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(54) Title: COMPOSITIONS AND METHODS FOR TREATING CANCER

(57) Abstract: The present disclosure relates to compounds that are capable penetrating to the blood brain barrier to modulate the activity of EGFR tyrosine kinase. The disclosure further relates to methods of treating glioblastoma and other EGFR mediated cancers. The disclosure further relates to methods of treating glioblastoma and other EGFR mediated cancers that have been determined to have altered glucose metabolism in the presence of inhibitors. The present disclosure also provides methods of administering to a subject a glucose metabolism inhibitor and a cytoplasmic p53 stabilizer.

COMPOSITIONS AND METHODS FOR TREATING CANCER

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 63/081,235 filed September 21, 2020, the contents of which are fully incorporated by reference herein.

STATEMENT OF GOVERNMENT SUPPORT

This invention was made with government support under Grant Numbers CA151819, CA211015, CA213133, awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

Glioblastoma (glioblastoma multiforme; GBM) accounts for the majority of primary malignant brain tumors in adults. Amplification and mutation of the epidermal growth factor receptor (EGFR) gene is a signature genetic abnormality encountered in GBM (Sugawa, et al. (1990) Proc. Natl. Acad. Sci. 87: 8602-8606; Ekstrand, et al. (1992) Proc. Natl. Acad. Sci. 89: 4309-4313). A range of potential therapies that target EGFR or its mutant constitutively active form, ΔEGFR, including tyrosine kinase inhibitors (TKIs), monoclonal antibodies, vaccines, and RNA-based agents, are currently in development or in clinical trials for the treatment of GBM. However, to date their efficacy in the clinic has so far been limited by both upfront and acquired drug resistance (Taylor, et al. (2012) Curr. Cancer Drug Targets. 12:197-209). A major limitation is that current therapies such as erlotinib, lapatinib, gefitinib and afatinib are poorly brain penetrant (Razier, et al. (2010) Neuro-Oncology 12:95-103; Reardon, et al. (2015) Neuro-Oncology 17:430-439; Thiessen, et al. (2010) Cancer Chemother. Pharmacol. 65:353-361).

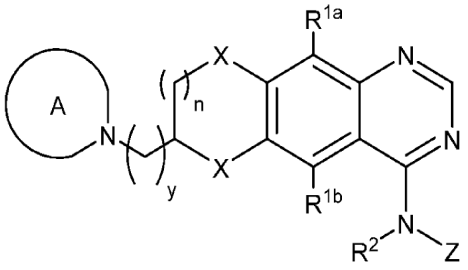
Molecular targeted therapies have revolutionized cancer treatment and paved the path for modern precision medicine. However, despite well-defined actionable genetic alterations, targeted drugs have failed in glioblastoma (GBM) patients. This is in large part due to insufficient CNS penetration of most targeted agents to levels necessary for tumor kill; potentially evoking robust adaptive mechanisms to drive therapeutic resistance. While drug combinations that inhibit both the primary lesion and the compensatory signaling pathway(s) are appealing, these combination therapy strategies have been hampered by enhanced toxicities leading to subthreshold dosing of each drug.

An alternative therapeutic approach targets an oncogenic driver to modify an important functional property for tumor survival, rendering cells vulnerable to an orthogonal second hit. This "synthetic lethal" strategy may be particularly attractive when the oncogene-regulated functional network(s) intersect with tumor cell death pathways. In a certain example, oncogenic signaling drives glucose metabolism to suppress intrinsic apoptosis and promote survival. Inhibition of oncogenic drivers with targeted therapies can trigger the intrinsic apoptotic machinery as a direct consequence of attenuated glucose consumption. The intertwined nature of these tumorigenic pathways may present therapeutic opportunities for rational combination treatments, however, this has yet to be investigated.

In view of the foregoing, there remains a clinical need for brain penetrant chemotherapeutics for the treatment of glioblastoma and other cancers.

SUMMARY OF THE DISCLOSURE

In one aspect, the present disclosure provides compounds having a structure represented by Formula Ia, Ib, Ic, or Id:



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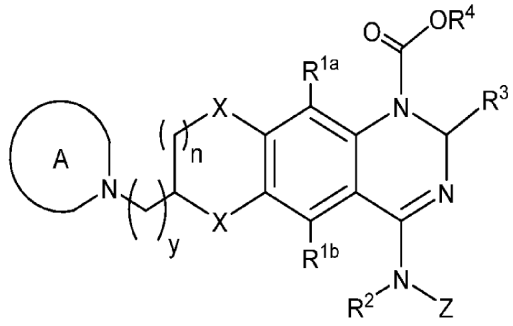

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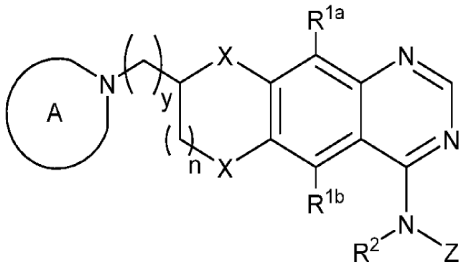

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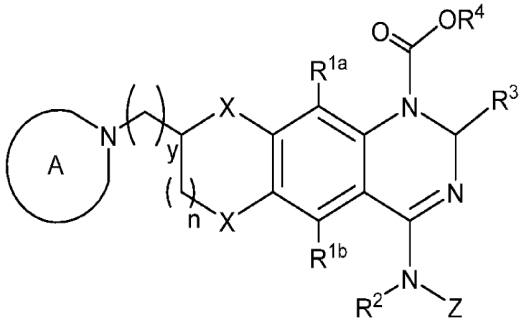


Id

or a pharmaceutically acceptable salt thereof, wherein:

A is a heterocyclyl;

Z is aryl or heteroaryl;

each X is independently selected from O, S, and NH;

R^{1a} and R^{1b} are each independently selected from hydrogen, alkyl, halo, CN, and NO_2;

R^2 is hydrogen, alkyl, or acyl;

R^3 is alkoxy;

R^4 is alkyl;

n is 1-3; and

y is 1-3.

In certain aspects, the present disclosure provides methods of inhibiting EGFR or ΔEGFR, comprising administering to a subject an amount of a compound of the disclosure.

In certain aspects, the present disclosure provides methods of treating cancer comprising administering to a subject in need of a treatment for cancer an amount of a compound of the disclosure. In some embodiments, the cancer is glioblastoma multiforme.

In certain aspects, the present disclosure provides methods of treating cancer comprising administering to a subject a glucose metabolism inhibitor and a cytoplasmic p53 stabilizer, wherein the glucose metabolism inhibitor is a compound of the disclosure. In some embodiments, the cancer is glioblastoma multiforme.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A shows the enantiomeric purity of synthetic intermediate **5** as determined by chiral SFC (Chiralpak AD-3 column, 40% MeOH). **FIG. 1B** shows the enantiomeric purity of synthetic intermediate **(S)-5** as determined by chiral SFC (Chiralpak AD-3 column, 40% MeOH). **FIG. 1C** shows the enantiomeric purity of synthetic intermediate **(R)-5** as determined by chiral SFC (Chiralpak AD-3 column, 40% MeOH). **FIG. 1D** shows the disastereomeric purity of Mosher ester derivatives **5** as determined by chiral SFC (Chiralpak AD-3 column, 40% MeOH).

FIG. 2 depicts the activities of erlotinib, lapatinib, gefitinib, and exemplary compounds of the disclosure against U87 EGFRwt.

FIG. 3 depicts the activities of erlotinib, lapatinib, gefitinib, and exemplary compounds of the disclosure against U87 EGFRvIII.

FIG. 4 depicts the activities of erlotinib, lapatinib, gefitinib, and exemplary compounds of the disclosure against HK301, a patient derived, EGFRvIII mutant GBM gliomasphere.

FIG. 5 depicts the activities of erlotinib, lapatinib, gefitinib, and exemplary compounds of the disclosure against GBM39, a patient derived, EGFRvIII mutant GBM gliomasphere.

FIG. 6 depicts the activities of erlotinib, lapatinib, and exemplary compounds of the disclosure in a GBM39 EGFRvIII mutant mouse model.

FIG. 7A depicts the activities of erlotinib and exemplary compounds of the disclosure in a HCC827 lung cancer EGFR mutant cell line. **FIG. 7B** depicts the activities of erlotinib and exemplary compounds of the disclosure in a PC9 lung cancer EGFR mutant cell line. **FIG. 7C** depicts the activities of erlotinib and exemplary compounds of the disclosure in a H838 lung cancer mutant cell line.

FIG. 8 depicts the activities of erlotinib and exemplary compounds of the disclosure in a PC9 lung cancer EGFR mutant mouse model.

FIG. 9 depicts certain metabolites of exemplary compounds of the disclosure.

FIG. 10A depicts the activities of exemplary compounds of the disclosure against HK301.

FIG. 10B depicts the activities of exemplary compounds of the disclosure against GBM39. **FIG. 10C** depicts the activities of exemplary compounds of the disclosure against NHA.

FIG. 11A decpits the ADME characteristics of an exemplary compound of the disclosure in rats following PO admistration.

FIG. 11B decpits the ADME characteristics of an exemplary compound of the disclosure in rats following PO admistration.

FIG. 12A depicts the activity of certain compounds of the disclosure as compared against the current standard of care (i.e., Labpatinib, Erlotinib, Gefitinib, and AZD3759) against HK301, a patient derived, EGFRvIII mutant GBM gliomasphere.

FIG. 12B depicts the activity of certain compounds of the disclosure as compared against the current standard of care (i.e., Labpatinib, Erlotinib, Gefitinib, and AZD3759) against HK301, a patient derived, EGFRvIII mutant GBM gliomasphere.

