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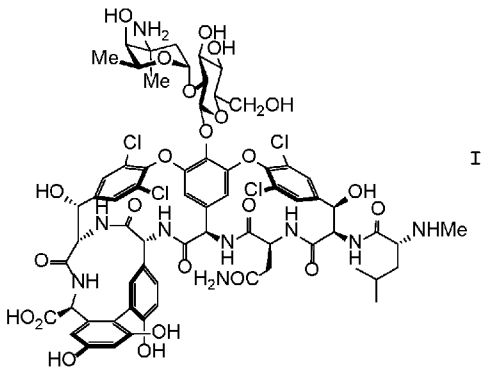

I

(57) **Abstract:** A total synthesis of a new class of vancomycin analogues of reduced synthetic complexity was developed. The synthesis, achieved by the addition of two aryl chloride substituents to provide tetrachlorovancomcyin aglycon (Compound II), tetrachlorovancomcyin (Compound I), and their derivatives, permitted a streamlined total synthesis of the new class of glycopeptide antibiotics by removing atropisomer stereochemical control and enabled the simultaneous and further activated S_NAr macrocyclizations that establish the tricyclic skeleton of Compound I. In addition to the antimicrobial evaluation of tetrachlorovancomycin (Compound I), the preparation of key binding pocket and peripherally-modi fied derivatives, which overcome vancomycin resistance and introduce independent and synergistic mechanisms of action, revealed their exceptional antimicrobial potency and provide the foundation for use of this new class of synthetic glycopeptide analogues. Also disclosed are a pharmaceutical composition containing bactericidal amount of tetrachlorovancomycin, a derivative thereof or a salt of either dissolved or dispersed in a pharmaceutically acceptable diluent.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 24/31453

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 38/14, A61K 38/04, A61K 38/14 (2024.01)
ADD. A61K 38/12 (2024.01)

CPC - INV. A61K 38/14, A61K 38/04, A61K 38/14
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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)
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 data base consulted during the international search (name of data base 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.
Y	OKANO et al. "Total Syntheses of Vancomycin Related Glycopeptide Antibiotics and Key Analogues", Chem Rev. 2017 September 27; 117(18): pp 11952-11993, especially: pg 4, para 4; pg 6, para 2; pg 9, para 2; pg 46, Figure 1, formula 1; pg 71, Scheme 1; pg 72 Scheme 2; pg 77, Scheme 7.	1
Y	KRAUS et al. "Second Generation Analogs of the Cancer Drug Clinical Candidate Tipifarnib for Anti-Chagas Disease Drug Discovery", J. Med. Chem. 2010, 53, pp 3887-3898, especially: pg 3888, col 2 to pg 3889, col 1, para 1; pg 3888, Figure 1; pg 3890, Table 1.	1
A	CROWLEY et al. "Total Synthesis and Evaluation of [psi[CH2NH]Tpg4]Vancomycin Aglycon: Reengineering Vancomycin for Dual D-Ala-D-Ala and Dala- D-Lac Binding", J Am Chem Soc. 2006 March 8; 128(9): pp 2885-2892, especially: pg 2, para 2 to pg 3, para 1; pg 11, Figure 1, formula 1; pg 12, Figure 2, formula 5; pg 15, Scheme 2, formula 14 to formula 15.	1
A	RAMAKRISHNAN "Antibacterial Activities and Modes of Action of Vancomycin and Related Glycopeptides", ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1991, p. 605-609.	1

☐ 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
"D" document cited by the applicant in the international application
"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	Date of mailing of the international search report
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Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 24/31453

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:
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

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.

--Box III - Lack of Unity--

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 searched, the appropriate additional search fees must be paid.

Group I+: Claims 1-5 and 7-18, directed to a compound that corresponds in structure to that shown in Formula III, the compound listed in claim 7, claim 8, claim 17, or claim 18, or a pharmaceutically acceptable salt of said compounds. The compound of Formula III will be searched to the extent that it encompasses the first species of claim 1, wherein -C(=X)- is the first substructure: -C(=O)-; R1 is consisting of hydrido; R2 is OH. It is believed that claims 1 encompasses this first named invention, and thus this claim will be searched without fee to the extent that it encompasses the first species of claim 1. This first named invention has been selected 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 of Formula III, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. 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. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of claim 1, wherein -C(=X)- is the second substructure: -C(=S)-; R1 is consisting of hydrido; R2 is OH (i.e. claim 1).

The groups of inventions 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:

Special Technical Features:

Group I+ includes the technical feature of a unique compound of Formula III, which is not required by any other invention of Group I+.

Common Technical Features:

The inventions of Groups I+ share the technical feature of a compound that corresponds in structure to that shown in Formula III, the compound listed in claim 7, claim 8, claim 17, or claim 18, or a pharmaceutically acceptable salt of said compounds.

These shared technical features, however, do not provide a contribution over the prior art, because the shared technical features are obvious over the article entitled "Total Synthesis and Evaluation of [psi[CH2NH]Tpg4]Vancomycin Aglycon: Reengineering Vancomycin for Dual D-Ala-D-Ala and Dala- D-Lac Binding" by Crowley et al. (hereinafter 'Crowley') in view of the article entitled "Second Generation Analogs of the Cancer Drug Clinical Candidate Tipifarnib for Anti-Chagas Disease Drug Discovery" by Kraus et al. (hereinafter 'Kraus').

