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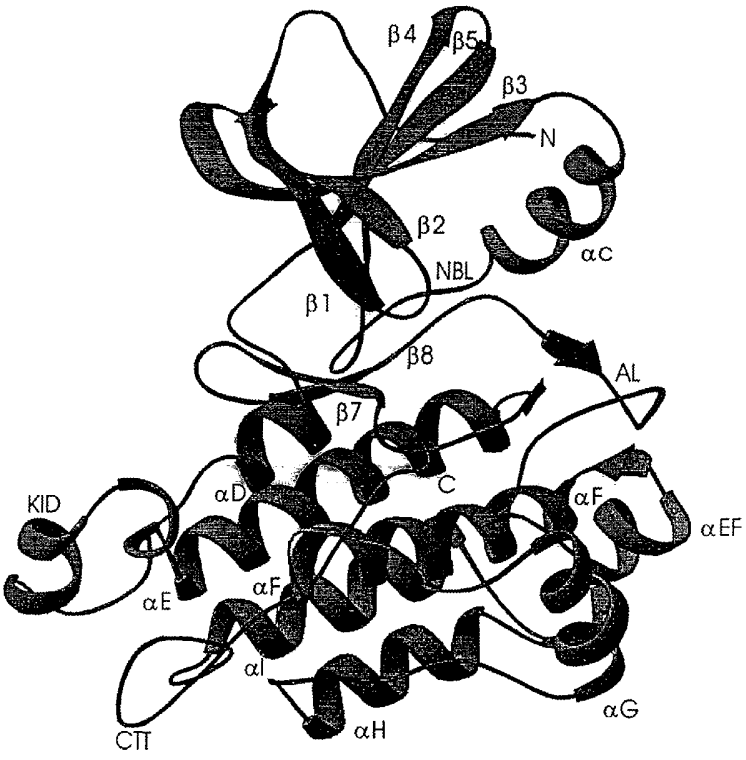
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[Continued on next page]

(54) Title: CRYSTALLIZED CYTOPLASMIC TIE2 RECEPTOR TYROSINE KINASE DOMAIN AND METHOD OF DETERMINING AND DESIGNING MODULATORS OF THE SAME



(57) Abstract: A solved three-dimensional crystal structure of a cytoplasmic Tie2 receptor tyrosine kinase domain is disclosed, along with four crystal forms of the cytoplasmic Tie2 receptor tyrosine kinase domain. The crystal forms include non- and monophosphorylated forms of the cytoplasmic Tie2 receptor tyrosine kinase domain. Methods of designing modulators of the biological activity of the cytoplasmic Tie2 receptor tyrosine kinase domain are also disclosed.

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INTERNATIONAL SEARCH REPORT

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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, WPI Data, BIOSIS, 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.
Y	WO 95 13387 A (MAX PLANCK GESELLSCHAFT) 18 May 1995 (1995-05-18) * See Fig 3 (TEK) and page 4 (Fig. 3); TEK = 1124 aa -> identical with SEQ.ID.No 2 / APPL); and page 36, line 25 - page 37, line 27 * --- -/--	1,3-5,7, 8,13,14, 17-21, 25, 27-30, 34-41, 45,46

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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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.
Y	MOHAMMADI ET AL: "Structure of the FGF receptor tyrosine kinase domain reveals a novel autoinhibitory mechanism" CELL, vol. 86, 1996, pages 577-587, XP002219716 cited in the application * See page 577 (introduction), page 586 (Crystallization and data collection); compare page 32 of the Description *	1,3-5,7, 8,13,14, 17-21, 25, 27-30, 34-41, 45,46
A	CALVERT: "Allelic and locus heterogeneity in inherited venous malformations" HUMAN MOLECULAR GENETICS, vol. 8, 1999, pages 1279-1289, XP002219717 * See the Abstract -> Y897S *	42
A	ROBERTSON ET AL: "RTK mutations and human syndromes when good receptors turn bad" TIG, vol. 16, June 2000 (2000-06), pages 265-271, XP004200112 * See page 266 (Figure 1 -> Tie2) and page 268 (Tyrosine kinase with Ig and EGF (TIE) family: Tie2) *	1-52
A	HIMANEN ET AL: "Crystal structure of the ligand-binding domain of the receptor tyrosine kinase EphB2" NATURE, vol. 396, 3 December 1998 (1998-12-03), pages 486-491, XP002134939 ISSN: 0028-0836 * See page 486 (Summary) and page 490 (Methods) *	1-52
A	DJORDJEVIC: "Crystallization and preliminary x-ray studies of NADPH-cytochrome P450 reductase" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, USA, vol. 92, 1995, pages 3214-3218, XP002219719 * See page 3215 (Crystallization of CPR) *	1-52
P,X	SHEWCHUK: "Structure of the Tie2 RTK domain: Self-inhibition by the nucleotide binding loop, activation loop, and C-terminal tail" STRUCTURE, vol. 8, November 2000 (2000-11), pages 1105-1113, XP001115087 * See the whole document; corresponding deposition at PDB (= 1FVR), release date 20-Sept-2001) *	1-5, 7-14, 17-25, 27-46, 48-52

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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.
E	WO 01 72778 A (BASF AKTIENGESELLSCHAFT) 4 October 2001 (2001-10-04) * See SEQ.ID.No 1 (= SEQ.ID.No 2 / APPL) and SEQ.ID.NO 2 (= 99.8 % of SEQ.ID.No 4 / APPL -> 7-323:11-327; i.e. except spacer, and -RNL- (-RDL-/APPL) about position 170); p. 9ff and pp. 45-54 *	28-30, 34-41

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter al Application No
PCT/US 01/27486

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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WO 0172778 A	04-10-2001	AU 8726801 A	08-10-2001
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