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01203087.0 13 August 2001 (13.08.2001) EP(71) Applicant (for all designated States except US):
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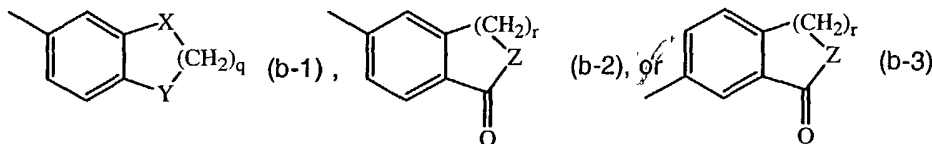
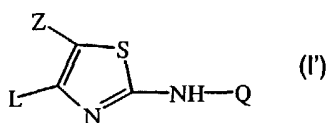
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GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
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(54) Title: 2-AMINO-4,5-TRISUBSTITUTED THIAZOLYL DERIVATIVES AND THEIR USE AGAINST AUTOIMMUNE DISEASES



(57) Abstract: This invention concerns the use of a compound of formula (I'), a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof, wherein Z is halo; C₁₋₆alkyl; C₁₋₆ alkylcarbonyl; C₁₋₆alkyloxy-carbonyl; aminocarbonyl; C₁₋₆alkyl substituted with hydroxy, carboxyl, cyano, amino, amino substituted with piperidinyl, amino sub-stituted with C₁₋₆alkyl substituted piperidinyl, mono -or di(C₁₋₆alkyl)amino, aminocarbonyl, mono -or di(C₁₋₆alkyl)aminocarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyloxy, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl; polyhaloC₁₋₆alkyl; cyano; amino; mono -or di(C₁₋₆alkyl)aminocarbonyl; C₁₋₆alkyloxycarbonyl; C₁₋₆alkylcarbonyloxy; aminoS(=O)₂; mono -or di(C₁₋₆alkyl)aminoS(=O)₂; -C(=N-R^x)NR^yR^z; Q is optionally substituted C₃₋₆cycloalkyl, phenyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzthiazolyl, benzoxazolyl, benzimidazolyl, indazolyl, or imidazopyridyl, or Q is a radical of formula (b-1), (b-2), or (b-3), L is optionally sub-stituted phenyl or an optionally substituted monocyclic 5 or 6-membered partially saturated or aromatic heterocycle or a bicyclic partially saturated or aromatic heterocycle; aryl is optionally substituted phenyl; for the manufacture of a medicament for the pre-vention or the treatment of inflammatory and/or auto-immune diseases mediated through TNF-α and/or IL-12.



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- *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, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ,

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- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
- *of inventorship (Rule 4.17(iv)) for US only*

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A. CLASSIFICATION OF SUBJECT MATTER

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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)

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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, EMBASE, BIOSIS, MEDLINE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 154 190 A (MERCK PATENT GMBH) 11 September 1985 (1985-09-11) claim 1 page 98, line 1,7; example 22 page 1, line 5 -page 4, line 5 page 10, line 18 - line 19 page 14, line 8 page 18, line 15	1-8,10, 12-16
X	EP 0 790 057 A (HISAMITSU PHARMACEUTICAL CO) 20 August 1997 (1997-08-20) page 14; examples 104,116-118 claims 1-7	1,2,4
X	US 3 933 838 A (MANGHISI ELSO ET AL) 20 January 1976 (1976-01-20) claims 3,4	1,2
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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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

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Date of the actual completion of the international search

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International Publication No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DRIDI, K. ET AL: "Reaction of mercaptoacetate and halides containing activated methylenes with thiocarbamoylimidates: a novel approach to the synthesis of aminothiazole derivatives" SYNTHETIC COMMUNICATIONS (1998), 28(1), 167-174, XP008005382 page 167, line 1 - line 3 page 172; examples 4A,4C ---	1,2
X	NAGATOMI, H. ET AL: "Studies on the antiinflammatory activity and ulcerogenic adverse effect o thiazole derivatives, especially 2-amino-thiazoleacetic acid derivatives" ARZNEIM.-FORSCH. (1984), 34(5), 599-603, XP001074027 table 2 page 599, column 1, line 1 -column 2, line 10 ---	1,2
A	RICHTER, MONIKA ET AL: "Reaction behavior of selected carboxylic acid amides towards heterocumulenes. Synthesis of N-aroyle(heteroaroyl)guanidines, aroylisothioureas, and 2-aminothiazoles" Z. CHEM. (1982), 22(3), 103-4, XP008005386 examples 4C,4D; table 2 ---	5
A	BADACHIKAR, S. V. ET AL: "Antiinflammatory, analgesic and antibacterial activities of 4-(2'-dialkyl/diarylamino-4'-phenyl-5'-thiazolylcarbonyl)-3-arylsydnonones" INDIAN J. CHEM., SECT. B (1986), 25B(4), 444-6, XP008005384 page 444, column 1, line 15 - line 19 ---	
A	CORSARO, ANTONINO ET AL: "A convenient synthesis of 2-(alkylamino)- and 2-(arylamino)-4-aryl-5- cyanothiazoles" HETEROCYCLES (1985), 23(10), 2645-9, XP008005385 example 3C; table 1 ---	5
A	US 4 649 146 A (TAKAYA TAKAO ET AL) 10 March 1987 (1987-03-10) examples 3,9,10 claims 1,9 --- -/--	

