Patent Right	Date	July 18, 2019	Court	Intellectual Property High Court, Fourth Division
	Case number	2018 (Gyo-Ke) 10133		

- A case in which, with regard to the trial decision that dismissed a request for a trial for correction seeking the correction of the scope of claims of the Patent titled "1-[(6,7-SUBSTITUTED ALKOXYQUINOXALINYL)AMINOCARBONYL]-4-(HETERO)ARYLPIPERAZINE DERIVATIVES", the court has dismissed the Plaintiff's claim, stating that the determination of whether or not a correction "substantially enlarges or alters the scope of claims" of Article 126, paragraph (6) of the Patent Act should be made with a criterion of the recitation of the scope of claims before and after the correction, and it is reasonable to decide whether the correction corresponds to the "substantial" enlargement or alteration from a viewpoint of whether the correction might cause unexpected disadvantage for a third party, and the above correction obviously causes unexpected disadvantage for a third party who relies on the indication of the recitation of the claims before the correction, and thus substantially alters the scope of claims.

Case type: Rescission of Trial Decision of Refusal of Correction

Result: Dismissed

References: Article 126, paragraph (6) of the Patent Act

Number of related rights, etc.: Patent No. 6097946, Correction No. 2017-390124

Summary of the Judgment

1. Plaintiffs are patentee of the Patent (Patent No. 6097946) titled "1-[(6,7-SUBSTITUTED ALKOXYQUINOXALINYL)AMINOCARBONYL]-4-(HETERO)ARYLPIPERAZINE DERIVATIVES" and demanded a trial for correction (Correction No. 2017-390124) to correct Claim 1 and cancel Claims 2 to 5.

The trial decision made a decision to the effect that "The demand for trial of the case was groundless." (hereinafter referred to as "the trial decision"), stating that the matters of correction according to Claim 1 in Correction do not comply with the requirement as provided in each item of the proviso to Article 126, paragraph (1) of the Patent Act and paragraph (6) of the same article, and thus the correction by the matters of correction is not acceptable, and the matters of correction according to Claims 1 to 5 of a group of claims are also not acceptable.

Plaintiffs filed a suit seeking for the rescission of the trial decision.

2. The court decision has made the following determination and dismissed the Plaintiffs' claims.

(1) In view of the fact that when a trial decision to the effect that a correction should be accepted is final and binding, the effects of the correction are retroactive to a filing

(Article 128 of the Patent Act), and the effects of the patent right of the patent invention whose technical scope is determined on the basis of the description of the corrected scope of claims extends to third parties, the determination as to whether or not a correction "substantially enlarges or alters the scope of claims" of Article 126, paragraph (6) of the Act should be made with a criterion of the recitation of the scope of claims before and after the correction. Whether a correction corresponds to "substantial" enlargement or alteration should be determined from a viewpoint of whether the correction might cause unexpected disadvantage for a third party.

Further, regarding the recitation of the scope of claims, the first paragraph of Article 36, paragraph (5) of the Act specifies that the scope of claims should describe all the matters that the applicant finds to be necessary for defining the invention for which a patent is sought separately for each claim. The gist of this provision can be seen such that it is required to describe matters that the applicant itself determines as "all the matters that the applicant finds to be necessary for defining the invention for which a patent is sought" for each claim in order to find an invention from one claim. Thus it is objectively reasonable to understand what an applicant itself has determined as "all the matters that the applicant finds to be necessary for defining the invention for which a patent is sought" even in a case that there are overlapping descriptions in one claim, so long as the descriptions are consistent with each other.

(2) In view of the recitation of Claim 1 before Correction and the description, the matters of correction 2 correct "chlorine" of "R^2" recited in Claim 1 before Correction to "hydrogen". Thus it aims to alter the scope of the claims but does not correspond to a restrictive alteration. Further, the matters of correction 2 alter from a group of compounds where "R^2" before Correction is chlorine to a group of compounds where "R^2" after Correction is hydrogen. Thus this alteration obviously causes unexpected disadvantage for a third party who relies on the indication of the recitation of Claim 1 before Correction.

Therefore, the matters of correction 2 are recognized as substantially altering the scope of claims, and thus do not conform to the requirement of Article 126, paragraph (6) of the Patent Act. The determination of the trial decision with the same gist is not erroneous.

Judgment rendered on July 18, 2019
2018 (Gyo-Ke) 10133 A case of seeking rescission of JPO decision
Date of conclusion of oral argument: June 20, 2019

Judgment

Plaintiff: Rexhan pharmaceuticals, incorporated

Plaintiff: Korea Research Institute of Chemical Technology

Defendant: Commissioner of the Japan Patent Office

Main text

1. The Plaintiffs' request shall be dismissed.
2. The court costs shall be borne by Plaintiffs.
3. An additional period for filing a final appeal and a petition for acceptance of the final appeal against this judgment shall be 30 days.

Facts and reasons

No. 1 Claim

The trial decision made on May 8, 2018 by Japan Patent Office with respect to Correction No. 2017-390124 shall be rescinded.

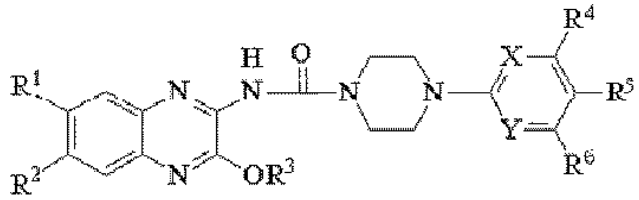
No. 2 Outline of the case

1. History of the procedures, etc. in Japan Patent Office

(1) Plaintiffs filed a patent application (Patent Application No. 2007-542886, hereinafter referred to as "the present application") with an international application date of October 18, 2005 (priority date: November 17, 2004, claiming priority: South Korea) for an invention titled "1-[(6,7-SUBSTITUTED ALKOXYQUINOXALINYL)AMINOCARBONYL]-4-(HETERO)ARYLPIPERAZINE DERIVATIVES" and a patent right was registered on March 3, 2017 (Patent No. 6097946, number of claims: 8, hereinafter this patent is referred to as "the Patent" Exhibits Ko 2, 19).

(2) Plaintiffs demanded a trial for correction on November 20, 2017 to correct Claim 1 and cancel Claims 2 to 5 with Claims 1 to 8 as a group of claims (The case of Correction No. 2017-390124) (Exhibit Ko 3), and received a notice of reasons for refusal of the correction on January 5, 2018 (Exhibit Ko 6), and thus submitted a

written opinion on March 1 of the same year (Exhibit Ko 7).
Thereafter, Japan Patent Office made a trial decision on May 8 of the same year to the effect that "The demand for trial of the case was groundless." (Hereinafter referred to as "the trial decision") and its certified copies were served to Plaintiff on May 17 of the same year.
(3) Plaintiffs filed a suit for the case seeking for the rescission of the trial decision on September 12, 2018.
2. The recitation of the Claims
(1) Before the Correction
The recitation of Claims 1 to 9 of the scope of the claims before the Correction (as of the registration of the Patent) is set forth as below (Exhibit Ko 2).
[Claim 1]
A compound of 1-[(6,7-substituted alkoxyquinoxalinyl)aminocarbonyl]-4-(hetero)arylpiperazine derivatives and their pharmaceutically acceptable salts thereof, represented by the following chemical formula (1):



(1)

wherein
X and Y are independently N or C-R^7,
R^1 is fluorine;
R^2 is chlorine;
R^3 is C_1-C_3 alkyl;
R^4, R^5, R^6 and R^7 are independently hydrogen, a C_1-C_3 alkoxy, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkylcarbonyl, halogen, cyano, or nitro,
with the proviso that R^1 and R^2 are not simultaneously hydrogen.
[Claim 2]
The compound of the formula (1) as claimed in Claim 1, wherein X and Y are independently N, C-H, C-F, C-Cl, C-CN, C-CH_3 or C-OCH_3.
[Claim 3]
The compound of the formula (1) as claimed in Claim 1, wherein R^3 is methyl.
[Claim 4]
The compound of the formula (1) as claimed in Claim 1, wherein R^4, R^5 and R^6 are independently hydrogen, Cl, Br, nitro, methyl, trifluoromethyl, methoxy or acetyl.