FIG. 13A depicts the activity of certain compounds of the disclosure as compared against the current standard of care (i.e., Labpatinib, Erlotinib, Gefitinib, and AZD3759) against GBM39, a patient derived, EGFRvIII mutant GBM gliomasphere. **FIG. 13B** depicts the activity of certain compounds of the disclosure as compared against the current standard

of care (i.e., Labpatinib, Erlotinib, Gefitinib, and AZD3759) against GBM39, a patient derived, EGFRvIII mutant GBM gliomasphere.

FIG. 14A depicts the activity of AZD3759, AZD9291, and JGK068S against certain EGFR mutants. **FIG. 14B** depicts the activity of AZD3759, AZD9291, and JGK068S against pEGFR A263P. **FIG. 14C** depicts the activity of AZD3759, AZD9291, and JGK068S against pEGFR A289V. **FIG. 14D** depicts the activity of AZD3759, AZD9291, and JGK068S against pEGFR A289D. **FIG. 14E** depicts the activity of AZD3759, AZD9291, and JGK068S against pEGFR G598V.

FIG. 15A depicts the activity of certain compounds of the disclosure.

FIG. 15B depicts the activity of certain compounds of the disclosure.

DETAILED DESCRIPTION OF THE DISCLOSURE

Gliomas are the most commonly occurring form of brain tumor, with glioblastoma multiforme (GBM) being most malignant form, causing 3–4% of all cancer-related deaths (Louis et al. (2007) *Acta. Neuropathol.* 114: 97-109.). The World Health Organization defines GBM as a grade IV cancer characterized as malignant, mitotically active, and predisposed to necrosis. GBM has a very poor prognosis with a 5-year survival rate of 4–5% with the median survival rate of GBM being 12.6 months (McLendon et al. (2003) *Cancer.* 98 :1745-1748.). This can be attributed to unique treatment limitations such as a high average age of onset, tumor location, and poor current understandings of the tumor pathophysiology (Louis et al. (2007) *Acta. Neuropathol.* 114: 97-109).The current standard of care for GBM includes tumor resection with concurrent radiotherapy and chemotherapy and in recent years there have been few marked improvements that increase survival rates (Stewart, et al. (2002) *Lancet.* 359:1011-1018.).

The standard for GBM chemotherapy is temozolomide (TMZ), which is a brain-penetrant alkylating agent that methylates purines (A or G) in DNA and induces apoptosis (Stupp, et al. (2005) *N. Engl. J. Med.* 352:987-996). However, TMZ use has drawbacks in that significant risk arises from DNA damage in healthy cells and that GBM cells can rapidly develop resistance towards the drug (Carlsson, et al. (2014) *EMBO. Mol. Med.* 6: 1359-1370). As such, additional chemotherapy options are urgently required.

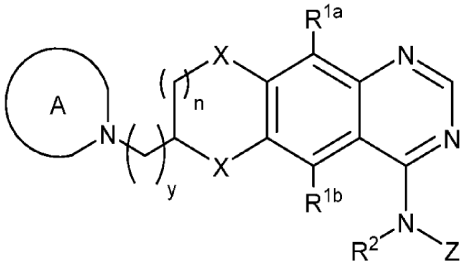
EGFR is a member of the HER superfamily of receptor tyrosine kinases together with ERBB2, ERBB3, and ERBB4. A common driver of GBM progression is EGFR amplification, which is found in nearly 40% of all GBM cases (Hynes et al. (2005) *Nat. Rev.*

Cancer. 5: 341-354; Hatanpaa et al. (2010) *Neoplasia*. 12 :675-684). Additionally, EGFR amplification is associated with the presence of EGFR protein variants: in 68% of EGFR mutants there is a deletion in the N-terminal ligand-binding region between amino acids 6 and 273. These deletions in the ligand-binding domains of EGFR can lead to ligand-independent activation of EGFR (Yamazaki et al. (1990) *Jpn. J. Cancer Res.* 81: 773-779.).

Thus, there is a need for potent tyrosine kinase inhibitors that have the ability to cross the blood brain barrier and inhibit EGFR and its isoforms.

Compounds of the Disclosure

In one aspect, the present disclosure provides compounds having a structure represented by Formula Ia, Ib, Ic, or Id:



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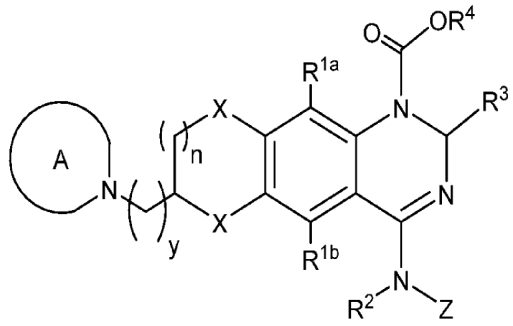

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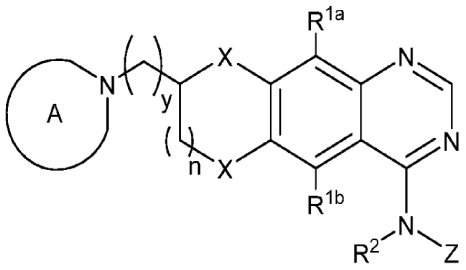

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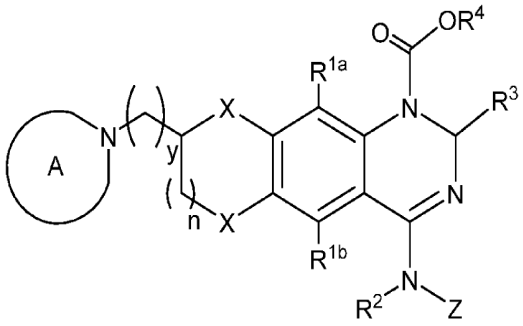


Id

or a pharmaceutically acceptable salt thereof, wherein:

A is a heterocyclyl;

Z is aryl or heteroaryl;

each X is independently selected from O, S, and NH;

R^{1a} and R^{1b} are each independently selected from hydrogen, alkyl, halo, CN, and NO_2;

R^2 is hydrogen, alkyl, or acyl;

R^3 is alkoxy;

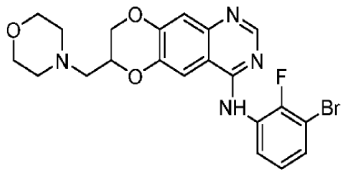
R^4 is alkyl;

n is 1-3; and

y is 1-3.

In certain embodiments, the compounds disclosed herein have improved properties as compared to those known in the art (e.g., increased solubility, metabolic stability, bioavailability, brain penetration, potency, selectivity, and reduced toxicity). For example, the compounds have a decreased basicity as compared to those known in the art.

