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(71) Applicants (for all designated States except US): BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM [US/US]; 201 West 7th Street, Austin, TX 78701 (US). THE REGENTS OF THE UNIVERSITY OF CALIFORNIA [US/US]; 22nd floor, 300 Lakeside Drive, Oakland, CA 94612-3550 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BUDDE, Raymond, J., A. [US/US]; 4618 Holt, Bellaire, TX 77401 (US). ELLMAN, Jonathan, A. [US/US]; 5450 Masonic Avenue, Oakland, CA 94618 (US). LEVIN, Victor, A. [US/US]; 6344 Vanderbilt, Houston, TX 77005-3416 (US). GALLICK, Gary, E. [US/US]; 3202 Riverlawn Drive, Kingwood, TX 79339 (US). NEWMAN, Robert, A. [US/US]; 4404 Balboa Drive, Sugar Land, TX 77479 (US).

(74) Agent: HIBLER, David, W.; Arnold, White & Durkee, P.O. Box 4433, Houston, TX 77210 (US).

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Published

With international search report.

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29 July 1999 (29.07.99)

(54) Title: 2,3-BENZODIAZEPIN-2-ONE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS INHIBITORS OF PROTEIN TYROSINE KINASES

$$X \xrightarrow{R_1} O$$

$$R_2$$

$$R_3$$

$$(1)$$

(57) Abstract

Disclosed herein are small molecule, non-peptidyl inhibitors of protein tyrosine kinases, and methods for their use. The instant inhibitors are based on a 1,4-benzodiazepin-2-one nucleus. A compound represented by structural formula (I), where R₁, R₂ and R₃ are independently described as Y bonded to W, where Y is a 0-6 atom straight or branched saturated or unsaturated chain group comprising C, N, O or S as shown in Table 1, and W is hydrogen or any three membered, four membered, five membered, six membered or fused bicyclic ring system comprising C, N, O or S as shown in Tables 4-9; X is separately and independently selected from Table 2; and salts of said compound. Methods are provided for inhibition of specific protein tyrosine kinases, for example pp60^{c-src}. Methods are further provided for the use of these inhibitors in situations where the inhibition of a protein tyrosine kinase is indicated, for example, in the treatment of certain diseases in mammals, including humans.

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INTERNATIONAL SEARCH REPORT

International Application No PCT/US 98/21327

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07D243/24 A61 ÎPC 6 A61K31/55 According to International Patent Classification (IPC) or to both national classification and IPC Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07D 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) C. DOCUMENTS CONSIDERED TO BE RELEVANT Relevant to claim No. Citation of document, with indication, where appropriate, of the relevant passages Category ° EP 0 045 452 A (HOFFMANN LA ROCHE) 1-5,9,Χ 13-15 10 February 1982 see claims 1-13,15,16 BUNIN B.A. & ELLMAN J.A.: "A general and 1 - 5χ expedient method for the solid-phase synthesis of 1,4-benzodiazepine derivatives' JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 114, no. 27, 1992, pages 10997-10998, XP002072683 cited in the application see the whole document -/--Patent family members are listed in annex. Further documents are listed in the continuation of box C. Χ Opecial categories of cited documents: "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 "A" document defining the general state of the art which is not considered to be of particular relevance invention "E" earlier document but published on or after the international "X" document of particular relevance; the claimed invention filing date cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another "Y" document of particular relevance; the claimed invention citation or other special reason (as specified) cannot be considered to involve an inventive step when the document is combined with one or more other such docu-*O* document referring to an oral disclosure, use, exhibition or ments, such combination being obvious to a person skilled *P* document published prior to the international filing date but later than the priority date claimed "&" document member of the same patent family Date of mailing of the international search report Date of the actual completion of the international search **28**, 05, 99 11 February 1999 Name and mailing address of the ISA Authorized officer 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 HARTRAMPF G.W.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/21327

