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(71) Applicant (for all designated States except US):
SIGMA-TAU INDUSTRIE FARMACEUTICHE RIUNITE S.P.A. [IT/IT]; Viale Skakespeare, 47, I-00144 Rome (IT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **FANTO³, Nicola** [IT/IT]; Via Giulio Cesare, 3, I-00040 Pomezia (IT).
TINTI, Maria, Ornella [IT/IT]; Via Ernesto Basile, 81, I-00182 Rome (IT).

(74) Agent: **SPADARO, Marco**; c/o Sigma-Tau Industrie Farmaceutiche Riunite S.p.A., Via Pontina, Km. 30,400, I-00040 Pomezia (IT).

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Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG)
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designation US
- of inventorship (Rule 4.17(iv)) for US only

Published:

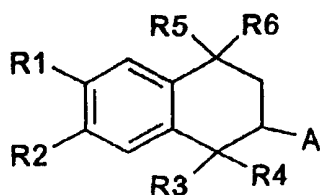
- with international search report

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

2 May 2002

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: 2,6,7-SUBSTITUTED TETRALINES USEFUL FOR THE PREPARATION OF MEDICAMENTS WITH PHOSPHODIESTERASE IV INHIBITORY ACTIVITY



(I)

(57) Abstract: Formula (I) compounds are described where the groups are as defined in the description, as well as processes for their preparation and their use as medicaments, particularly for the preparation of medicaments with phosphodiesterase IV inhibitory activity.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IT 01/00311

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C271/24 C07C233/32 C07C217/74 C07C225/20 C07C265/10
C07C61/00

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 33762 A (FORESTA PIERO ;MORETTI GIAN PIERO (IT); SIGMA TAU IND FARMACEUTI () 6 August 1998 (1998-08-06) claims 1,4,5 ---	5-10
X	WO 99 15494 A (FORESTA PIERO ;FANTO NICOLA (IT); MORETTI GIAN PIERO (IT); SIGMA T) 1 April 1999 (1999-04-01) claims 3,6 --- -/--	5-10

☒ 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.

"&" document member of the same patent family

Date of the actual completion of the international search

22 January 2002

Date of mailing of the international search report

31 Jan 2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Bedel, C

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IT 01/00311

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WEINSTOCK J ET AL: "SYNTHESIS AND DOPAMINERGIC ACTIVITY OF SOME HALOGENATED MONO- AND DIHYDROXYLATED 2-AMINOTETRALINS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 29, no. 9, 1 September 1986 (1986-09-01), pages 1615-1627, XP000568884 ISSN: 0022-2623 scheme IV page 1619 page 1624; example 26A -----	5,6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IT 01/00311

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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.: 2,4
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:
see FURTHER INFORMATION sheet PCT/ISA/210
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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional 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 an additional fee, this Authority did not invite payment of any additional fee.
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.:
5-10 (part)
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.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 2,4

The initial phase of the search revealed a very large number of documents 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). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to:.....

The compounds given in claim 5 where R5 and R6 together are not a keto or oxime group and their corresponding use.

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.

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

1. Claims: 3, 5-10

The compounds per se of formula (I) in which R5 and R6 together are the keto or oxime group (as per claim 3) as well as their use as pharmaceutical.

1.1. Claims: 7-9

the compounds of formula (I) for the second therapeutic use of claim 7-9

2. Claims: 2,4-10(all partially)

The compounds of formula(I) where R5 and R6 are different from the keto or oxime group

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/IT 01/00311

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9833762	A	06-08-1998	IT RM970050 A1	03-08-1998
			EP 0968174 A1	05-01-2000
			WO 9833762 A1	06-08-1998
			JP 2001509802 T	24-07-2001
			US 6225501 B1	01-05-2001
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WO 9915494	A	01-04-1999	IT RM970568 A1	22-03-1999
			AU 738565 B2	20-09-2001
			AU 9366298 A	12-04-1999
			BR 9812368 A	19-09-2000
			CN 1276782 T	13-12-2000
			EP 1017667 A1	12-07-2000
			WO 9915494 A1	01-04-1999
			JP 2001517649 T	09-10-2001
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