In certain embodiments, the compound is not selected from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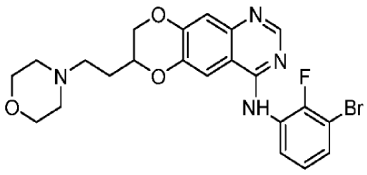
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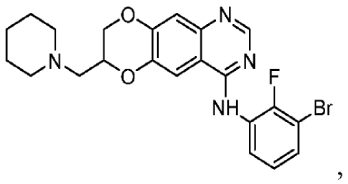
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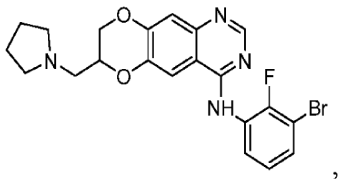
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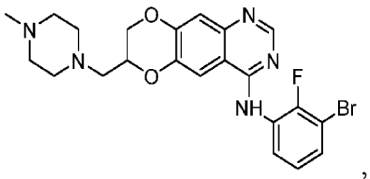
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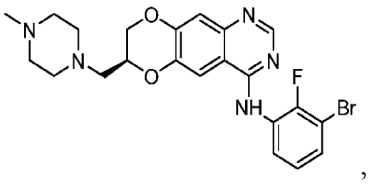
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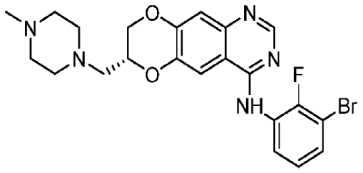
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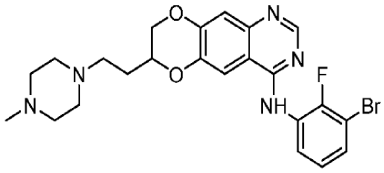
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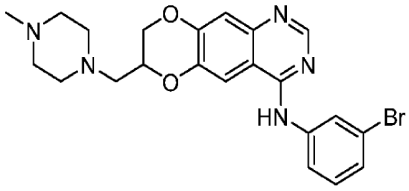
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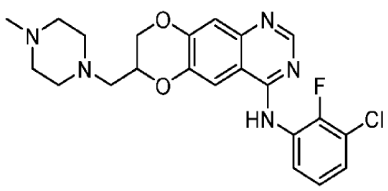
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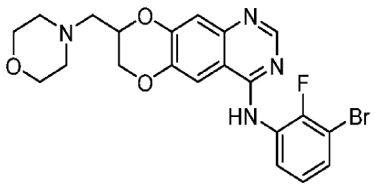
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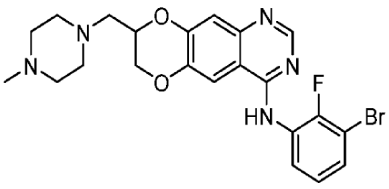
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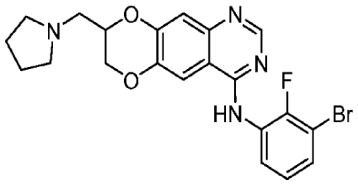
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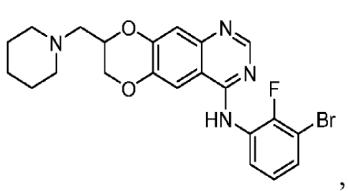
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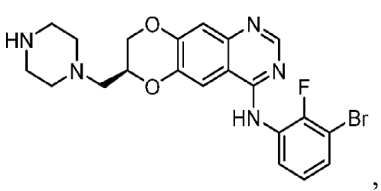
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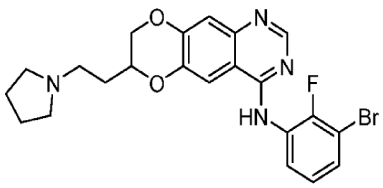
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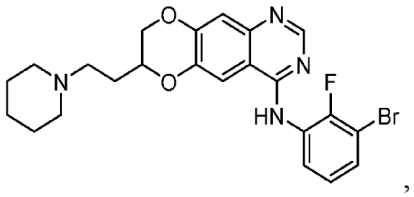
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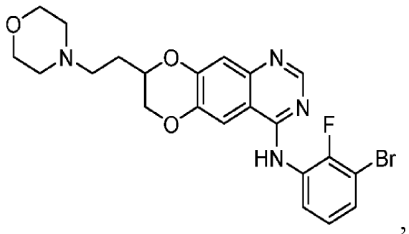
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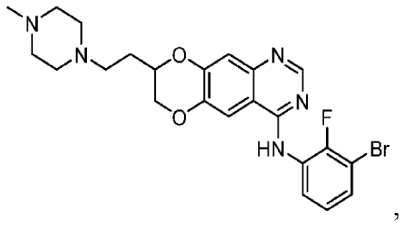
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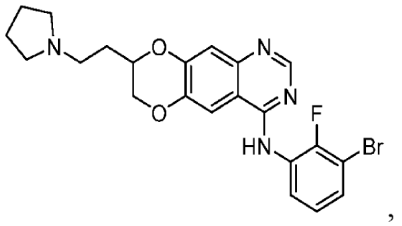
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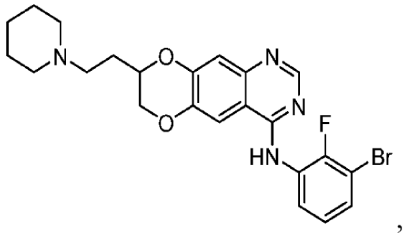
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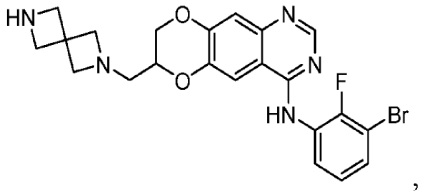
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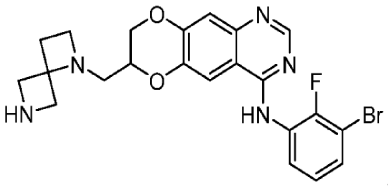
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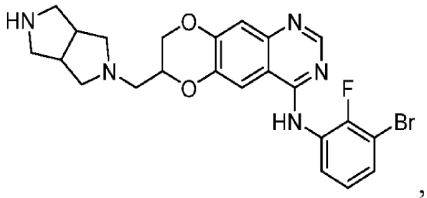
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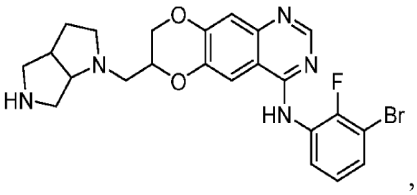
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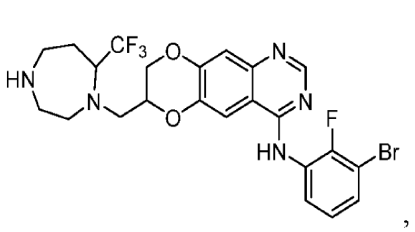
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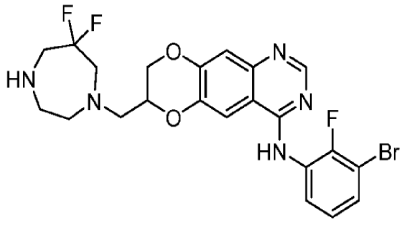
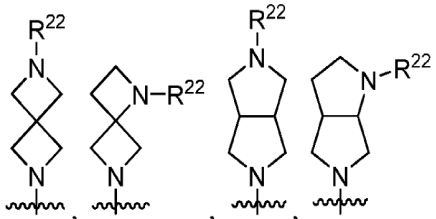
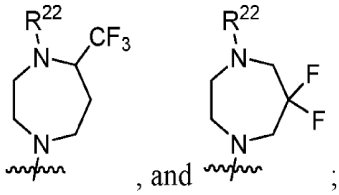

; or a pharmaceutically acceptable salt thereof.

In certain embodiments of Formula I, A is not diazepanyl substituted with fluoro (e.g., 6,6-difluorodiazepanyl) or a bicycle (e.g., a spirocycle).

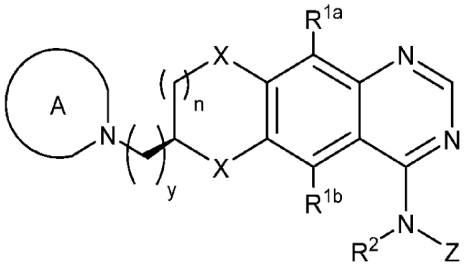
In certain embodiments of Formula I, A is not 6,6-difluorodiazepanyl or a spirocycle.

In certain embodiments of Formula I, A is not diazepanyl or a bicycle.

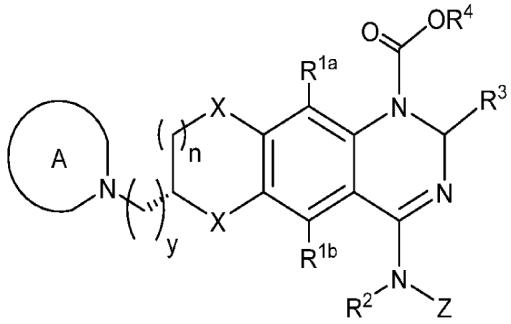
In certain embodiments of Formula I, A is not  ,  , and ; and

R^{22} is selected from C_1-C_6 alkyl and C_3-C_6 cycloalkyl, each of which is optionally substituted with one or more halogen, or a pharmaceutically acceptable salt thereof.

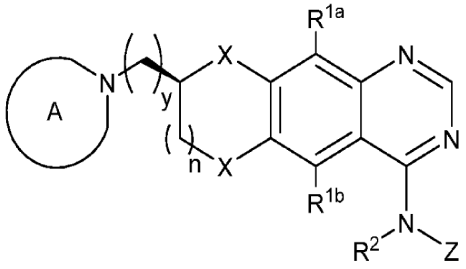
In certain embodiments, the compound has a structure represented by Formula Ie, If, Ig, or Ih:



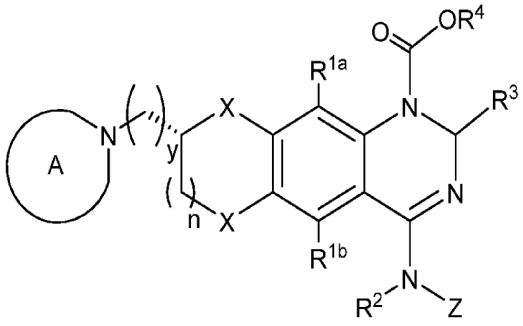
Ie



If



Ig



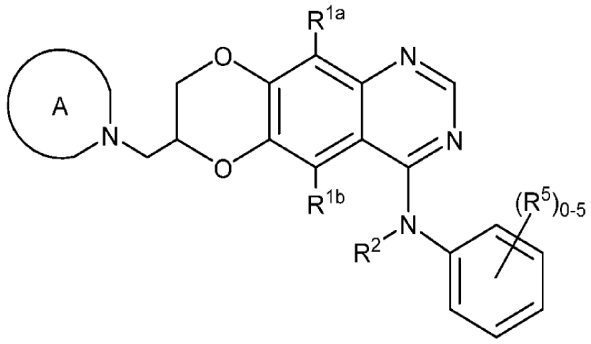
Ih

or a pharmaceutically acceptable salt thereof.

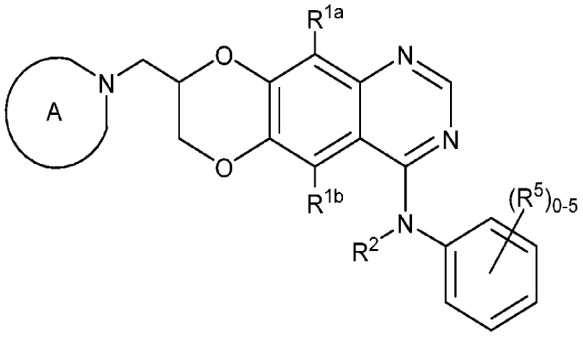
In certain embodiments of Formula I, if R^{1a} is hydrogen, then R^{1b} is selected from alkyl, halo, CN, and NO_2. In other embodiments of Formula I, if R^{1b} is hydrogen, then R^{1a} is

selected from alkyl, halo, CN, and NO_2. In yet other embodiments of Formula I, R^{1a} or R^{1b} is selected from alkyl, halo, CN, and NO_2.