Crowley teaches a compound that corresponds in structure to that shown in Formula III wherein -C(=X)- is the first substructure; R1 is consisting of hydrido; R2 is OH (pg 11, Figure 1, formula 1), but Crowley doesn't teach the second chlorine atom on each of the phenyl rings in the structure. However, Crowley further teaches that the synthesis of the mono-chloro substituted compound is problematic because the two rings form atropisomers (pg 2, para 2 to pg 3, para 1, The desired analogue 5 was anticipated to be prepared by a route analogous to that developed for vancomycin,4 with notable modifications. Thus, two aromatic nucleophilic substitution reactions with formation of the biaryl ethers would be enlisted for CD and DE macrocyclization, a key macrolactamization reaction would be employed for cyclization of the AB ring system, and the defined order of CD, AB, and DE ring closures was expected to permit sequential control of the atropisomer stereochemistry of each of the newly formed ring systems or their immediate precursors, Figure 2... Key unknown features of the approach include the feasibility of conducting the critical CD ring closure enlisting the residue 4 protected amine versus amide, the resulting unknown atropisomer stereochemical issues (kinetic and thermodynamic diastereoselectivity), and the impact the deep-seated structural change would have on the conformational features of the CD or ABCD ring systems and those of the final molecule; see also pg 12, Figure 2, formula 5; see also pg 15, Scheme 2, formula 14 to formula 15). Furthermore, Kraus teaches that atropisomerism (axial chirality) of a single ortho-chlorine atom was eliminated using a symmetrical disubstitution of a phenyl ring (pg 3888, col 2 to pg 3889, col 1, para 1, Although 2 is one of the most potent anti-T. cruzi compounds reported to date, subsequent studies showed that there is hindered rotation about the bond connecting the 3-chlorophenyl group and the quinolone ring presumably because of a clash between the ortho methyl group and the vinylic proton of the quinolone ring. Thus 2 is a mixture of rotamers with the ortho methyl group either above or below the plane of the quinolone ring... We thus went on to design new analogs that either lack a 2-substitutent on the 3-chlorophenyl ring or have a C2-symmetric ring in order to avoid rotamer formation; see also pg 3888, Figure 1; see also pg 3888, Figure 1; see also pg 3890, Table 1, formula 2 and formulas 14-16, especially formula 15 for dichloro substitution). Therefore, it would have been obvious to a person having ordinary skill in the art to prepare the derivative of the compound of Crowley with dichloro substitution because this compound is suggested by the teachings of Crowley in view of Kraus. It would have been further obvious to combine Kraus with Crowley because Crowley teaches that axial chirality of an ortho-chloro substituted phenyl ring is synthetically problematic (pg 2, para 2 to pg 3, para 1, The desired analogue 5 was anticipated to be prepared by a route analogous to that developed for vancomycin,4 with notable modifications. Thus, two aromatic nucleophilic substitution reactions with formation of the biaryl ethers would be enlisted for CD and DE macrocyclization, a key macrolactamization reaction would be employed for cyclization of the AB ring system, and the defined order of CD, AB, and DE ring closures was expected to permit sequential control of the atropisomer stereochemistry of each of the newly formed ring systems or their immediate precursors, Figure 2... Key unknown features of the approach include the feasibility of conducting the critical CD ring closure enlisting the residue 4 protected amine versus amide, the resulting unknown atropisomer stereochemical issues (kinetic and thermodynamic diastereoselectivity), and the impact the deep-seated structural change would have on the conformational features of the CD or ABCD ring systems and those of the final molecule; see also pg 12, Figure 2, formula 5; see also pg 15, Scheme 2, formula 14 to formula 15) and Kraus teaches that a ortho,ortho-dichloro substituted phenyl moiety eliminates axial chirality for an ortho-chloro subtituted phenyl group (pg 3888, col 2 to pg 3889, col 1, para 1, Although 2 is one of the most potent anti-T. cruzi compounds reported to date, subsequent studies showed that there is hindered rotation about the bond connecting the 3-chlorophenyl group and the quinolone ring presumably because of a clash between the ortho methyl group and the vinylic proton of the quinolone ring. Thus 2 is a mixture of rotamers with the ortho methyl group either above or below the plane of the quinolone ring... We thus went on to design new analogs that either lack a 2-substitutent on the 3-chlorophenyl ring or have a C2-symmetric ring in order to avoid rotamer formation; see also pg 3888, Figure 1; see also pg 3888, Figure 1; see also pg 3890, Table 1, formula 2 and formulas 14-16, especially formula 15 for dichloro substitution) and the ortho,ortho-dichloro substitued derivative of the compound of Crowley would not have this issue.

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As said compound was known in the art, this cannot be considered a special technical feature that would otherwise unify the inventions of Group I+.

The inventions of Group I+ thus lack unity under PCT Rule 13.

Note: Claim 6 lacks clarity. Claim 6 references "the structural formula below", but no formula is listed in claim 6, and no meaningful search could be performed for claim 6. Therefore, for the purpose of completing this ISR, claim 6 was not included in the opinion.