



(51) International Patent Classification:
A61K 31/10 (2006.01)

(21) International Application Number:
PCT/US2013/060294

(22) International Filing Date:
18 September 2013 (18.09.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/703,368 20 September 2012 (20.09.2012) US

(71) Applicant: TEMPLE UNIVERSITY - OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION [US/US]; Broad Street And Montgomery Avenue, Philadelphia, PA 19122 (US).

(72) Inventors: REDDY, M., V., Ramana; 921 Saint Joseph Drive, Upper Darby, PA 19082 (US). REDDY, E., Premkumar; 547 Atterbury Road, Villanova, PA 19085 (US).

(74) Agents: MONACO, Daniel, A. et al.; Drinker Biddle & Reath LLP, One Logan Square, Ste. 2000, Philadelphia, PA 19103-6996 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,

MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

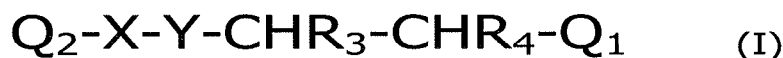
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(88) Date of publication of the international search report:
26 June 2014

(54) Title: SUBSTITUTED ALKYL DIARYL DERIVATIVES, METHODS OF PREPARATION AND USES



(57) Abstract: Compounds according to Formula I are provided: and salts thereof, wherein Q₁, Q₂, R₃, R₄, X, and Y are as defined herein. Methods for preparing compounds of Formula I are also provided, as well as methods of treating cellular proliferative disorders, such as cancer, using compounds of Formula (I).



INTERNATIONAL SEARCH REPORT

013/000294-00-00-2014

International application No.

PCT/US 13/60294

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/10 (2013.01)

USPC - 514/712; 514/709

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(8): A61K 31/10 (2013.01)

USPC: 514/712; 514/709

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/646; 514/665; 514/706; 514/708; 562/429; 562/430

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

PatBase, Google Scholar, SureChem, PubWEST

aralkyl, arylalkyl, sulfide, benzyl, phenethyl, phenylethyl, sulfane, sulfone, (phenethylsulfanylmethyl)benzene, rigosertib, analog, derivative, hydrogenated, saturated, cancer, treat

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,443,477 A (WITTE et al.) 17 April 1984 (17.04.1984) col 8, ln 19-46; col 19, ln 1-3	1 and 32
Y	US 2009/0124828 A1 (REDDY et al.) 24 February 2009 (24.02.2009) para [0005], [0034]	1-3, 5-14 and 32
Y	US 2011/0054037 A1 (SAFAVY) 03 March 2011 (03.03.2011) para [0006]-[0009], [0092], [0167], Table 1	1-2, 12 and 32
Y	US 5,545,750 A (KEMPF et al.) 13 August 1996 (13.08.1996) col 1, ln 25-49; col 18, ln 11-13, Table 2	1-3, 5-14 and 32
A	US 5,070,099 A (HALL et al.) 03 December 1991 (03.12.1991) Abstract	1-3, 5-14 and 32

☐ Further documents are listed in the continuation of Box C.

* 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 application or patent 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

12 April 2014 (12.04.2014)

Date of mailing of the international search report

06 MAY 2014

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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.:
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:

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 No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+: Claims 1-17 and 32-35 directed to composition comprising a compound of Formula (I) selected from compounds listed in claims 12-16. Group I+ will be searched to the extent that it reads on a compound of Formula (I) (Q2-X-Y-CHR3-CHR4-Q1), wherein Q2 is 4-chlorophenyl; X is CH₂; Y is S; R3 and R4 are each H and Q1 is 4-fluorophenyl (the first listed compound of claim 12, namely, 4-chlorobenzyl-4-fluorophenethylsulfane). It is believed that claims 1-2, 12 and 32 read on this first named invention. Applicants must indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a compound of Formula (I) represented by the first listed compound of claim 15, namely, N-(4-methoxyphenethyl)-4-methylbenzenesulfonamide, for which Q2 is 4-methylbenzene; X is -S(=O)₂-; Y is NH; R3 and R4 are each H and Q1 is 4-methoxyphenyl (i.e. claims 1-2 and 15).

--Please see continuation in Attached 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 additional fees, this Authority did not invite payment of additional fees.
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.:
Claims 1-3, 5-14 and 32 [Note: Claims 1-2, 12 and 32- first invention; Claims 1-3, 5-14 and 32 - the elected second invention]
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 and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

Attachment to Box.No.III: -- Continued from Box.No.III--

Group II+: Claims 18-31 directed to processes for making compounds of Formula (I), having Formulae Ia, Ib, Ic, Id, If, Ig and Ii. An exemplary election would be a process of making a compound of Formula (I) having Formula (Ia) (i.e. claims 18-19).

Group III: Claims 36-40 directed to a method of treating an individual suffering from a cellular proliferative disorder, comprising administering to the individual an effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt thereof.

The inventions listed as Groups I+, II+, and III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features

The special technical feature of each invention of Group I+ is its structural feature, which is not in any other invention of Group I+.

The special technical feature of each invention of Group II+ is its structural feature, which is not in any other invention of Group II+.

Groups I+-II+ do not include a method of treating an individual suffering from a cellular proliferative disorder, as required by Group III.

Groups I+ and III do not include a process for making a compound of Formula (I) as required by Group II+.

Common Technical Features

The inventions of Groups I+, II+, and III are related as composition (group I+) and method of making (group II+) and method of use (group III); and share the common technical feature of a compound of Formula (I).

The compounds of Group I+ also share the common core structure of a compound of Formula (I).

This shared technical feature, however, does not represent a contribution over prior art, because the shared technical feature is anticipated by US 4,443,477 A to Witte et al. (hereinafter 'Witte'), which teaches a compound of Formula (I), wherein

Q1 is aryl substituted with one substituent selected from carboxy;

Q2 is unsubstituted aryl;

X is -S(=O)₂;

Y is -N(R1)-, wherein R1 is H; and

R3 and R4 are each H, wherein the compound meets the proviso that if X is -S(=O)₂, then Y is -N(R1)- (col 19, ln 1-3, Example 10, 4-(2-Benzenesulphonamidoethyl)-benzoic acid).

As the compound of Formula (I) was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

The inventions of Group II+ share the common technical feature of a process for making a compound of Formula (I). This shared technical feature, however, does not represent a contribution over prior art, because the shared technical feature is anticipated by Witte, which discloses a process for making a compound of Formula Ic, said process comprising reacting a compound of Formula CC with a compound of Formula DD, wherein Q1 is aryl substituted with carboxy; Q2 is aryl, substituted with -O-R10, wherein R10 is C1 alkyl; R3 and R4 are each H and L is a leaving group, Cl (col 15, ln 5-20; col 15, ln 33-38, 4-(2-(4-methoxybenzenesulphonamido)-ethyl)-benzoic acid) from 4-(2-aminoethyl)benzoic acid hydrochloride and 4-methoxybenzenesulphochloride). As this process was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the inventions of group II+.

Therefore, Groups I+, II+, and III lack unity under PCT Rule 13.2 because they do not share a same or corresponding special technical feature providing a contribution over the prior art.

Note: Applicant's LOU response states, 'The claims of Group I which read on the above compound are claims 1, 2, 4-11, 12 (tenth-listed compound), 13 (second-listed compound), 14 and 32.'

However, claim 4 was found to read on a non-elected compound and claim 3 reads on the elected compound. Therefore, claims 1-3, 5-14 and 32 were searched as the second invention.