In certain embodiments of Formula I, the compound has a structure represented by Formula IIa or IIb:



IIa

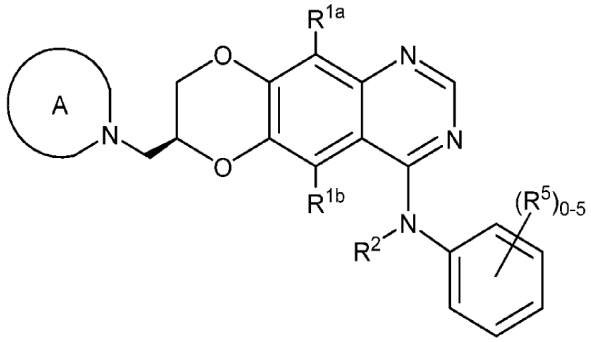


IIb

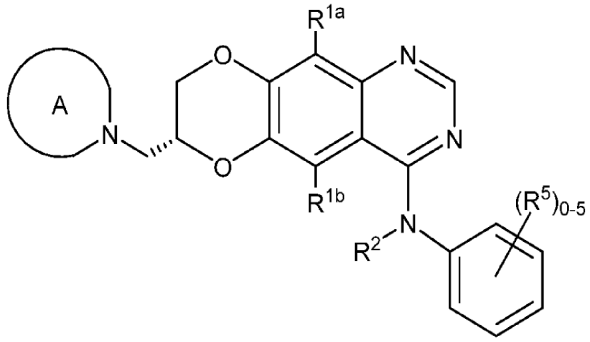
or a pharmaceutically acceptable salt thereof, wherein

each instance of R^5 is independently selected from alkyl, alkenyl, alkynyl, halo, hydroxyl, carboxyl, acyl, acetyl, ester, thioester, alkoxy, phosphoryl, amino, amide, cyano, nitro, azido, alkylthio, alkenyl, alkynyl, cycloalkyl, heterocyclylalkyl, heteroaralkyl, sulfonamide, aryl, heteroaryl, heterocyclyl, and aralkyl.

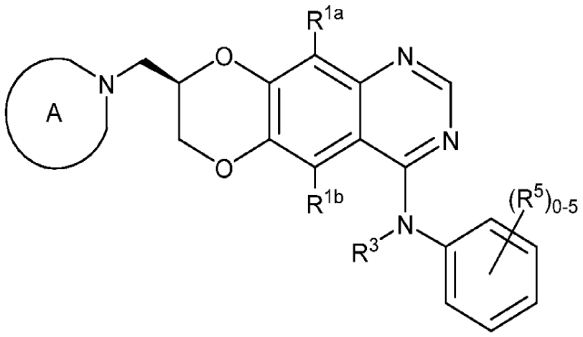
In certain embodiments of Formula I or II, the compound has a structure represented by Formula IIc, IId, IIe, or IIf:



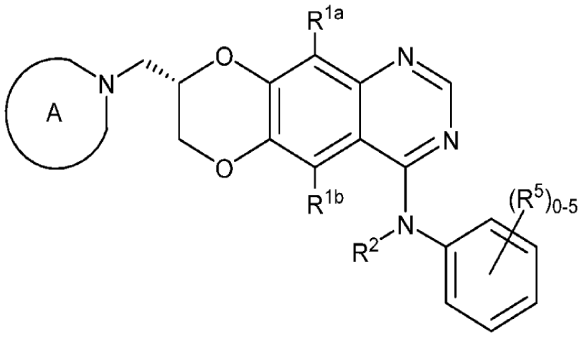
IIc



IId

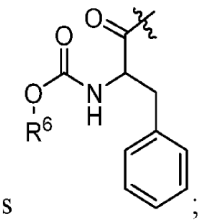


IIe



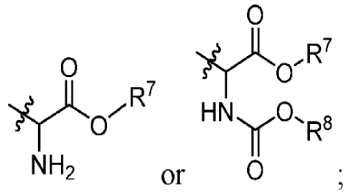
IIf

or a pharmaceutically acceptable salt thereof.

In certain embodiments of Formula I or Formula II, R^2 is hydrogen. In certain preferred embodiments, R^2 is H. In other embodiments, R^2 is acyl. In yet other embodiments R^2 is alkylacyl. In yet further embodiments, R^2 is alkyloxyacyl. In yet further embodiments, R^2 is acyloxyalkyl. In certain embodiments, R^2 is  ; and

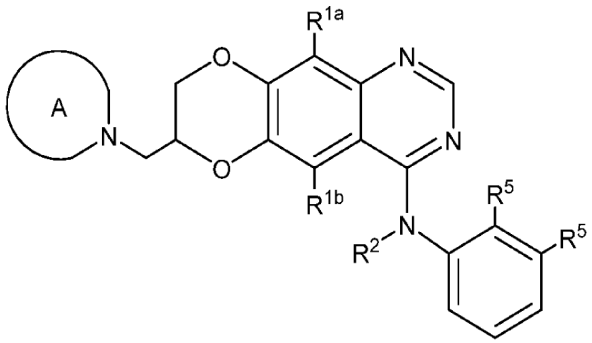
R^6 is alkyl.

In certain embodiments of Formula I or II, Z is 2-fluoro-3-chlorophenyl, 2-fluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,4,6-trifluorophenyl, pentafluorophenyl, 2-fluoro-3-bromophenyl, 2-fluoro-3-ethynylphenyl, and 2-fluoro-3-(trifluoromethyl)phenyl. In certain embodiments, Z is 3-ethynylphenyl. In certain embodiments, Z is 3-chloro-4-((3-fluorobenzyl)oxy)benzene. In certain embodiments, Z is 3-chloro-2-(trifluoromethyl)phenyl. In certain preferred embodiments, Z is 2-fluoro-3-bromophenyl. In certain embodiments, Z is 2-fluoro-5-bromophenyl. In certain embodiments, Z is 2,6-difluoro-5-bromophenyl. In certain embodiments, Z is substituted with one R^5 selected from

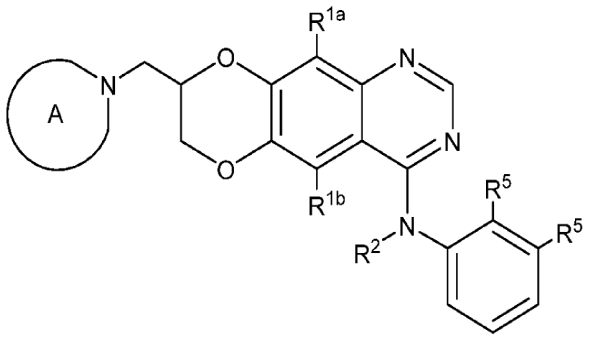
 or ; and

R^7 and R^8 are independently selected from alkyl.

In certain embodiments of Formula I or II, the compound has a structure represented by Formula IIIa or IIIb:



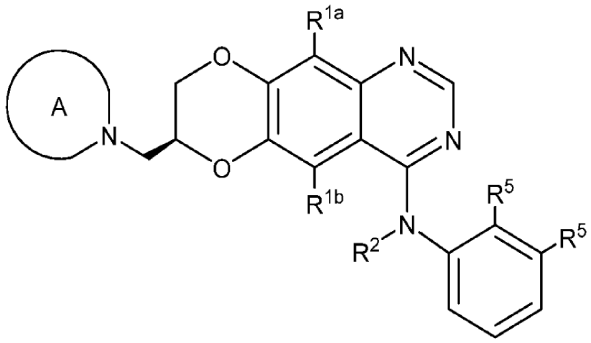
IIIa



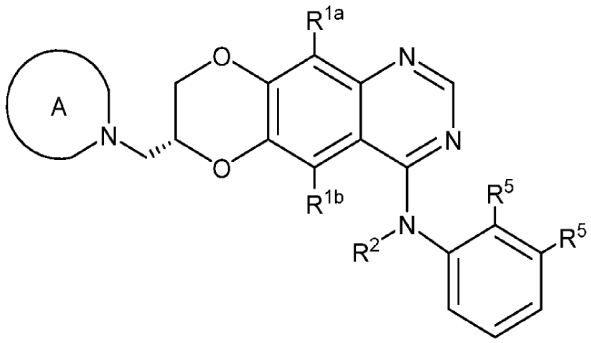
IIIb

or a pharmaceutically acceptable salt thereof.

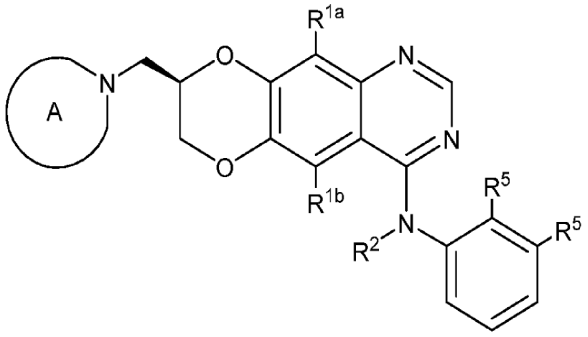
In certain embodiments of Formula I, II, or III, the compound has a structure represented by formula IIIc, IIId, IIIe, or IIIf:



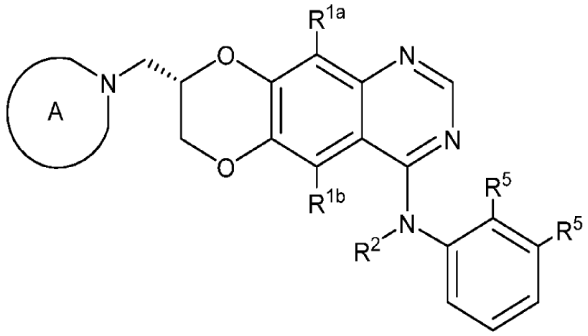
IIIc



IIId



IIIe



IIIf

or a pharmaceutically acceptable salt thereof.