[Claim 5]

The compound of the formula (1) as claimed in Claim 1, wherein R^7 is hydrogen, F, Cl, cyano, methyl or methoxy.

[Claim 6]

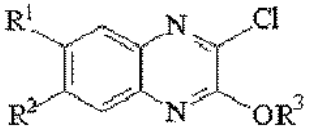
A process for the preparation of 1-[(6,7-substituted alkoxyquinoxalinyl)aminocarbonyl]-4-(hetero)arylpiperazine derivatives, comprising the steps of:

reacting a compound of the following chemical formula (6) with 1.0-5.0 equivalents of 2,4-dimethoxybenzylamine to give a compound of the following chemical formula (7);

reacting the compound of the formula (7) with trifluoroacetic acid (TFA) in dichloromethane solution to give a compound of the following chemical formula (2);

reacting 6,7-substituted-2-alkoxy-3-aminoquinoxaline represented by the following chemical formula (2) with 1.0-1.5 equivalents of a donor agent represented by L-C(=O)-L' group in the presence of base in a solvent at a temperature of room temperature to 100°C to obtain a compound represented by the following chemical formula (3); and

reacting a compound represented by the chemical formula (3) with 1.0-1.5 equivalents of 1-(hetero)arylpiperazine derivatives represented by the following chemical formula (4) in the presence of a base in a solvent at a temperature of 50°C to 100°C to obtain a compound represented by the following chemical formula (1).



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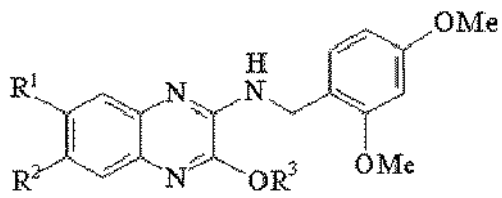

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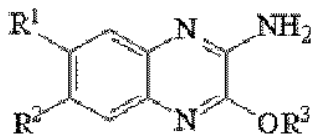

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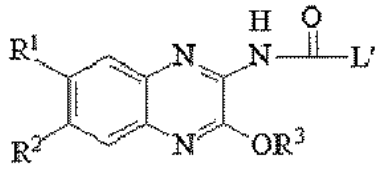

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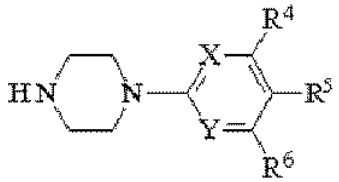

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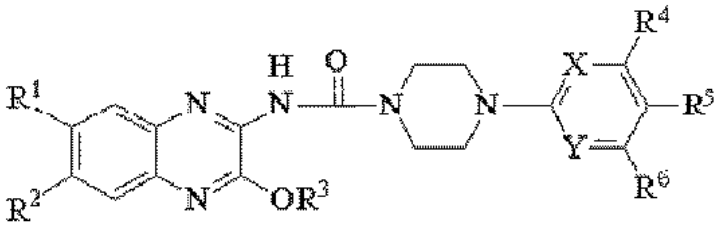


(1)

wherein X, Y, R^1, R^2, R^3, R^4, R^5 and R^6 are the same as defined in Claim 1, and L and L' are independently imidazole, Cl, ethoxy, phenoxy or 4-nitrophenoxy.

[Claim 7]

A pharmaceutical composition comprising 1-[(6,7-substituted alkoxyquinoxalinyl)aminocarbonyl]-4-(hetero)arylpiperazine derivatives, represented by the chemical formula (1) of Claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent or carrier:

[Claim 8]

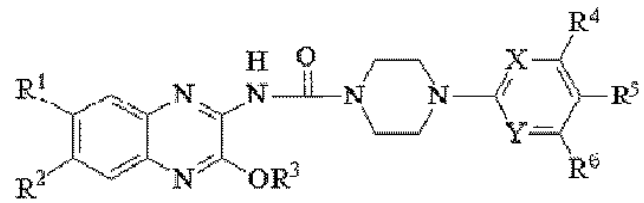
The pharmaceutical of Claim 7 which is an anti-proliferative agent.

(2) After the Correction

The recitation of Claims 1, and 6 to 8 of the scope of the claims after the Correction is set forth as below (underlined portions are corrected parts by the Correction, Exhibit Ko 3).

[Claim 1]

A compound of 1-[(6,7-substituted alkoxyquinoxalinyl)aminocarbonyl]-4-(hetero)arylpiperazine derivatives and their pharmaceutically acceptable salts thereof, represented by the following chemical formula (1):



(1)

wherein

X and Y are C-H,

R^1 is fluorine;

R^2 is hydrogen;

R^3 is methyl;

R^4 is methoxy, R^5 is hydrogen, and R^6 is methoxy.

[Claim 6]

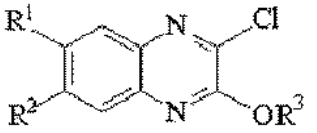
A process for the preparation of 1-[(6,7-substituted alkoxyquinoxalinyl)aminocarbonyl]-4-(hetero)arylpiperazine derivatives, comprising the steps of:

reacting a compound of the following chemical formula (6) with 1.0-5.0 equivalents of 2,4-dimethoxybenzylamine to give a compound of the following chemical formula (7);

reacting the compound of the formula (7) with trifluoroacetic acid (TFA) to give a compound of the following chemical formula (2);

reacting 6,7-substituted-2-alkoxy-3-aminoquinoxaline represented by the following chemical formula (2) with 1.0-1.5 equivalents of a donor agent represented by L-C(=O)-L' group in the presence of a base in a solvent at a temperature of room temperature to 100°C to obtain a compound represented by the following chemical formula (3); and

reacting a compound represented by the chemical formula (3) with 1.0-1.5 equivalents of 1-(hetero)arylpiperazine derivatives represented by the following chemical formula (4) in the presence of a base in a solvent at a temperature of 50°C to 100°C to obtain a compound represented by the following chemical formula (1).