| | I . | 1/05 98/2132/ |
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| | ation) DOCUMENTS CONSIDERED TO BE RELEVANT | 101 |
| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | JAMES G.L. ET AL.: "Benzodiazepine peptidomimetics: Potent inhibitors of Ras farnesylation in animal cells" SCIENCE, vol. 260, 25 June 1993, pages 1937-1942, XP002028520 see the whole document | 1-5,9, 13-15 |
| X | HOBBS DE WITT S. ET AL.: ""Diversomers": An approach to nonpeptide, nonoligomeric chemical diversity" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 90, no. 15, August 1993, pages 6909-6913, XP000651795 cited in the application see page 6910 - page 6913; table 1 | 1-5,9, 13-15 |
| X | WO 94 06291 A (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 31 March 1994 see page 8 - page 40; claims 1-19 | 1-5 |
| X | BUNIN B.A. ET AL.: "The combinatorial synthesis and chemical and biological evaluation of a 1,4-benzodiazepine library" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 91, May 1994, pages 4708-4712, XP002092989 cited in the application see the whole document | 1-5,9, 13-15 |
| X | WO 95 25118 A (TRUSTEES OF TUFTS UNIVERSITY) 21 September 1995 see claims 1,10,14 | 1-5,9, 13-15 |
| X | WO 96 05827 A (MERCK & CO INC.) 29 February 1996 see the whole document | 1-5,9, 13-15 |
| X | BUNIN-B.A. ET AL.: "Synthesis and evaluation of 1,4-benzodiazepine libraries" METHODS IN ENZYMOLOGY, vol. 267, 1996, pages 448-465, XP002072681 cited in the application see the whole document | 1-15 |
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International application No. PCT/US 98/21327

INTERNATIONAL SEARCH REPORT

| Box I | Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet) |
|-----------|--|
| This Inte | rnational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons: |
| 1. X | Claims Nos.: 16-44 because they relate to subject matter not required to be searched by this Authority, namely: |
| | Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy |
| 2. X | Claims Nos.: 1-5,9,13-15 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 Inte | ernational 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.: |
| 4. X | 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.: 1-5 (part), 6-8, 9 (part), 10-12, 13-15 (part) |
| Remar | k 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

Claims Nos.: 1-5,9,13-15

An ambiguity arises from the definition of radicals R1, R2, R3, X, Y and W in claims 1 and 9 which are defined with reference to tables in the description, contrary to Rule 6.2.(a) PCT and thus contravenes Article 6 PCT.

The definition of the compounds of formula (I) is too general and/or encompasses too broad a range of different chemical groups, only partly supported by examples given in the description. The vast number of theoretically conceivable compounds resulting from claims 1 and 9 drafted in such an ambiguous way precludes a comprehensive search. The search was performed on the basis of those claims which are clear and concise and in the light of the examples and reasonable generalisations thereof and includes compounds having therapeutical activities.

Despite the above limitation the search revealed too many relevant documents so that the search report shall not be considered complete, since the search had to be further limited to compounds of claims 6 to 8 and 10 to 12 and those of figure 3/7, cf. Articles 6 PCT, 15(4) PCT and Rule 33 PCT, and the PCT International Search Guidelines chapters III-3.6, III-3.7, VIII-2 and X-6.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-5 (partially), 6-8, 9 (partially), 10-12, 13-15 (partially)

1,4-Benzodiazepin-2-one derivatives of formula (I) wherein R3 denotes an optionally X1-X5-substituted phenyl moiety, based on present example 1 the only preparation method of these compounds outlined in the present application which starts from aminobenzophenones, and pharmaceutical compositions comprising said compounds

2. Claims: 1-5, 9, 13-15 (all partially)

All other 1,4-benzodiazepin-2-one derivatives wherein R3 is other than an optionally substituted phenyl moiety, and the pharmaceutical compositions comprising said compounds

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No PCT/US 98/21327

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|--|---------------------|--|--|
| EP 0045452 / | A 10-02-1982 | AU 7339781 A CA 1157855 A DK 341181 A JP 57058674 A PH 17045 A US 4327026 A ZA 8105115 A | 04-02-1982 29-11-1983 01-02-1982 08-04-1982 17-05-1984 27-04-1982 25-08-1982 |
| WO 9406291 | A 31-03-1994 | US 5288514 A AU 4923193 A US 5545568 A | 22-02-1994 12-04-1994 13-08-1996 |
| WO 9525118 | A 21-09-1995 | US 5580979 A US 5776902 A | 03-12-1996 07-07-1998 |
| WO 9605827 | A 29-02-1996 | AU 692916 B AU 3330495 A CA 2195973 A EP 0776203 A US 5633251 A | 18-06-1998 14-03-1996 29-02-1996 04-06-1997 27-05-1997 |