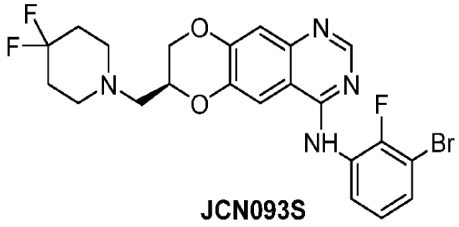
In certain embodiments of Formula I, II, or III, R^{1a} is hydrogen. In other embodiments, R^{1a} is halo (e.g., fluoro).

In certain embodiments of Formula I, II, or III, R^{1b} is hydrogen. In other embodiments, R^{1b} is halo (e.g., fluoro).

In certain preferred embodiments of Formula I, II, or III, A is azetidinyl, piperidinyl, piperazinyl, diazepanyl, or diazabicycloheptanyl.

In certain embodiments of Formula I, II, or III, A is substituted with alkyl, alkenyl, alkynyl, halo, hydroxyl, carboxyl, acyl, acetyl, ester, thioester, alkoxy, phosphoryl, amino, amide, cyano, nitro, azido, alkylthio, alkenyl, alkynyl, cycloalkyl, heterocyclylalkyl, heteroaralkyl, sulfonamide, aryl, heteroaryl, heterocyclyl, and aralkyl. In certain preferred embodiments, A is substituted with alkyl (e.g., methyl or trifluoromethyl), amino (e.g., alkylamino, such as methylamino or trifluoromethylamino; or acylamino, such as acetylamino), or halo (e.g., fluoro).

In one aspect, the compound of the disclosure is selected from



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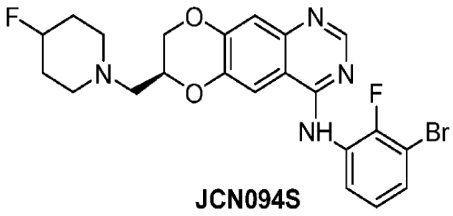

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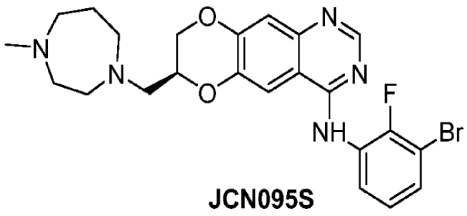

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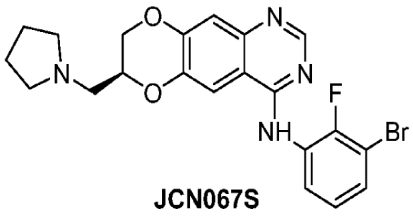

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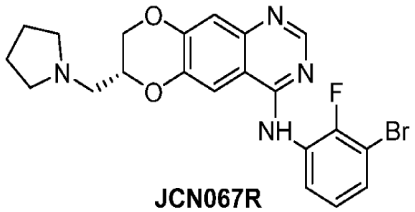

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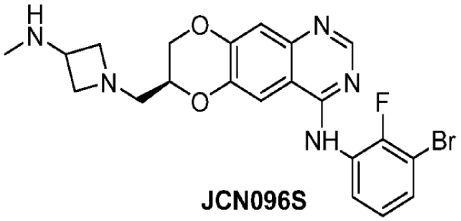

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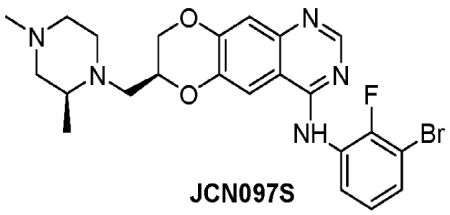

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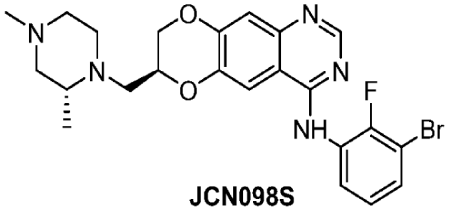

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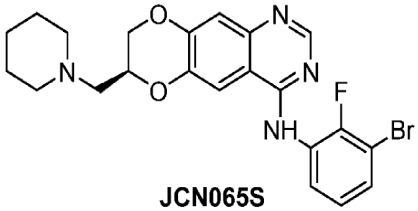

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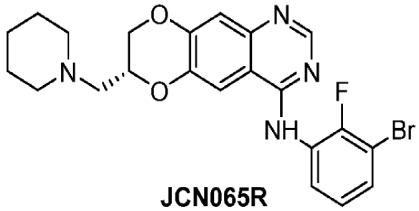

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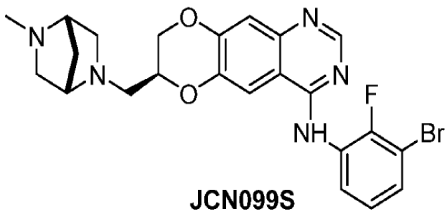

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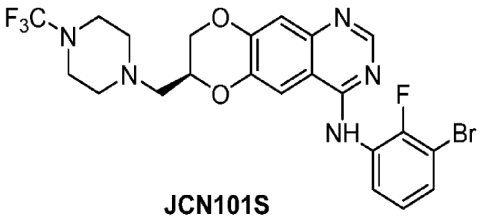

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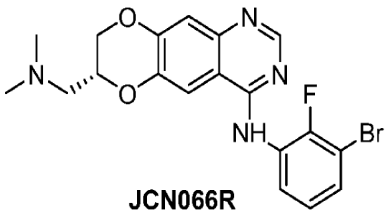

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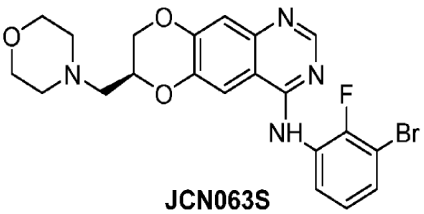

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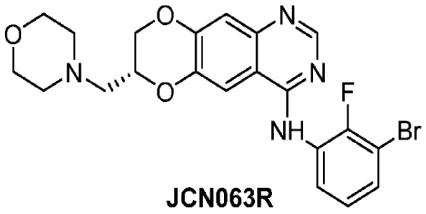

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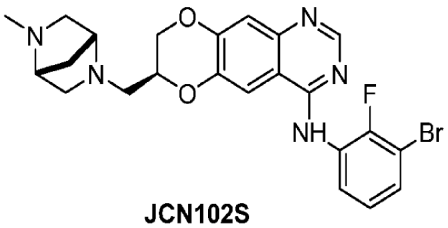

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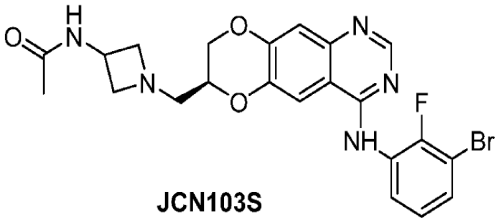


JCN103S ; or a pharmaceutically acceptable salt thereof.

Compounds, methods of treatment, and methods of preparation related to those disclosed herein are disclosed in PCT/US2018/052858, filed September 26, 2020, and PCT/US2020/022743, filed March 13, 2020, the contents of each of which are fully incorporated by reference herein.

Methods of Treatment

In certain aspects, the present disclosure provides methods of inhibiting EGFR or ΔEGFR, comprising administering to a subject an amount of a compound of the disclosure.

In certain aspects, the present disclosure provides methods of treating cancer comprising of administering to a subject in need of a treatment for cancer an amount of a compound of the disclosure. In certain embodiments, the cancer is bladder cancer, bone cancer, brain cancer, breast cancer, cardiac cancer, cervical cancer, colon cancer, colorectal cancer, esophageal cancer, fibrosarcoma, gastric cancer, gastrointestinal cancer, head, spine and neck cancer, Kaposi's sarcoma, kidney cancer, leukemia, liver cancer, lymphoma, melanoma, multiple myeloma, pancreatic cancer, penile cancer, testicular germ cell cancer, thymoma carcinoma, thymic carcinoma, lung cancer, ovarian cancer, or prostate cancer. In certain embodiments, the cancer is glioma, astrocytoma or glioblastoma. In certain embodiments, the cancer is glioblastoma. In certain embodiments, the cancer is glioblastoma multiforme. In certain embodiments, the method reduces cancer cell proliferation.

In certain aspects, the present disclosure provides methods of treating cancer in a subject, the method comprising administering to the subject a glucose metabolism inhibitor and an additional agent, wherein the glucose metabolism is a compound of the disclosure or a pharmaceutically acceptable salt thereof and the additional agent is a cytoplasmic p53 stabilizer. In certain embodiments, the cancer is bladder cancer, bone cancer, brain cancer,

breast cancer, cardiac cancer, cervical cancer, colon cancer, colorectal cancer, esophageal cancer, fibrosarcoma, gastric cancer, gastrointestinal cancer, head, spine and neck cancer, Kaposi's sarcoma, kidney cancer, leukemia, liver cancer, lymphoma, melanoma, multiple myeloma, pancreatic cancer, penile cancer, testicular germ cell cancer, thymoma carcinoma, thymic carcinoma, lung cancer, ovarian cancer, or prostate cancer. In certain embodiments, the cancer is glioma, astrocytoma or glioblastoma. In certain embodiments, the cancer is glioblastoma. In certain embodiments, the cancer is glioblastoma multiforme. In certain embodiments, the method reduces cancer cell proliferation. In certain embodiments, the cancer is relapsed or refractory. In other embodiments, the cancer is treatment naïve.