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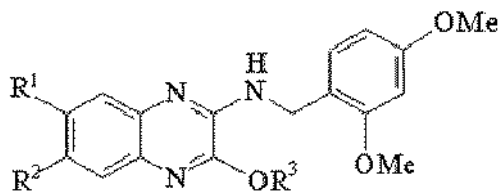

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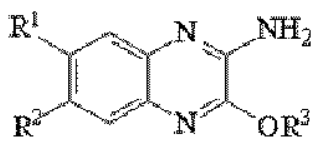

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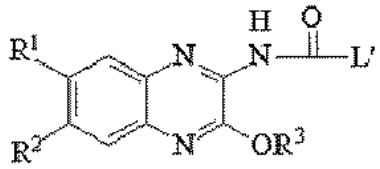

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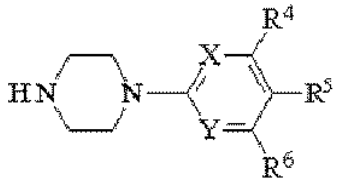

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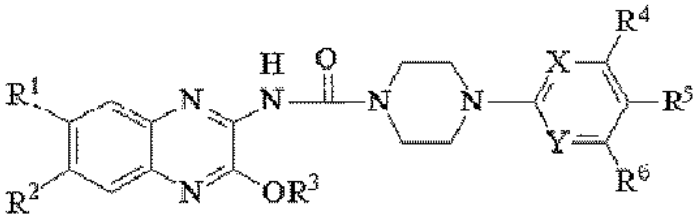


(1)

wherein X, Y, R^1, R^2, R^3, R^4, R^5 and R^6 are the same as defined in Claim 1, and L and L' are independently imidazole, Cl, ethoxy, phenoxy, or 4-nitrophenoxy.

[Claim 7]

A pharmaceutical composition comprising 1-[(6,7-substituted alkoxyquinoxalinyl)aminocarbonyl]-4-(hetero)arylpiperazine derivatives, represented by the chemical formula (1) of Claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent or carrier:

[Claim 8]

The pharmaceutical composition of Claim 7 which is an anti-proliferative agent.

3. Summary of reasons of trial decision

The reason for the trial decision is as per the attached written trial decision (copy).

The summary is [i] Correction 2 according to Claim 1 in the Correction does not comply with the requirement as provided in each item of the proviso to Article 126, paragraph (1) of the Patent Act and paragraph (6) of the same article, and thus the correction of Correction 2 is not acceptable, [ii] the correction of Correction 1, 3 to 13 according to Claims 1 to 5 of a group of claims is also not acceptable, since the correction of Correction 2 is not acceptable.

Correction according to Claim 1 and the determination of the trial decision about Correction 2 are set forth as below.

(1) Correction matter according to Claim 1

A. Correction 1

To correct "X and Y are independently N or C-R^7" of Claim 1 before the

correction to "X and Y are C-H".

B. Correction 2

To correct "R^2 is chlorine" of Claim 1 before the correction to "R^2 is hydrogen".

C. Correction 3

To correct "R^3 is C_1-C_3 alkyl" of Claim 1 before the correction to "R^3 is methyl".

D. Correction 4

To correct "R^4," of Claim 1 before the correction to "R^4 is methoxy,".

E. Correction 5

To correct "R5," of Claim 1 before the correction to "R^5 is hydrogen,".

F. Correction 6

To correct "R^6 and" of Claim 1 before the correction to "and R^6 is methoxy".

G. Correction 7

To delete the recitation of "R^7 is" of Claim 1 before the correction.

H. Correction 8

To delete the recitation of "R^4, R^5, R^6, and R^7 are independently hydrogen, a C_1-C_3 alkoxy, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkylcarbonyl, halogen, cyano or nitro" of Claim 1 before the correction.

I. Correction 9

To delete the recitation of "with the proviso that R^1 and R^2 are not simultaneously hydrogen" of Claim 1 before the correction.

(2) Determination about Correction 2

A. Conformance with the requirement of each item of the proviso to Article 126, paragraph (1) of the Patent Act

(A) Clarification of an ambiguous description (item (iii) of the proviso to Article 126, paragraph (1) of the Patent Act)

To find that a correction aims for "clarification of an ambiguous description", it is required to correct an ambiguous description of the patented specification or the scope of claims itself, or an ambiguous description due to the unreasonableness of the other description in relation to the patented specification or the scope of claims, and clarify its original meaning.

The recitation of "R^2 is chlorine" of Claim 1 before the Correction is not ambiguous by itself, nor unreasonable from the description of the specification of the application (hereinafter referred to as "the specification"), nor can it be said that the recitation of "with the proviso that R^1 and R^2 are not simultaneously hydrogen" of Claim 1 is unreasonable. Further, it cannot be said that to make R^2 "hydrogen" is a

correction clarifying the original meaning. Thus it cannot be said that Correction 2 corrects an ambiguous description and clarifies its original meaning.

Therefore, Correction 2 is not a correction for the purpose of the clarification of ambiguous statement.

(B) Restriction of the scope of claims (item (i) of the proviso to Article 126, paragraph (1) of the Patent Act)

Correction 2 corrects a substituent group of compound 1 of "R^2 is chlorine" in Claim 1 before the Correction to "R^2 is hydrogen", which alters the scope of claims, and thus obviously does not restrict the scope of the claims.

(C) Correcting errors or mistranslations (item (ii) of the proviso to Article 126, paragraph (1) of the Patent Act)

a. Correcting errors

The fact that a substituent group of a compound represented by chemical formula (1) of Claim 1 before the Correction of R^2 is chlorine is not a technically unreasonable point. It is consistent with the recitation of the proviso. It cannot be said that the recitation of the claims is obviously erroneous by itself.

Further, it can be said in chemical formula (1) that the specification describes with a specific description that "R^2" is chlorine. Thus it cannot be said that the recitation of the claims is obviously erroneous in relation to the description of the patented specification.

Furthermore, the specification describes various substituent groups as alternatives of "R^2", and also describes a plurality of compounds in the examples. Even in a case where "R^1" is "fluorine", two kinds of groups of compounds of "hydrogen or fluorine" are described in "R^2". In view of this, it cannot be said that the description of "R^2 is hydrogen" is a correct description, and it is determined as an obvious matter.

Therefore, Correction 2 is not a correction for the purpose of the correction of errors.

b. Correcting mistranslations

Regarding R^2, according to the specification and Claim 1 of the scope of claims as of the International filing date (hereinafter referred to as "the specification etc. of the international application in the international filing date" Exhibit Ko 17), the description of [22] and [23] of the specification and paragraph [0009] of the specification (Exhibit Ko 2) that "... R^2 are each a hydrogen atom, C_1-C_6 alkoxy, C_1-C_6 alkyl or halogen, ... Said halogen denotes fluorine, chlorine, bromine or iodine.", the meaning of the description of the patented specification and the scope of claims is

not different from the meaning of the description corresponding to the specification, etc. of the international application as of the international filing date, and thus Correction 2 is not a correction for the purpose of correcting mistranslations.

(D) Correction aiming to rewrite a claim that cites another claim into a claim that does not cite that other claim (item (iv) of the proviso to Article 126, paragraph (6) of the Patent Act)

It is obvious that Correction 2 is not a correction aiming to rewrite a claim that cites another claim into a claim that does not cite that other claim.

B. Conformance to the requirement of Article 126, paragraph (6) of the Patent Act

Correction 2 corrects "R^2 is chlorine" of Claim 1 before the Correction with "R^2 is hydrogen", which alters a group of compounds recited in the scope of the claims according to Claim 1 before the Correction into a different group of compounds after the Correction, and thus obviously substantially alters the scope of the claims.

Therefore, Correction 2 does not conform to Article 126, paragraph (6) of the Patent Act.