INTERNATIONAL SEARCH REPORT

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PCT/EP 02/08955

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 000 775 A (GRABIAK RAYMOND C ET AL) 19 March 1991 (1991-03-19) claim 2 ---	
A	LIEBSCHER J ET AL: "RING TRANSFORMATIONS VIA BRIDGED 1,3-DICARBONYL HETEROANALOGS;PART II. SYNTHESIS OF 4-(OMEGA-AMINOALKYL)-THIAZOLES BY A NOVEL RING TRANSFORMATION REACTION OF SEMICYCLIC THIOACYLAMIDINES WITH ACIDIC METHYL HALIDES" SYNTHESIS, GEORG THIEME VERLAG. STUTTGART, DE, vol. 12, 1989, pages 968-970, XP001026249 ISSN: 0039-7881 example 5C ---	
A	GAWANDE N G ET AL: "SYNTHESIS OF THIAZOLYL-PYRAZOLINES & ISOXAZOLINES FROM ACRYLOTHIAZOLES & THEIR MICROBIAL ACTIVITY" INDIAN JOURNAL OF CHEMISTRY, SECTION B: ORGANIC, INCL. MEDICINAL, PUBLICATIONS & INFORMATIONS DIRECTORATE, NEW DELHI, IN, vol. 26B, April 1987 (1987-04), pages 351-355, XP001027320 ISSN: 0019-5103 example IV page 351, column 2, paragraph 3 abstract ---	
A	REDDY B RAMCHANDRA ET AL: "Activity of acryloylthiazoles, thiazolylaminopyrimidines and thiazolylthiopyrimidines on Aspergillus flavus Link. ex Fries in vitro" INDIAN BOTANICAL REPORTER, MARATHWADA UNIVERSITY, AURANGABAD, IN, vol. 4, no. 2, 1985, pages 144-147, XP001026807 ISSN: 0254-4091 page 145; examples III,,IV -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0154190	A	11-09-1985	DE 3406329 A1	22-08-1985
			AU 3892685 A	29-08-1985
			EP 0154190 A1	11-09-1985
			ES 8606279 A1	01-10-1986
			HU 39161 A2	28-08-1986
			JP 61010557 A	18-01-1986
			ZA 8501335 A	30-10-1985
EP 0790057	A	20-08-1997	AU 689972 B2	09-04-1998
			AU 3880995 A	19-06-1996
			DE 69526958 D1	11-07-2002
			DE 69526958 T2	16-01-2003
			EP 0790057 A1	20-08-1997
			JP 3023178 B2	21-03-2000
			US 5856347 A	05-01-1999
			CA 2206315 A1	06-06-1996
			WO 9616650 A1	06-06-1996
			TW 414708 B	11-12-2000
US 3933838	A	20-01-1976	AU 5246773 A	22-08-1974
			BE 795907 A1	18-06-1973
			CA 1006525 A1	08-03-1977
			DE 2309251 A1	06-09-1973
			DE 2365526 A1	31-07-1975
			ES 412052 A1	01-05-1976
			FR 2181764 A1	07-12-1973
			GB 1425505 A	18-02-1976
			NL 7302528 A	28-08-1973
			JP 837207 C	15-12-1976
			JP 48097868 A	13-12-1973
			JP 51012630 B	21-04-1976
			ZA 7301208 A	27-03-1974
US 4649146	A	10-03-1987	DK 41084 A	01-08-1984
			EP 0117082 A2	29-08-1984
			ES 8504749 A1	16-07-1985
			ES 8601983 A1	01-03-1986
			JP 1868735 C	06-09-1994
			JP 5079677 B	04-11-1993
			JP 59193878 A	02-11-1984
			KR 9107976 B1	05-10-1991
			US 4735957 A	05-04-1988
US 5000775	A	19-03-1991	NONE	