In certain embodiments, the subject has been determined to be susceptible to the glucose metabolism inhibitor by a method comprising:

a. obtaining a first blood sample from the subject;
b. placing the subject on a ketogenic diet;
c. obtaining a second blood sample from the subject after being placed on a ketogenic diet for a period of time;
d. measuring glucose level in the first and in the second blood sample;
e. comparing the glucose level in the second blood sample with the glucose level in the first blood sample; and
f. determining that the subject is susceptible if the glucose level in the second blood sample is reduced as compared to glucose levels in the first blood sample.

In certain embodiments, the reduction in the glucose level between the second blood sample and the first blood sample is about or greater than 0.15 mM. In certain embodiments, the reduction in the glucose level between the second blood sample and the first blood sample is about or greater than 0.20 mM. In certain embodiments, the reduction in the glucose level between the second blood sample and the first blood sample is in the range of 0.15 mM - 2.0 mM. In certain embodiments, the reduction in the glucose level between the second blood sample and the first blood sample is in the range of 0.25 mM – 1.0 mM.

In certain embodiments, the cytoplasmic p53 stabilizer is an MDM2 inhibitor. In certain embodiments, the MDM2 inhibitor is a nutlin. In certain embodiments, the MDM2 inhibitor is nutlin-3 or idasanutlin. In certain embodiments, the subject is administererd 50 mg to 1600 mg of idasanutlin. In certain embodiments, the subject is administererd 100 mg of idasanutlin. In certain embodiments, the subject is administered 150 mg of

idasanutlin. In certain embodiments, the subject is administered 300 mg of idasanutlin. In certain embodiments, the subject is administered 400 mg of idasanutlin. In certain embodiments, the subject is administered 600 mg of idasanutlin. In certain embodiments, the subject is administered 1600 mg of idasanutlin. In other embodiments, the MDM2 inhibitor is RO5045337, RO5503781, RO6839921, SAR405838, DS-3032, DS-3032b, or AMG-232.

In certain embodiments, the cytoplasmic p53 stabilizer is a BCL-2 inhibitor. In certain embodiments, the BCL-2 inhibitor is antisense oligodeoxynucleotide G3139, mRNA antagonist SPC2996, venetoclax (ABT-199), GDC-0199, obatoclax, paclitaxel, navitoclax (ABT-263), ABT-737, NU-0129, S 055746, or APG-1252.

In certain embodiments, the cytoplasmic p53 stabilizer is a Bcl-xL inhibitor. In certain embodiments, the Bcl-xL inhibitor is WEHI 539, ABT-263, ABT-199, ABT-737, sabutoclax, AT101, TW-37, APG-1252, or gambogic acid.

In certain embodiments, the glucose metabolism inhibitor and the cytoplasmic p53 stabilizer are administered in the same composition. In other embodiments, the glucose metabolism inhibitor and the cytoplasmic p53 stabilizer are administered in separate compositions.

In certain embodiments, the method further comprises administration of an additional therapy.

Types and stages of Gliomas

Primary malignant brain tumors are tumors that start in the brain or spine are known collectively as gliomas. Gliomas are not a specific type of cancer but are a term used to describe tumors that originate in glial cells. Examples of primary malignant brain tumors include astrocytomas, pilocytic astrocytomas, pleomorphic xanthoastrocytomas, diffuse astrocytomas, anaplastic astrocytomas, GBMs, gangliogliomas, oligodendrogliomas, ependymomas. According to the WHO classification of brain tumors, astrocytomas have been categorized into four grades, determined by the underlying pathology. The characteristics that are used to classify gliomas include mitoses, cellular or nuclear atypia, and vascular proliferation and necrosis with pseudopalisading features. Malignant (or high-grade) gliomas include anaplastic glioma (WHO grade III) as well as glioblastoma multiforme (GBM; WHO grade IV). These are the most aggressive brain tumors with the worst prognosis.

GBMs is the most common, complex, treatment resistant, and deadliest type of brain cancer, accounting for 45% of all brain cancers, with nearly 11,000 men, women, and children diagnosed each year. GBM (also known as grade-4 astrocytoma and glioblastoma multiforme) are the most common types of malignant (cancerous) primary brain tumors. They are extremely aggressive for a number of reasons. First, glioblastoma cells multiply quickly, as they secrete substances that stimulate a rich blood supply. They also have an ability to invade and infiltrate long distances into the normal brain by sending microscopic tendrils of tumor alongside normal cells. Two types of glioblastomas are known. Primary GBM are the most common form; they grow quickly and often cause symptoms early. Secondary glioblastomas are less common, accounting for about 10 percent of all GBMs. They progress from low-grade diffuse astrocytoma or anaplastic astrocytoma, and are more often found in younger patients. Secondary GBM are preferentially located in the frontal lobe and carry a better prognosis.

GBM is usually treated by combined multi-modal treatment plan including surgical removal of the tumor, radiation and chemotherapy. First, as much tumor as possible is removed during surgery. The tumor's location in the brain often determines how much of it can be safely removed. After surgery, radiation and chemotherapy slow the growth of remaining tumor cells. The oral chemotherapy drug temozolomide is most often used for six weeks, and then monthly thereafter. Another drug, bevacizumab (known as Avastin®), is also used during treatment. This drug attacks the tumor's ability to recruit blood supply, often slowing or even stopping tumor growth.

Novel investigational treatments are also used and these may involve adding treatments to the standard therapy or replacing one part of the standard therapy with a different treatment that may work better. Some of these treatments include immunotherapy such as vaccine immunotherapies, or low-dose pulses of electricity to the area of the brain where the tumor exists and nano therapies involving spherical nucleic acids (SNAs) such as NU-0129. In some embodiments, the methods of the current disclosure are used in combination with one or more of the aforementioned therapies.

Embodiments of the methods and compositions discussed herein are also contemplated to be applicable to other types of cancers, including but not limited to lung cancer, non-CNS cancers, CNS cancers, and CNS metastases such as brain metastases, leptomeningeal metastases, choroidal metastases, spinal cord metastases, and others.

Cytoplasmic p53 Stabilizers

The inventors have demonstrated that the pharmacological p53 stabilization, such as with a CNS-penetrant small molecule, for example, was synergistically lethal with the inhibition of EGFR-driven glucose uptake in patient-derived, primary GBM models. The inventors have demonstrated, for the first time, that the non-transcriptional functions of p53 can have a critical role in stimulating intrinsic apoptosis in metabolic responders. Accordingly, the methods of treatment described herein comprise the administration of cytoplasmic p53 stabilizer(s) in combination with glucose metabolism inhibitors. Cytoplasmic p53 stabilizer(s) and glucose metabolism inhibitors can be administered in the same or in different compositions, cocomitantly or sequentially. It is contemplated that in some embodiments a single p53 stabilizer is used and in other embodiments more than on p53 stabilizer is used. For example, the combination of nutlin with ABT 737 (which binds BCL-2 and BCL-X_L) is reported to synergistically target the balance of pro-apoptotic and anti-apotptoic proteins at the mitochondrial level, thereby promoting cell death. (Hoe *et al.* 2014. Nature Reviews. Vol. 13. pp. 217) As intended herein, a cytoplasmic p53 stabilizer is any small molecule, antibody, peptide, protein, nucleic acid or derivatives thereof that can pharmacologically stabilize or activate p53 directly or indirectly. The stabilization of cytoplasmic p53 leads to priming cells, such as cancer cells, for apoptosis.

MDM2 *antagonists*

Protein levels of p53 within cells are tightly controlled and kept low by its negative regulator, the E3 ubiquitin protein ligase MDM2. In embodiments of the methods or composition of the current disclosure, the cytoplasmic p53 stabilizer is an MDM2 antagonist/inhibitor. In some embodiments, the MDM2 antagonist is a nutlin. In further embodiments, the nutlin is nutlin-3 or idasanutlin. In other embodiments, the MDM2 antagonist is RO5045337 (also known as RG7112), RO5503781, RO6839921, SAR405838 (also known as MI-773), DS-3032, DS-3032b, or AMG-232 or any other MDM2 inhibitor.

Other compounds within the scope of the current methods known to bind MDM-2 include Ro-2443, MI-219, MI-713, MI-888, DS-3032b, benzodiazepinediones (for example, TDP521252), sulphonamides (for example, NSC279287), chromenotriazolopyrimidine, morpholinone and piperidinones (AM-8553), terphenyls, chalcones, pyrazoles, imidazoles, imidazole-indoles, isoindolinone, pyrrolidinone (for example, PXN822), priaxon, piperidines, naturally derived prenylated xanthones, SAH-8 (stapled peptides) sMTide-02, sMTide-02a

(stapled peptides), ATSP-7041 (stapled peptide), spiroligomer (α-helix mimic). Other compounds that are known to cause protein folding of MDM2 include PRIMA-1MET (also known as APR-246) Aprea 102–105, PK083, PK5174, PK5196, PK7088, benzothiazoles, stictic acid and NSC319726.

BCL-2 Inhibitors

In further embodiments of the current methods or compositions, the cytoplasmic p53 stabilizer is a BCL-2 inhibitor. In some embodiments, the BCL-2 inhibitor is, for example, antisense oligodeoxynucleotide G3139, mRNA antagonist SPC2996, venetoclax (ABT-199), GDC-0199, obatoclax, paclitaxel, navitoclax (ABT-263), ABT-737, NU-0129, S 055746, APG-1252 or any other BCL-2 inhibitor.

Bcl-xL Inhibitors

In yet further embodiments of the current methods or compositions, the cytoplasmic p53 stabilizer is a Bcl-xL inhibitor. In some embodiments, the Bcl-xL inhibitor is, for example, WEHI 539, ABT-263, ABT-199, ABT-737, sabutoclax, AT101, TW-37, APG-1252, gambogic acid or any other Bcl-xL inhibitor.