C. Summary

As seen above, Correction 2 according to Claim 1 does not aim to any of the items of the proviso to Article 126, paragraph (1) of the Patent Act, nor does it conform to the requirement as provided in the paragraph (6) of the same article, and thus the correction of Correction 2 cannot be accepted.

(omitted)

No. 4 Judgment of this court

1. Conformance of Correction 2 to the requirement of Article 126, paragraph (6) of the Patent Act

(1) Described matters of the description

A. The specification (Exhibit Ko 2) has the following descriptions (See the attachment with regard to Table 1 and Table 2 cited by the following description):

(A) [0001]

The present invention relates to novel quinoxaline-piperazine compounds, l-[(6,7-substituted alkoxyquinoxalinyl)aminocarbonyl]-4-(hetero)arylpiperazine derivatives and pharmaceutically acceptable salts thereof, a process for the preparation thereof, and therapeutic methods for the treatment of hyperproliferative disorders, including cancers, by administering quinoxaline-piperazine compounds.

[0002]

Background Art

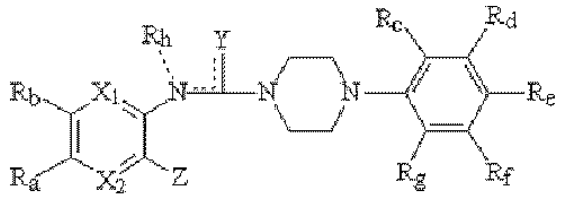
Chemotherapeutics kill tumor cells by interfering with various stages of the cell division process. There are a number of classes of chemotherapeutics including alkylating agents (e.g., cyclophosphamide, carmustine, cisplatin), antimetabolites (e.g., methotrexate, 5-FU, gemcitabine), cytotoxic antibiotics (e.g., doxorubicin, mitomycin), and plant derivatives (e.g., paclitaxel, vincristine, etoposide). Chemotherapy is used as a primary treatment for leukemia, other blood cancers, and inoperable or metastatic solid cancers.

However, current chemotherapeutic agents have a few problems, including limited efficacy, debilitating adverse side effects, and development of multidrug resistance.

Novel piperazine compounds may provide potent new therapeutic molecules for the treatment of disorders such as tumors. In association with new development of an anti-tumor agent, U. S. Patent Application Publication No. 2003/0092910 presents piperazine compounds having formula (A).

[0003]

Chemical formula A



[0004]

In U. S. Patent Application Publication No. 2003/0092910, the preparation of l-[(2-alkoxyquinoxalin-3-yl]aminocarbonyl-4-arylpiperazine is presented wherein Ra and Rb are fused to form a C3-C4 unsaturated ring. But the compounds of formula A have only a hydrogen atom at the C-5, C-6, C-7, and C-8 positions of the quinoxaline ring.

Namely, the compounds listed in U. S. Patent Application Publication No. 2003/0092910 have no other group except hydrogen at the C-6 position of the quinoxaline ring of l-[(2-alkoxyquinoxalin-3-yl)aminocarbonyl-4-arylpiperazine and compounds with groups other than hydrogen at the C-6 position of quinoxaline have not been prepared and tested as antitumor agents.

(B) [0005]

The present invention has studied l-[(2-alkoxyquinoxalin-3-yl)aminocarbonyl-

4-arylpiperazine derivatives because of its prominent antitumor activities with very low toxicities and present novel l-[(6,7-substituted alkoxyquinoxalinyl)aminocarbonyl]-4-(hetero)arylpiperazine derivatives with functional groups other than hydrogen at the C-6 position of the quinoxaline ring thereof, the process of preparation and strong antitumor activities of these new compounds.

Accordingly, one object of the present invention is to provide the novel compounds, l-[(6,7-substituted alkoxyquinoxalinyl)aminocarbonyl]-4-(hetero)arylpiperazine derivatives.

Another object of the present invention is to provide a process for the preparation of the novel compounds, l-[(6,7-substituted alkoxyquinoxalinyl)aminocarbonyl]-4-(hetero)arylpiperazine derivatives.

A further object of the present invention is to provide a use of l-[(6,7-substituted alkoxyquinoxalinyl)aminocarbonyl]-4-(hetero)arylpiperazine derivatives as an antitumor agent.

[0007]

The present invention comprises a novel quinoxaline-piperazine derivative of chemical formula (1) or its pharmaceutically acceptable salt, a process for the preparation thereof, and their use in the treatment of a hyperproliferative disorder, disease, or condition in a subject (e.g., a human patient or other animal subject). Methods according to the present invention comprise administering to a subject an effective amount of a quinoxaline-piperazine compound according to the present invention. Such a treatment can, e.g., prevent, ameliorate, and/or inhibit symptoms of the hyperproliferative condition, and/or can prevent or inhibit cellular proliferation or growth, for instance in a tumor, such as a malignant neoplasm. A treatment strategy of the present invention would decrease the tumor burden, at least to a measurable degree, and improve survival of patients suffering from the hyperproliferative condition. Among the diseases, disorders, and conditions susceptible to treatment by agents of the present invention are neoplasms, and more specifically tumors of various origins (lung, colon, stomach, smooth muscle, esophagus, non-Hodgkin's lymphoma, non-small cell lung cancer, etc.).

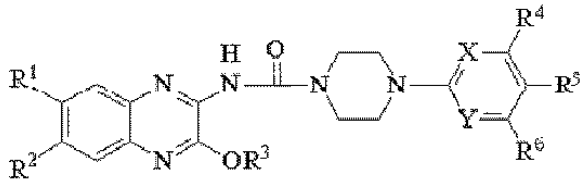
(C) [0008]

Compounds Useful in Methods According To the Present Invention

Compounds useful in methods of the present invention include quinoxaline-piperazine derivatives having formula (1), l-[(6,7-substituted alkoxyquinoxalinyl)aminocarbonyl]-4-(hetero)arylpiperazine derivatives.

[0009]

chemical formula (1)



(1)

wherein X and Y are independently N or C-R^7; R^1 and R^2 are independently hydrogen, a C_1-C_6 alkoxy, C_1-C_6 alkyl, or halogen; R^3 is a C_1-C_6 alkyl; R^4, R^5, R^6 and R^7 are independently hydrogen, a C_1-C_6 alkoxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylcarbonyl, halogen, cyano, or nitro.

Said halogen denotes fluorine, chlorine, bromine, or iodine.

Said alkoxy denotes a C_1-C_6 alkoxy containing methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, and t-butoxy.

Said alkyl denotes a C_1-C_6 alkyl containing methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, n-hexyl, isohexyl, and cyclohexyl.

Said haloalkyl denotes a C_1-C_6 alkyl, for example trifluoromethyl, in which hydrogen was exchanged with a halogen such as F or Cl.

Said alkylcarbonyl denotes a carbonyl ketonized with an alkyl such as methylcarbonyl or ethylcarbonyl.

[0010]

It is preferably understood that, in the structure of formula (1), X and Y are independently N, C-H, C-F, C-Cl, C-CN, C-CH_3, or C-OCH_3, R^1 and R^2 are hydrogen, F, Cl, methyl or methoxy, R^3 is methyl, R^4, R^5, and R^6 are independently hydrogen, Cl, Br, nitro, methyl, trifluoromethyl, methoxy or acetyl, and R^7 is hydrogen, F, Cl, cyano, methyl, or methoxy."

(D) "[Examples]

[0023]

The present invention may be further clarified by reference to the following Examples, which serve to exemplify some of the preferred embodiments, and not to limit the present invention in any way.

