRNA in a subject in need thereof said method comprising administration of a therapeutically effective amount of a compound that has a preferential specificity and/or binding affinity to human tRNA3Lys (see Col. 2 Lns. 30-48, The chimeric primers effectively block HIV-1 reverse transcription, making them a novel, highly target specific, and unique anti-HIV-1 therapeutic agent. In addition, the tRNA3Lys portion contains within its mature coding sequence the elements required for transcription by human RNA polymerase III, thereby making it feasible to insert the gene, rather than the RNA into human cells).

Further, US 7,208,497 B2 to Dorwald et al. teach a method comprising administering a therapeutically effective amount of one or more compounds of the shared core structure of formulas (I) and (II) (see Col. 22 Lns. 62-67, a method for the treatment of diseases and disorders related to the histamine H3 receptor the method comprising administering to a subject in need thereof an effective amount of a compound of the formula (I); Cols. 43-44, Example No 32, 2-(4-Fluorophenyl)-1-(4-propypiperazin-1-yl)-ethanone; which corresponds to a compound of formula (II): wherein X is O; Y is O; R1 and R connected together to form a ring; wherein the ring is substituted with one or more alkyl; R2 and R3 are independently and individually H; R6 is independently and individually halo; and pharmaceutically acceptable salts, solvates, prodrugs, polymorphs, stereoisomers, and tautomers thereof, see applicant's Paras. [00056]-[00058]). As said method and compound was known in the art at the time of invention, this cannot be considered a special technical feature that would otherwise unify the compounds sharing the core structure of formulas (I) and (II).

Additionally, US 2008/0207760 A1 to Huang teaches a method comprising administering a therapeutically effective amount of one or more compounds of the shared core structure of formula (III) (see Abstract, methods of inhibition of HCV replication by replicase complex defect inducers; Pg. 146, Compound 616-2 which corresponds to a compound of formula (III): wherein n is 1; R is aryl; R2 is independently and individually H; and pharmaceutically acceptable salts, solvates, prodrugs, polymorphs, stereoisomers, and tautomers thereof, see applicant's Paras. [00060]-[00061]). As said method and compound was known in the art at the time of invention, this cannot be considered a special technical feature that would otherwise unify the compounds sharing the core structure of formula (III).
Moreover, US 6,303,604 B1 to Moschel et al. teach a method comprising administering a therapeutically effective amount of one or more compounds of the shared core structure of formulas (IV), (V), and (VI) (see Para. Col. 2 Lns. 1-10), a method of enhancing the chemotherapeutic treatment of tumor cells in a mammal with an anitneoplastic alkylating agent which causes cytotoxic lesions at the 06-position of guanine, by administering to a mammal an effective amount of one of the aforesaid derivatives, 2,4-diamino-6-benzoxys-triazine, which corresponds to a compound of formula (IV); wherein R1 and R2 are independently and individually H; R3 and R4 are independently and individually H; R5 is independently and individually alkyl; and pharmaceutically acceptable salts, solvates, prodrugs, polymorphs, stereoisomers, and tautomers thereof, see applicant’s Paras. [0062]-[0067]). As said method and compound was known in the art at the time of invention, this cannot be considered a special technical feature that would otherwise unify the compounds sharing the core structure of formulas (IV), (V), and (VI).

Further, US 2011/018300 A1 to Harris et al. teach a method comprising administering a therapeutically effective amount of one or more compounds of the shared core structure of formula (VII) (see Para. [0023]) a method for modulating blood glucose levels in a subject comprising administering to a subject an effective amount of a compound according to the present invention: Para. [0055]. In another preferred embodiment, the compound is compound 15: or an enantiomer, optical isomer, diastereomer, N-oxide, crystalline form, hydrate, or pharmaceutically acceptable salt thereof; which corresponds to a compound of formula (VII); wherein R2 is -OR; R and R1 are C1 alkyl; A is O; and pharmaceutically acceptable salts, solvates, prodrugs, polymorphs, stereoisomers, and tautomers thereof, see applicant’s Paras. [0068]-[0069]). As said method and compound was known in the art at the time of invention, this cannot be considered a special technical feature that would otherwise unify the compounds sharing the core structure of formula (VII).

Additionally, US 2008/0200467 A1 to Patel et al. teach a method comprising administering a therapeutically effective amount of one or more compounds of the shared core structure of formula (VIII) (see Pg. 13, second shown structure in left Col.; Para. [0311]), compounds and their pharmaceutical compositions, to their preparation, and to their uses for treating diseases mediated by soluble epoxide hydrolase (sEH), which corresponds to a compound of formula (VIII); wherein X is O; R1 and R are connected together to form a ring; wherein the ring is substituted or unsubstituted aryl; Z is substituted or unsubstituted aryl; and pharmaceutically acceptable salts, solvates, prodrugs, polymorphs, stereoisomers, and tautomers thereof, see applicant’s Paras. [0070]-[0074]). As said method and compound was known in the art at the time of invention, this cannot be considered a special technical feature that would otherwise unify the compounds sharing the core structure of formula (VIII).

Moreover, US 6,417,393 B1 to Christophersen et al. teach a method comprising administering a therapeutically effective amount of one or more compounds of the shared core structure of formula (IX) (see Col. 1 Lns. 10-19, phenyl derivatives which are valuable blockers of chloride channels and as such useful for the treatment of sickle cell anaemia, brain oedema following ischaemia or tumours, diuretics, hypertension (diuretic) and for the reduction of the intracocular pressure for the treatment of disorders such as glaucoma, . . . Col. 14 Lns. 7-20, Example 13, N-(3-Trifluoromethylphenyl)-N-(2-ethylxylocarbonylphenyl)-1,2-diaminoethane; which corresponds to a compound of formula (IX); wherein each instance of X is independently C1 alkyl; Z is independently aryl; and pharmaceutically acceptable salts, solvates, prodrugs, polymorphs, stereoisomers, and tautomers thereof, see applicant’s Paras. [0075]-[0079]). As said method and compound was known in the art at the time of invention, this cannot be considered a special technical feature that would otherwise unify the compounds sharing the core structure of formula (IX).

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

<End Box III: Observations where unity of invention is lacking>