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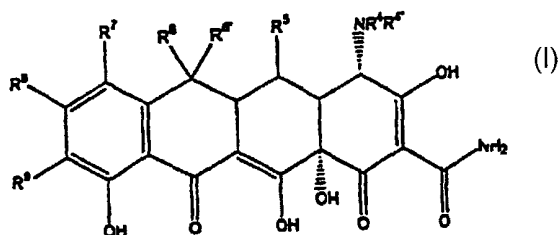
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 7,8 AND 9-SUBSTITUTED TETRACYCLINE COMPOUNDS



(57) Abstract: 7,8 and 9-substituted tetracycline compounds of the formula (I) wherein: R⁴ and R^{4'} are each methyl; R⁵ is hydrogen or hydroxyl; R⁶ and R^{6'} are each independently hydrogen, methyl, or hydroxyl; R⁷ is hydrogen, lower alkenyl, lower alkynyl, phenyl, halophenyl, acyl, phenylalkynyl, heteroaryl, or dimethylamino; and R⁸ is hydrogen, phenyl, nitrophenyl, halo, or lower alkynyl; and R⁹ is hydrogen, amino, acetamide, or lower alkynyl; and provided that at least one of R⁷, R⁸, or R⁹ is not hydrogen, methods of treating tetracycline responsive states, and pharmaceutical compositions containing the 7, 8 and 9-substituted tetracycline compounds are described.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/20558

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C237/26 A61K31/65 A61P31/04

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 7 C07C A61K

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

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

EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KOZA D J: "SYNTHESIS OF 7-SUBSTITUTED TETRACYCLINE DERIVATIVES" ORGANIC LETTERS, ACS, WASHINGTON, DC, US, vol. 2, no. 6, 2000, pages 815-817, XP000943852 ISSN: 1523-7060 page 817 --- -/--	1-8, 14-26

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in 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 document 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.
- *G* document member of the same patent family

Date of the actual completion of the international search

24 January 2002

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05/02/2002

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/20558

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KOZA D J: "The synthesis of 8-substituted tetracycline derivatives, the first 8-position carbon-carbon bond" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 41, no. 26, 24 June 2000 (2000-06-24), pages 5017-5020, XP004212489 ISSN: 0040-4039 page 5018, line 2 - line 5; examples 5A, 5C, 6A, 6B -----	1,3, 9-12, 15-26

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.2

Claims Nos.: 1-3, 17-26 (all in part), 15 (entirely)

The initial phase of the search revealed a very large number of documents potentially relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). It must be pointed out that the present general formula (I) includes well-known compounds such as e.g. minocycline ($R_4 = R_4' = CH_3$; $R_5 = R_6 = R_6' = R_8 = R_9 = H$; $R_7 = \text{dimethylamino}$).

In addition, the precise structure of one of the compounds mentioned in the claims, namely that of claim 15, is not clear, in that it cannot be determined whether the acetamide group is linked to the tetracycline central group by the nitrogen atom (group $CH_3-C(=O)-NH-$) or by the carbon atom (group $-CH_2-C(=O)-NH_2$).

For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, and guided by the gist of the application as described by the examples, the search has been restricted to the compounds of claims 4-14 and 16, as well as pharmaceutical compositions containing them, and use thereof.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-26

7-, 8- And 9-substituted tetracyclines, pharmaceutical compositions containing them, and use thereof.

1.1. Claims: 1, 3(both in part), 2, 4-8,
14 (all entirely), 17-26(part)

7-Substituted tetracycline derivatives, pharmaceutical compositions containing them, and use thereof

1.2. Claims: 1, 3 (both in part), 9-12 (entirely),
17-26(part)

8-Substituted tetracycline derivatives, pharmaceutical compositions containing them, and use thereof.

1.3. Claims: 1, 3 (both in part), 15, 16, (both entirely),
17-26(part)

9-Substituted tetracycline derivatives, pharmaceutical compositions containing them, and use thereof.

Please note that all inventions mentioned under item 1, although not necessarily linked by a common inventive concept, could be searched without effort justifying an additional fee.