(Example 1)... (Compound 1)...

[0246]

(Example 196)... (Compound 196)...

[0247]

The structures of Compounds 1 to 196 are shown in the following Table 1.

[0256]

Animal Experiment

1. Growth of cancer cell lines

Cancer cells used in this study to determine the effect of quinazoline compounds were obtained from the following sources: Human OVCAR-3 (ovary), MCF-7 (breast, hormone-dependent), MDA-MB-231 (breast), PC3 (prostate), HepG2 (liver), A549 (lung), Caki-1 (kidney), HT-29 (colon), HCT116 (colon), and PANC-1 (pancreas) from the American Type Culture Collection (ATCC) (Manassas, VA); MKN-45 (stomach) from DSMZ (Germany); UMRC2 (kidney) from the U. S. National Cancer Institute (Bethesda, MD); Huvec (human umbilical vein endothelial cells), HEK293 (human embryonic kidney) and SK-OV-3 (ovary) from Korean Cell Line Bank (Seoul, South Korea). ... All cells were incubated at 37°C under humidified 5% CO_2.

[0257]

2. Cell Growth Inhibition Assay

The growth inhibition of the substituted quinoxaline-piperazine compounds against a variety of human tumor cells was evaluated. The relative importance of particular substituent groups on the compounds was also studied. The substituted piperazine derivative compounds, prepared as described above, were tested, along with DMSO as a control. ...

To translate the OD_{530} values into the number of live cells in each well, the OD_{530} values were compared to those on standard OD_{530} - versus - cell number curves. The percent survival was calculated using the formula:

% Survival = live cell number [test] /live cell number [control] x 100

The IC_{50} values were calculated by non-linear regression analysis.

Using QSAR and combinatorial chemistry techniques, a large number of compounds, including the compounds shown in Table 1a-1f above, were synthesized. The synthesized compounds were screened against at least three cell lines, PANC-1, MDA-MB-231, and UMRC2, at approximately l μM concentration. Compounds showing activity in at least one of these cell lines were selected for further screening. From these compounds, 50 compounds were selected for further evaluation as broad spectrum anti-proliferative agents as shown in the following Table 2.

[0260]

Industrial Applicability

The novel compounds of the present invention may provide novel quinoxaline-piperazine derivatives or pharmaceutically acceptable salts thereof which have strong anti-proliferative effect and are useful for treating hyperproliferative disorders,

including cancers, by administering quinoxaline-piperazine compounds.

B. According to the described matter of the aforesaid A, it is recognized that the specification has the following disclosure:

(A) "The present invention" has studied l-[(2-alkoxyquinoxalin-3-yl)aminocarbonyl-4-arylpiperazine derivatives because of their prominent antitumor activities with very low toxicities and present novel l-[(6,7-substituted alkoxyquinoxalinyl)aminocarbonyl]-4-(hetero)arylpiperazine derivatives with functional groups other than hydrogen at the C-6 position of the quinoxaline ring thereof, and the process of preparation and strong antitumor activities of these new compounds ([0005]).

(B) The treatment by "the present invention" causes effects to prevent, ameliorate, and (or) inhibit hyperproliferative disorders, and improve survival of patients suffering from the hyperproliferative condition ([0005], [0007]).

(2) Whether or not Correction 2 substantially alters the scope of claims

A. In view of the fact that when a trial decision to the effect that a correction should be accepted is final and binding, the effects of the correction are retroactive to a filing (Article 128 of the Patent Act) and the effects of the patent right of the patent invention which technical scope is determined on the basis of the description of the corrected scope of claims extends to third parties, the determination as to whether or not a correction “substantially enlarges or alters the scope of claims" of Article 126, paragraph (6) of the Act should be made with a criterion of the recitation of the scope of claims before and after the correction. Whether a correction corresponds to "substantial" enlargement or alteration should be determined from a viewpoint of whether the correction might cause unexpected disadvantage for third party.

Further, regarding the recitation of the scope of claims, the first paragraph of Article 36, paragraph (5) of the Act specifies that the scope of claims should describe all the matters that the applicant finds to be necessary for defining the invention for which a patent is sought separately for each claim. The gist of this provision can be seen that it is required to describe matters that the applicant itself determines as "all the matters necessary used to specify the invention for which a patent is sought by the applicant" for each claim in order to find an invention from one claim. Thus it is objectively reasonable to understand that an applicant itself has determined as "all the matters necessary used to specify the invention for which a patent is sought by the applicant" even in a case that there are overlapping descriptions in one claim as long as the descriptions are inconsistent with each other.

Taking the above as given, it is determined as to whether or not Correction 2

substantially alters the scope of claims.

B. A language of "with the proviso that R^1 and R^2 are not simultaneously hydrogen" of the proviso in Claim 1 before the correction only specifies literally that both R^1 and R^2 are not simultaneously hydrogen. It cannot even be seen as specifying that either R^1 or R^2 is always a hydrogen atom.

Consequently, taking the whole recitation of Claim 1 before the Correction, it describes that "R^1 is fluorine" and "R^2 is chlorine", which obviously specifies "R^1" as "fluorine" and "R^2" as "chlorine". Further, this description can also be seen as meaning that both R^1 and R^2 are not hydrogen atoms. Thus in that sense, it overlaps the description of the proviso, but they are not inconsistent with each other.

Further, in the description of the specification that "in the aforesaid chemical formula (1), ... R^1 and R^2 are each a hydrogen atom, a C_1-C_6 alkoxy, C_1-C_6 alkyl, or halogen, ... Said halogen denotes fluorine, chlorine, bromine, or iodine." ([0009]) and "In a compound represented by the aforesaid chemical formula (1) of the present invention, particularly preferably ... R^1 and R^2 are hydrogen, F, Cl, methyl, or methoxy" ([0010]), F(fluorine) and Cl(chlorine) are disclosed as examples of R^1 and R^2 of chemical formula (1). Thus to specify "R^1" as "fluorine" and "R^2" as "chlorine" in Claim 1 before the Correction is consistent in relation to the description of the specification.

Consequently, it can be seen that the description of "R^1 is fluorine" and "R^2 is chlorine" with the description of the proviso is recognized as "matters that the applicant finds to be necessary for defining the invention for which a patent is sought ". It cannot be said that the definition of R^1 and R^2 in Claim 1 before the Correction is indefinite.

As seen above, Correction 2 corrects "chlorine" of "R^2" recited in Claim 1 before the Correction to "hydrogen". Thus it aims to alter the scope of the claims. Further, it cannot be seen from the language of "R^1 is fluorine" and "R^2 is chlorine" of Claim 1 before the Correction that R^1 substantially means "fluorine or hydrogen" and R^2 substantially means "fluorine or hydrogen". Thus the alteration of the scope of claims by Correction 2 does not correspond to the alteration in a limited way.

Further, Correction 2 alters the invention according to Claim 1 from a group of compounds having a substituent group of Compound 1 of "R^2" of chlorine recited in Claim 1 before the Correction to a group of compounds having a group of compounds having "R^2" of hydrogen after the correction. Thus this alteration obviously causes unexpected disadvantage for third party who relies on the recitation of Claim 1 before the correction.

Therefore, Correction 2 is recognized as substantially altering the scope of claims, and thus does not conform to the requirement of Article 126, paragraph (6) of the Patent Act. The determination of the trial decision with the same gist is not erroneous.