Methods of Assessment

Glucose Uptake Tests

In embodiments of the methods and compositions of the current disclosure, the subject with GBM or cancer is classified to be either a "metabolic responder" or a "metabolic non-responder" *i.e.* determined to be susceptible to glucose metabolism inhibitors. In certain embodiments, the classification of the subject is prior to administering to the subject a treatment comprising a glucose metabolism inhibitor and a cytoplasmic p53 stabilizer. Accordingly, the current disclosure provides for methods for assessing a cancer, classifying a subject, determining the susceptibility of a subject to treatments involve analysis of glucose metabolism, glycolysis or glucose uptake. Methods to classify a subject as a metabolic responder is described in details in Example 1. Techniques to monitor glycolysis and glucose uptake is provided by T. TeSlaa and M.A. Teitell. 2014. Methods in Enzymology, Volume 542, pp. 92-114, incorporated herein by reference.

Glycolysis is the intracellular biochemical conversion of one molecule of glucose into two molecules of pyruvate with the concurrent generation of two molecules of ATP. Pyruvate is a metabolic intermediate with several potential fates including entrance into the

tricarboxylic acid (TCA) cycle within mitochondria to produce NADH and $FADH_2$. Alternatively, pyruvate can be converted into lactate in the cytosol by lactate dehydrogenase with concurrent regeneration of NAD^+ from NADH. An increased flux through glycolysis supports the proliferation of cancer cells by providing, for example, additional energy in the form of ATP as well as glucose-derived metabolic intermediates for nucleotide, lipid, and protein biosynthesis. Warburg (Oncologia. 1956;9(2):75-83) first observed that proliferating tumor cells augment aerobic glycolysis, the conversion of glucose to lactate in the presence of oxygen, in contrast to nonmalignant cells that mainly respire when oxygen is available. This mitochondrial bypass, called the Warburg effect, occurs in rapidly proliferating cells including cancer cells, activated lymphocytes, and pluripotent stem cells. The Warburg effect has been exploited for clinical diagnostic tests that use positron emission tomography (PET) scanning to identify increased cellular uptake of fluorinated glucose analogs such as 2-deoxy-2-(^{18}F)-fluoro-D-glucose (also referred to herein as ^{18}F-deoxyglucose, ^{18}F-FDG, ^{18}FDG, or FDG)..

Thus, glycolysis represent a target for therapeutic and diagnostic methods. In the context of the current methods, the measurement of glucose uptake and lactate excretion by malignant cells may be useful to detect shifts in glucose catabolism and/or susceptibility to glucose metabolism inhibitors. Detecting such shifts is important for methods of treating GBM, methods of reducing the risk of ineffective therapy, methods for reducing the chances of tumor survival. For the purposes of this disclosure, ^{18}F-deoxyglucose PET serves in certain embodiments as a rapid non-invasive functional biomarker to predict sensitivity to p53 activation. This non-invasive anlaysis could be particularly valuable for malignant brain tumors where pharmacokinetic/pharmacodynamics assessment is extremely difficult and impractical. In some cases, delayed imaging protocols (41) and parametric response maps (PRMs) with MRI fusion can be useful for quantifying the changes in tumore ^{18}F-FDG uptake (42).

In certain aspects, the methods can relate to measuring glucose uptake and lactate production. For cells in culture, glycolytic flux can be quantified by measuring glucose uptake and lactate excretion. Glucose uptake into the cell is through glucose transporters (Glut1–Glut4), whereas lactate excretion is through monocarboxylate transporters (MCT1–MCT4) at the cell membrane.

Extracellular glucose and lactate

Methods to detect glucose uptake and lactate excretion include, for example, extracellular glucose or lactate kit, extracellular bioanalyzer, ECAR measurement, [3H]-2-DG or [14C]-2-DG uptake ^{18}FDG uptake or 2-NBDG uptake.

Commercially available kits and instruments are available to quantify glucose and lactate levels within cell culture media. Kit detection methods are usually colorimetric or fluorometric and are compatible with standard lab equipment such as spectrophotometers. BioProfile Analyzers (such as Nova Biomedical) or Biochemistry Analyzers (such as for example YSI Life Sciences) can measure levels of both glucose and lactate in cell culture media. GlucCell (Cesco BioProducts) can measure only glucose levels in cell culture media. While each commercial method has a different detection protocol, the collection of culture media for analysis is the same.

Extracellular acidification rate

Glycolysis can also be determined through measurements of the extracellular acidification rate (ECAR) of the surrounding media, which is predominately from the excretion of lactic cid per unit time after its conversion from pyruvate. The Seahorse extracellular flux (XF) analyzer (Seahorse Bioscience) is a tool for measuring glycolysis and oxidative phosphorylation (through oxygen consumption) simultaneously in the same cells.

Glucose analog uptake

Certain embodiments of the methods of the current disclosure include the use of glucose analogs. As would be familiar to a person skilled in the art, to determine the glucose uptake rate by cells, a labeled isoform of glucose can be added to the cell culture media and then measured within cells after a given period of time. Exemplary types of glucose analogs for these studies include but are not limited to radioactive glucose analogs, such as 2-deoxy-D-[1,2-3H]-glucose, 2-deoxy-D-[1-14C]-glucose, or 2-deoxy-2-(^{18}F)-fluoro-D-glucose (^{18}FDG), or fluorescent glucose analogs, such as 2-[N-(7-nitrobenz-2-oxa-1,3-diaxol-4-yl)amino]-2-deoxyglucose (2-NBDG). Measurements of radioactive glucose analog uptake require a scintillation counter, whereas 2-NBDG uptake is usually measured by flow cytometry or fluorescent microscopy. In some embodiments, the glucose uptake is measured by the uptake of radio-labelled glucose 2-deoxy-2-[fluorine-18]fluoro- D-glucose (^{18}F-FDG). In further embodiments, detecting the ^{18}F-FDG is by positron emission tomography (PET). In some embodiments, the biopsy is taken from a GBM tumor. A detailed description of an example of measuring ^{18}F-FDG is provided in the examples below.

In certain aspects, the methods can relate to comparing glucose uptake of a biological sample such as a tumor sample with a control. Fold increases or decreases may be, be at least, or be at most 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, 14-, 15-, 16-, 17-, 18-, 19-, 20-, 25-, 30-, 35-, 40-, 45-, 50-, 55-, 60-, 65-, 70-, 75-, 80-, 85-, 90-, 95-, 100- or more, or any range derivable therein. Alternatively, differences in expression between a sample and a reference may be expressed as a percent decrease or increase, such as at least or at most 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 300, 400, 500, 600, 700, 800, 900, 1000% difference, or any range derivable therein.

Other ways to express relative expression levels are with normalized or relative numbers such as 0.001, 0.002, 0.003, 0.004, 0.005, 0.006, 0.007, 0.008, 0.009, 0.01, 0.02, 0.03. 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7. 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, or any range derivable therein. In some embodiments, the levels can be relative to a control.

Algorithms, such as the weighted voting programs, can be used to facilitate the evaluation of biomarker levels. In addition, other clinical evidence can be combined with the biomarker-based test to reduce the risk of false evaluations. Other cytogenetic evaluations may be considered in some embodiments.

Pharmaceutical Compositions

The compositions and methods of the present invention may be utilized to treat an individual in need thereof. In certain embodiments, the individual is a mammal such as a human, or a non-human mammal. When administered to an animal, such as a human, the composition or the compound is preferably administered as a pharmaceutical composition comprising, for example, a compound of the invention and a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well known in the art and include, for example, aqueous solutions such as water or physiologically buffered saline or other solvents or vehicles such as glycols, glycerol, oils such as olive oil, or injectable organic esters. In preferred embodiments, when such pharmaceutical compositions are for human

administration, particularly for invasive routes of administration (i.e., routes, such as injection or implantation, that circumvent transport or diffusion through an epithelial barrier), the aqueous solution is pyrogen-free, or substantially pyrogen-free. The excipients can be chosen, for example, to effect delayed release of an agent or to selectively target one or more cells, tissues or organs. The pharmaceutical composition can be in dosage unit form such as tablet, capsule (including sprinkle capsule and gelatin capsule), granule, lyophile for reconstitution, powder, solution, syrup, suppository, injection or the like. The composition can also be present in a transdermal delivery system, e.g., a skin patch. The composition can also be present in a solution suitable for topical administration, such as a lotion, cream, or ointment.

A pharmaceutically acceptable carrier can contain physiologically acceptable agents that act, for example, to stabilize, increase solubility or to increase the absorption of a compound such as a compound of the invention. Such physiologically acceptable agents include, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. The choice of a pharmaceutically acceptable carrier, including a physiologically acceptable agent, depends, for example, on the route of administration of the composition. The preparation or pharmaceutical composition can be a selfemulsifying drug delivery system or a selfmicroemulsifying drug delivery system. The pharmaceutical composition (preparation) also can be a liposome or other polymer matrix, which can have incorporated therein, for example, a compound of the invention. Liposomes, for example, which comprise phospholipids or other lipids, are nontoxic, physiologically acceptable and metabolizable carriers that are relatively simple to make and administer.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to

the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

A pharmaceutical composition (preparation) can be administered to a subject by any of a number of routes of administration including, for example, orally (for example, drenches as in aqueous or non-aqueous solutions or suspensions, tablets, capsules (including sprinkle capsules and gelatin capsules), boluses, powders, granules, pastes for application to the tongue); absorption through the oral mucosa (e.g., sublingually); subcutaneously; transdermally (for example as a patch applied to the skin); and topically (for example, as a cream, ointment or spray applied to the skin). The compound may also be formulated for inhalation. In certain embodiments, a compound may be simply dissolved or suspended in sterile water. Details of appropriate routes of administration and compositions suitable for same can be found in, for example, U.S. Pat. Nos. 6,110,973, 5,763,493, 5,731,000, 5,541,231, 5,427,798, 5,358,970 and 4,172,896, as well as in patents cited therein.