(3) Plaintiffs' allegation

Plaintiffs allege that when a consideration is given to the recitation of Claim 1 before the Correction and the description of the specification and a reference is made to the prosecution history of the Patent, the recitation of "R^1 is fluorine and R^2 is chlorine" of the main text of Claim 1 before the Correction is ambiguous in relation to "R^1 and R^2 are not simultaneously hydrogen" of the proviso, and it can be seen that the scope of R^1 and R^2 of the main text substantially includes not only chlorine but also hydrogen, and Correction 2 deletes chlorine from a substantially recognized scope of R^2 to confine the scope of R^2, and thus it is not a correction that substantially alters the scope of claims.

As in the aforesaid (2)B, however, it is obvious from the recitation of Claim 1 of the scope of claims before the Correction that the recitation of "R^1 is fluorine" and "R^2 is chlorine" of the main text of Claim 1 before the Correction respectively specifies "R^1" as "fluorine" and "R^2" as "chlorine", and overlaps "R^1 and R^2 are not simultaneously hydrogen" of the proviso. The main text and the proviso are not inconsistent with each other, but are consistent in relation to the description of the specification, and thus it cannot be said that the description of the main text and the description of the proviso are ambiguous.

Subsequently, according to the prosecution history of the Patent, Claim 1 before the Correction (as of the registration of the Patent) was subjected to an amendment to Claim 1 after the primary amendment by the secondary amendment that was made together with a notice of appeal against an examiner's decision of refusal. In the appeal brief of appeals against an examiner's decision of refusal (Exhibit Otsu 3), it describes that "3.2. The above amendment restricts R^1 to fluorine and R^2 to chlorine in Claim 1 (corresponding to a restriction in a limited way of the scope of claims), ... is a legitimate amendment.", "3.3. The above amendment limits the compounds of the present invention to compounds causing excellent antitumor activity to the extent that cannot be expected by a person ordinarily skilled in the art and compounds equivalent to them in the pharmacological test results described in Table 2 of the specification of the present application, and 'Compounds showing an activity comparable to or inferior to that of Compound 42 of Cited Document 3 (e.g. Compounds 52, 73, 115, 136, 157, 193 etc.)' are clearly excluded." It can clearly be

seen from this description that the above amendment limits R^1 to fluorine, and limit R^2 to chlorine in Claim 1. Further, Compounds 52 and 73 of the description of the specification include hydrogen in R^2 and Compounds 115, 136, 157 include hydrogen in R^1. In view of the fact that the above description of the appeal brief of the notice of appeal against the examiner's decision of refusal is also consistent with the description of the specification, it cannot be said that the definition of R^1 and R^2 in Claim 1 before the Correction is ambiguous.

Further, the decision of refusal (Exhibit Ko 16) mentions that "Compound 10 of the present invention shows an excellent antitumor activity compared to Compound 42 of Cited Document 3". This description does not mean that the Examiner suggests including Compound 10 into the recitation of the scope of claims, as opposed to Plaintiffs' allegation. The recitation of the scope of claims should describe "matters necessary used to specify an invention for which a patent is sought" by an applicant itself (Article 36, paragraph (5) of the Patent Act). Plaintiffs should select the recitation of the scope of claims on their own account. In view of this, it cannot be said that the definition of R^1 and R^2 in Claim 1 before the Correction is ambiguous by considering the above description of the decision of refusal.

Furthermore, Plaintiffs point out that the recitation of "R^2 is chlorine" in the secondary amendment is inconsistent with the agreement on an amendment between Examiner and a Plaintiffs' representative of patent attorney Ogawa as circumstances to be considered as a prosecution history of the Patent. The agreement as Plaintiffs allege cannot be seen as equivalent to procedural documents including documents subject to the examination such as an application, the specification attached to the application, the scope of the claims and drawings, and documents according to the appeals against an examiner's decision of refusal in relation to the relationship with third party. Thus it cannot be considered in the construction of Claim 1 before the Correction.

Therefore, the above Plaintiffs' allegation is not acceptable.

(4) Summary

As seen above, Correction 2 does not conform to the requirement of Article 126, paragraph (6) of the Patent Act, and thus without determination about the remaining point, the correction of Correction 2 according to Claim 1 cannot be accepted.

Further, as long as the correction of Correction 2 according to Claim 1 is not accepted, the correction of Corrections 1, and 3 to 13 according to a group of claims of Claims 1 to 5 is also not acceptable.

Therefore, the determination of the trial decision to the effect that the Correction did not conform to the requirements of correction is not erroneous.

2. Conclusion

For the above reasons, none of reasons for rescission as Plaintiffs alleges has a point, thus the trial decision contains no illegality to be rescinded.

Therefore, the Plaintiffs' claim should be dismissed.

Intellectual Property High Court, Fourth Division

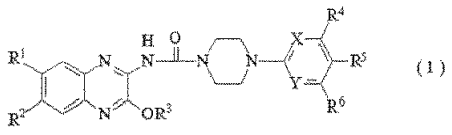
Presiding Judge OTAKA Ichiro

Judge KOKUBU Takafumi

Judge HAZUI Takuya

(Attachment)

Table 1



(1)

Compound	R^1	R^2	R^3	R^4	R^5	R^6	X	Y
1	F	H	Me	H	H	H	C-H	C-H
2	F	H	Me	H	H	H	C-OMe	C-H
3	F	H	Me	OMe	H	H	C-H	C-H
4	F	H	Me	H	OMe	H	C-H	C-H
5	F	H	Me	OMe	H	OMe	C-H	C-H
6	F	H	Me	OMe	OMe	OMe	C-H	C-H
7	F	H	Me	H	H	H	C-Me	C-H
8	F	H	Me	Me	H	H	C-H	C-H
9	F	H	Me	H	H	H	C-Me	C-Me
10	F	H	Me	Me	H	Me	C-H	C-H
11	F	H	Me	CF_3	H	H	C-H	C-H
12	F	H	Me	H	H	H	C-F	C-H
13	F	H	Me	H	F	H	C-H	C-H
14	F	H	Me	H	H	H	C-Cl	C-H
15	F	H	Me	Cl	H	H	C-H	C-H
16	F	H	Me	H	Cl	H	C-H	C-H
17	F	H	Me	H	H	H	C-CN	C-H
18	F	H	Me	H	Ac	H	C-H	C-H
19	F	H	Me	H	NO_2	H	C-H	C-H
20	F	H	Me	H	H	H	N	C-H
21	F	H	Me	H	H	H	N	N
22	Cl	H	Me	H	H	H	C-H	C-H
23	Cl	H	Me	H	H	H	C-OMe	C-H
24	Cl	H	Me	OMe	H	H	C-H	C-H
25	Cl	H	Me	H	OMe	H	C-H	C-H
26	Cl	H	Me	OMe	H	OMe	C-H	C-H
27	Cl	H	Me	OMe	OMe	OMe	C-H	C-H
28	Cl	H	Me	H	H	H	C-Me	C-H
29	Cl	H	Me	Me	H	H	C-H	C-H

30	Cl	H	Me	H	H	H	C-Me	C-Me
31	Cl	H	Me	Me	H	Me	C-H	C-H
32	Cl	H	Me	CF_3	H	H	C-H	C-H
33	Cl	H	Me	H	H	H	C-F	C-H
34	Cl	H	Me	H	F	H	C-H	C-H
35	Cl	H	Me	H	H	H	C-Cl	C-H
36	Cl	H	Me	Cl	H	H	C-H	C-H
37	Cl	H	Me	H	Cl	H	C-H	C-H
38	Cl	H	Me	H	H	H	C-CN	C-H
39	Cl	H	Me	H	Ac	H	C-H	C-H
40	Cl	H	Me	H	NO_2	H	C-H	C-H
41	Cl	H	Me	H	H	H	N	C-H
42	Cl	H	Me	H	H	H	N	N
43	Me	H	Me	H	H	H	C-H	C-H
44	Me	H	Me	H	H	H	C-OMe	C-H
45	Me	H	Me	OMe	H	H	C-H	C-H
46	Me	H	Me	H	OMe	H	C-H	C-H
47	Me	H	Me	OMe	H	OMe	C-H	C-H
48	Me	H	Me	OMe	OMe	OMe	C-H	C-H
49	Me	H	Me	H	H	H	C-Me	C-H
50	Me	H	Me	Me	H	H	C-H	C-H
51	Me	H	Me	H	H	H	C-Me	C-Me
52	Me	H	Me	Me	H	Me	C-H	C-H
53	Me	H	Me	CF_3	H	H	C-H	C-H
54	Me	H	Me	H	H	H	C-F	C-H
55	Me	H	Me	H	F	H	C-H	C-H
56	Me	H	Me	H	H	H	C-Cl	C-H
57	Me	H	Me	Cl	H	H	C-H	C-H
58	Me	H	Me	H	Cl	H	C-H	C-H
59	Me	H	Me	H	H	H	C-CN	C-H
60	Me	H	Me	H	Ac	H	C-H	C-H
61	Me	H	Me	H	NO_2	H	C-H	C-H
62	Me	H	Me	H	H	H	N	C-H
63	Me	H	Me	H	H	H	N	N
64	MeO	H	Me	H	H	H	C-H	C-H
65	MeO	H	Me	H	H	H	C-OMe	C-H

66	MeO	H	Me	OMe	H	H	C-H	C-H
67	MeO	H	Me	H	OMe	H	C-H	C-H
68	MeO	H	Me	OMe	H	OMe	C-H	C-H
69	MeO	H	Me	OMe	OMe	OMe	C-H	C-H
70	MeO	H	Me	H	H	H	C-Me	C-H
71	MeO	H	Me	Me	H	H	C-H	C-H
72	MeO	H	Me	H	H	H	C-Me	C-Me
73	MeO	H	Me	Me	H	Me	C-H	C-H
74	MeO	H	Me	CF_3	H	H	C-H	C-H
75	MeO	H	Me	H	H	H	C-F	C-H
76	MeO	H	Me	H	F	H	C-H	C-H
77	MeO	H	Me	H	H	H	C-Cl	C-H
78	MeO	H	Me	Cl	H	H	C-H	C-H
79	MeO	H	Me	H	Cl	H	C-H	C-H
80	MeO	H	Me	H	H	H	C-CN	C-H
81	MeO	H	Me	H	Ac	H	C-H	C-H
82	MeO	H	Me	H	NO_2	H	C-H	C-H
83	MeO	H	Me	H	H	H	N	C-H
84	MeO	H	Me	H	H	H	N	N
85	H	F	Me	H	H	H	C-H	C-H
86	H	F	Me	H	H	H	C-OMe	C-H
87	H	F	Me	OMe	H	H	C-H	C-H
88	H	F	Me	H	OMe	H	C-H	C-H
89	H	F	Me	OMe	H	OMe	C-H	C-H
90	H	F	Me	OMe	OMe	OMe	C-H	C-H
91	H	F	Me	H	H	H	C-Me	C-H
92	H	F	Me	Me	H	H	C-H	C-H
93	H	F	Me	H	H	H	C-Me	C-Me
94	H	F	Me	Me	H	Me	C-H	C-H
95	H	F	Me	CF_3	H	H	C-H	C-H
96	H	F	Me	H	H	H	C-F	C-H
97	H	F	Me	H	F	H	C-H	C-H
98	H	F	Me	H	H	H	C-Cl	C-H
99	H	F	Me	Cl	H	H	C-H	C-H
100	H	F	Me	H	Cl	H	C-H	C-H
101	H	F	Me	H	H	H	C-CN	C-H
102	H	F	Me	H	Ac	H	C-H	C-H
103	H	F	Me	H	NO_2	H	C-H	C-H
104	H	F	Me	H	H	H	N	C-H
105	H	F	Me	H	H	H	N	N

106	H	Cl	Me	H	H	H	C-H	C-H
107	H	Cl	Me	H	H	H	C-OMe	C-H
108	H	Cl	Me	OMe	H	H	C-H	C-H
109	H	Cl	Me	H	OMe	H	C-H	C-H
110	H	Cl	Me	OMe	H	OMe	C-H	C-H
111	H	Cl	Me	OMe	OMe	OMe	C-H	C-H
112	H	Cl	Me	H	H	H	C-Me	C-H
113	H	Cl	Me	Me	H	H	C-H	C-H
114	H	Cl	Me	H	H	H	C-Me	C-Me
115	H	Cl	Me	Me	H	Me	C-H	C-H
116	H	Cl	Me	CF_3	H	H	C-H	C-H
117	H	Cl	Me	H	H	H	C-F	C-H
118	H	Cl	Me	H	F	H	C-H	C-H
119	H	Cl	Me	H	H	H	C-Cl	C-H
120	H	Cl	Me	Cl	H	H	C-H	C-H
121	H	Cl	Me	H	Cl	H	C-H	C-H
122	H	Cl	Me	H	H	H	C-CN	C-H
123	H	Cl	Me	H	Ac	H	C-H	C-H
124	H	Cl	Me	H	NO_2	H	C-H	C-H
125	H	Cl	Me	H	H	H	N	C-H
126	H	Cl	Me	H	H	H	N	N
127	H	Me	Me	H	H	H	C-H	C-H
128	H	Me	Me	H	H	H	C-OMe	C-H
129	H	Me	Me	OMe	H	H	C-H	C-H
130	H	Me	Me	H	OMe	H	C-H	C-H
131	H	Me	Me	OMe	H	OMe	C-H	C-H
132	H	Me	Me	OMe	OMe	OMe	C-H	C-H
133	H	Me	Me	H	H	H	C-Me	C-H
134	H	Me	Me	Me	H	H	C-H	C-H
135	H	Me	Me	H	H	H	C-Me	C-Me
136	H	Me	Me	Me	H	Me	C-H	C-H
137	H	Me	Me	CF_3	H	H	C-H	C-H
138	H	Me	Me	H	H	H	C-F	C-H
139	H	Me	Me	H	F	H	C-H	C-H
140	H	Me	Me	H	H	H	C-Cl	C-H
141	H	Me	Me	Cl	H	H	C-H	C-H
142	H	Me	Me	H	Cl	H	C-H	C-H
143	H	Me	Me	H	H	H	C-CN	C-H

144	H	Me	Me	H	Ac	H	C-H	C-H
145	H	Me	Me	H	NO_2	H	C-H	C-H
146	H	Me	Me	H	H	H	N	C-H
147	H	Me	Me	H	H	H	N	N
148	H	MeO	Me	H	H	H	C-H	C-H
149	H	MeO	Me	H	H	H	C-OMe	C-H
150	H	MeO	Me	OMe	H	H	C-H	C-H
151	H	MeO	Me	H	OMe	H	C-H	C-H
152	H	MeO	Me	OMe	H	OMe	C-H	C-H
153	H	MeO	Me	OMe	OMe	OMe	C-H	C-H
154	H	MeO	Me	H	H	H	C-Me	C-H
155	H	MeO	Me	Me	H	H	C-H	C-H
156	H	MeO	Me	H	H	H	C-Me	C-Me
157	H	MeO	Me	Me	H	Me	C-H	C-H
158	H	MeO	Me	CF_3	H	H	C-H	C-H
159	H	MeO	Me	H	H	H	C-F	C-H
160	H	MeO	Me	H	F	H	C-H	C-H
161	H	MeO	Me	H	H	H	C-Cl	C-H
162	H	MeO	Me	Cl	H	H	C-H	C-H
163	H	MeO	Me	H	Cl	H	C-H	C-H
164	H	MeO	Me	H	H	H	C-CN	C-H
165	H	MeO	Me	H	Ac	H	C-H	C-H
166	H	MeO	Me	H	NO_2	H	C-H	C-H
167	H	MeO	Me	H	H	H	N	C-H
168	H	MeO	Me	H	H	H	N	N
169	F	F	Me	OMe	H	H	C-H	C-H
170	F	F	Me	OMe	H	OMe	C-H	C-H
171	F	F	Me	Me	H	H	C-H	C-H
172	F	F	Me	Me	H	Me	C-H	C-H
173	F	F	Me	CF_3	H	H	C-H	C-H
174	F	F	Me	Cl	H	H	C-H	C-H
175	F	F	Me	Br	H	H	C-H	C-H
176	Cl	Cl	Me	OMe	H	H	C-H	C-H
177	Cl	Cl	Me	OMe	H	OMe	C-H	C-H
178	Cl	Cl	Me	Me	H	H	C-H	C-H
179	Cl	Cl	Me	Me	H	Me	C-H	C-H
180	Cl	Cl	Me	CF_3	H	H	C-H	C-H

181	Cl	Cl	Me	Cl	H	H	C-H	C-H
182	Cl	Cl	Me	Br	H	H	C-H	C-H
183	Me	Me	Me	OMe	H	H	C-H	C-H
184	Me	Me	Me	OMe	H	OMe	C-H	C-H
185	Me	Me	Me	Me	H	H	C-H	C-H
186	Me	Me	Me	Me	H	Me	C-H	C-H
187	Me	Me	Me	CF_3	H	H	C-H	C-H
188	Me	Me	Me	Cl	H	H	C-H	C-H
189	Me	Me	Me	Br	H	H	C-H	C-H
190	MeO	MeO	Me	OMe	H	H	C-H	C-H
191	MeO	MeO	Me	OMe	H	OMe	C-H	C-H
192	MeO	MeO	Me	Me	H	H	C-H	C-H
193	MeO	MeO	Me	Me	H	Me	C-H	C-H
194	MeO	MeO	Me	CF_3	H	H	C-H	C-H
195	MeO	MeO	Me	Cl	H	H	C-H	C-H
196	MeO	MeO	Me	Br	H	H	C-H	C-H

Table 2

Compound No.	Cell growth inhibition of quinoxaline-piperazine compounds against human tumor cell line (IC_{50}, μM)													
	MDA-MB-231	UMRC2	PANC-1	MKN45	HepG2	HT29	HCT 116	PC-3	OVCAR 3	MCF7	Caki-1	A549	Hek 293	Huvec	SK-OV-3
2	0.064	0.10	0.35	0.093	0.12	0.15	0.16	0.22	0.076	0.19	0.11	0.20			
3	0.063	0.050	0.062	0.050	0.12	0.090	0.064	0.070	0.036	0.070	0.047	0.15			
6	0.012	0.013	0.021	0.020	0.019	0.021	0.019	0.021	0.012	0.025	0.011	0.021			
8	0.036	0.032	0.039	0.023	0.080	0.050	0.043	0.060	0.024	0.034	0.024	0.081			
10	0.023	0.022	0.024	0.027	0.021	0.031	0.025	0.022	0.025	0.031	0.019	0.023	0.25	0.05	0.1
11	0.25	0.39	1.06												
15	0.040	0.077	0.28	0.076	0.077	0.11	0.097	0.13	0.055	0.13	0.064	0.10			
24	0.41	0.68	1.66												
26	0.050	0.065	0.098	0.064	0.063	0.079	0.068	0.076	0.042	0.076	0.053	0.073			
29	0.16	0.30	0.95												
31	0.037	0.060	0.24	0.069	0.068	0.11	0.076	0.079	0.056	0.081	0.056	0.076	0.25	0.1	0.1
32	1.0	1.0	>1.0												
36	0.17	0.31	0.93												
45	0.27	0.45	1.31			0.05						0.25	0.5	0.5	1.0
47	0.032	0.039	0.070	0.040	0.045	0.048	0.047	0.063	0.023	0.063	0.029	0.055			
50	0.22	0.40	1.04												
52	0.050	0.050	0.28	0.080	0.081	0.14	0.10	0.11	0.065	0.12	0.071	0.097	0.1	0.1	0.25
53	>1.0	>1.0	>1.0												
57	0.14	0.24	0.64												
66	>1.0	>1.0	>1.0												
71	0.40	0.63	1.43												
73	0.057	0.10	0.33	0.081	0.081	0.12	0.11	0.14	0.059	0.097	0.066	0.11	0.1	0.1	0.1
78	>1.0	>1.0	>1.0												
87	>1.0	>1.0	>1.0												

92	0.21	0.37	0.95												
94	0.41	0.32	0.56	0.25	0.48	0.89	0.40	0.70	0.29	0.36	0.33	0.42	0.57	0.16	0.50
95	>1.0	>1.0	>1.0												
108	>1.0	>1.0	>1.0												
110	0.18	0.21	0.28	0.20	0.21	0.25	0.23	0.27	0.13	0.21	0.18	0.24			
113	0.30	0.40	0.61												
115	0.13	0.11	0.17	0.43	0.41	0.46	0.45	0.62	0.31	0.45	0.31	0.59	0.50	0.52	0.50
116	>1.0	>1.0	>1.0												
120	0.17	0.17	0.24				0.48		0.36	0.60	0.40	0.75			
129	>1.0	>1.0	>1.0												
131	0.16	0.23	0.36	0.22	0.23	0.34	0.25	0.35	0.14	0.24	0.19	0.24			
134	0.26	0.26	N/A												
136	0.045	0.057	0.28	0.18	0.19	0.24	0.20	0.25	0.14	0.21	0.13	0.21	0.24	0.15	0.10
141	0.25	0.25	N/A												
150	1.0	>1.0	>1.0												
155	0.23	0.39	0.96												
157	0.41	0.27	0.47	0.27	0.56	0.78	0.38	0.58	0.29	0.21	0.30	2.50	0.53	0.15	0.50
158	>1.0	>1.0	>1.0												
162	0.23	0.29	0.46												
167	>1.0	>1.0	>1.0												
172	0.70	0.56	1.00												
177	1.45	0.58	1.16												
191	0.69	0.49	0.90												
193	0.65	0.47	0.69												
194	0.75	0.79	1.40												
196	0.72	0.65	1.05												