The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

Methods of preparing these formulations or compositions include the step of bringing into association an active compound, such as a compound of the invention, with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules (including sprinkle capsules and gelatin capsules), cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), lyophile, powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. Compositions or compounds may also be administered as a bolus, electuary or paste.

To prepare solid dosage forms for oral administration (capsules (including sprinkle capsules and gelatin capsules), tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; (10) complexing agents, such as, modified and unmodified cyclodextrins; and (11) coloring agents. In the case of capsules (including sprinkle capsules and gelatin capsules), tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions, such as dragees, capsules (including sprinkle capsules and gelatin capsules), pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms useful for oral administration include pharmaceutically acceptable emulsions, lyophiles for reconstitution, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, cyclodextrins and derivatives thereof, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Dosage forms for the topical or transdermal administration include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to an active compound, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the active compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion. Pharmaceutical compositions suitable for parenteral

administration comprise one or more active compounds in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsulated matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include

poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissue.

For use in the methods of this invention, active compounds can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

Methods of introduction may also be provided by rechargeable or biodegradable devices. Various slow release polymeric devices have been developed and tested *in vivo* in recent years for the controlled delivery of drugs, including proteinaceous biopharmaceuticals. A variety of biocompatible polymers (including hydrogels), including both biodegradable and non-degradable polymers, can be used to form an implant for the sustained release of a compound at a particular target site.

Actual dosage levels of the active ingredients in the pharmaceutical compositions may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound or combination of compounds employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound(s) being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound(s) employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the therapeutically effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the pharmaceutical composition or compound at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. By "therapeutically effective amount" is meant the concentration of a compound that is sufficient to elicit the desired therapeutic effect. It is generally understood that the effective amount of the compound will vary according to the weight, sex, age, and medical history of the subject. Other factors which influence the effective amount may include, but are not limited to, the severity of the patient's condition, the disorder being treated, the stability of the compound,

and, if desired, another type of therapeutic agent being administered with the compound of the invention. A larger total dose can be delivered by multiple administrations of the agent. Methods to determine efficacy and dosage are known to those skilled in the art (Isselbacher et al. (1996) Harrison's Principles of Internal Medicine 13 ed., 1814-1882, herein incorporated by reference).

In general, a suitable daily dose of an active compound used in the compositions and methods of the invention will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above.

If desired, the effective daily dose of the active compound may be administered as one, two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. In certain embodiments of the present invention, the active compound may be administered two or three times daily. In preferred embodiments, the active compound will be administered once daily.

The patient receiving this treatment is any animal in need, including primates, in particular humans; and other mammals such as equines, cattle, swine, sheep, cats, and dogs; poultry; and pets in general.

In certain embodiments, compounds of the invention may be used alone or conjointly administered with another type of therapeutic agent.

The present disclosure includes the use of pharmaceutically acceptable salts of compounds of the invention in the compositions and methods of the present invention. In certain embodiments, contemplated salts of the invention include, but are not limited to, alkyl, dialkyl, trialkyl or tetra-alkyl ammonium salts. In certain embodiments, contemplated salts of the invention include, but are not limited to, L-arginine, benenthamine, benzathine, betaine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)ethanol, ethanolamine, ethylenediamine, N-methylglucamine, hydrabamine, 1H-imidazole, lithium, L-lysine, magnesium, 4-(2-hydroxyethyl)morpholine, piperazine, potassium, 1-(2-hydroxyethyl)pyrrolidine, sodium, triethanolamine, tromethamine, and zinc salts. In certain embodiments, contemplated salts of the invention include, but are not limited to, Na, Ca, K, Mg, Zn or other metal salts. In certain embodiments, contemplated salts of the invention include, but are not limited to, 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-hydroxyethanesulfonic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic

acid, acetic acid, adipic acid, l-ascorbic acid, l-aspartic acid, benzenesulfonic acid, benzoic acid, (+)-camphoric acid, (+)-camphor-10-sulfonic acid, capric acid (decanoic acid), caproic acid (hexanoic acid), caprylic acid (octanoic acid), carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, d-glucoheptonic acid, d-gluconic acid, d-glucuronic acid, glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, l-malic acid, malonic acid, mandelic acid, methanesulfonic acid , naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, proprionic acid, l-pyroglutamic acid, salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, l-tartaric acid, thiocyanic acid, p-toluenesulfonic acid, trifluoroacetic acid, and undecylenic acid acid salts.

The pharmaceutically acceptable acid addition salts can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically acceptable antioxidants include: (1) water-soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal-chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Definitions

Unless otherwise defined herein, scientific and technical terms used in this application shall have the meanings that are commonly understood by those of ordinary skill in the art.

Generally, nomenclature used in connection with, and techniques of, chemistry, cell and tissue culture, molecular biology, cell and cancer biology, neurobiology, neurochemistry, virology, immunology, microbiology, pharmacology, genetics and protein and nucleic acid chemistry, described herein, are those well known and commonly used in the art.

The methods and techniques of the present disclosure are generally performed, unless otherwise indicated, according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout this specification. See, e.g. "Principles of Neural Science", McGraw-Hill Medical, New York, N.Y. (2000); Motulsky, "Intuitive Biostatistics", Oxford University Press, Inc. (1995); Lodish et al., "Molecular Cell Biology, 4th ed.", W. H. Freeman & Co., New York (2000); Griffiths et al., "Introduction to Genetic Analysis, 7th ed.", W. H. Freeman & Co., N.Y. (1999); and Gilbert et al., "Developmental Biology, 6th ed.", Sinauer Associates, Inc., Sunderland, MA (2000).

Chemistry terms used herein, unless otherwise defined herein, are used according to conventional usage in the art, as exemplified by "The McGraw-Hill Dictionary of Chemical Terms", Parker S., Ed., McGraw-Hill, San Francisco, C.A. (1985).

All of the above, and any other publications, patents and published patent applications referred to in this application are specifically incorporated by reference herein. In case of conflict, the present specification, including its specific definitions, will control.

The term "agent" is used herein to denote a chemical compound (such as an organic or inorganic compound, a mixture of chemical compounds), a biological macromolecule (such as a nucleic acid, an antibody, including parts thereof as well as humanized, chimeric and human antibodies and monoclonal antibodies, a protein or portion thereof, e.g., a peptide, a lipid, a carbohydrate), or an extract made from biological materials such as bacteria, plants, fungi, or animal (particularly mammalian) cells or tissues. Agents include, for example, agents whose structure is known, and those whose structure is not known.

A "patient," "subject," or "individual" are used interchangeably and refer to either a human or a non-human animal. These terms include mammals, such as humans, primates, livestock animals (including bovines, porcines, etc.), companion animals (e.g., canines, felines, etc.) and rodents (e.g., mice and rats).

"Treating" a condition or patient refers to taking steps to obtain beneficial or desired results, including clinical results. Beneficial or desired clinical results can include, but are

not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of disease, stabilized (i.e. not worsening) state of disease, preventing spread of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

The term "preventing" is art-recognized, and when used in relation to a condition, such as a local recurrence (e.g., pain), a disease such as cancer, a syndrome complex such as heart failure or any other medical condition, is well understood in the art, and includes administration of a composition which reduces the frequency of, or delays the onset of, symptoms of a medical condition in a subject relative to a subject which does not receive the composition. Thus, prevention of cancer includes, for example, reducing the number of detectable cancerous growths in a population of patients receiving a prophylactic treatment relative to an untreated control population, and/or delaying the appearance of detectable cancerous growths in a treated population versus an untreated control population, e.g., by a statistically and/or clinically significant amount.

"Administering" or "administration of" a substance, a compound or an agent to a subject can be carried out using one of a variety of methods known to those skilled in the art. For example, a compound or an agent can be administered, intravenously, arterially, intradermally, intramuscularly, intraperitoneally, subcutaneously, ocularly, sublingually, orally (by ingestion), intranasally (by inhalation), intraspinally, intracerebrally, and transdermally (by absorption, e.g., through a skin duct). A compound or agent can also appropriately be introduced by rechargeable or biodegradable polymeric devices or other devices, e.g., patches and pumps, or formulations, which provide for the extended, slow or controlled release of the compound or agent. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

Appropriate methods of administering a substance, a compound or an agent to a subject will also depend, for example, on the age and/or the physical condition of the subject and the chemical and biological properties of the compound or agent (e.g., solubility, digestibility, bioavailability, stability and toxicity). In some embodiments, a compound or an agent is administered orally, e.g., to a subject by ingestion. In some embodiments, the orally administered compound or agent is in an extended release, slow release formulation,

extended release, delayed release, or delayed and extended release, or administered using a device for such slow release, extended release, delayed release, or delayed and extended release.

As used herein, the phrase "conjoint administration" refers to any form of administration of two or more different therapeutic agents such that the second agent is administered while the previously administered therapeutic agent is still effective in the body (e.g., the two agents are simultaneously effective in the patient, which may include synergistic effects of the two agents). For example, the different therapeutic compounds can be administered either in the same formulation or in separate formulations, either concomitantly or sequentially. Thus, an individual who receives such treatment can benefit from a combined effect of different therapeutic agents.

A "therapeutically effective amount" or a "therapeutically effective dose" of a drug or agent is an amount of a drug or an agent that, when administered to a subject will have the intended therapeutic effect. The full therapeutic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a therapeutically effective amount may be administered in one or more administrations. The precise effective amount needed for a subject will depend upon, for example, the subject's size, health and age, and the nature and extent of the condition being treated, such as cancer or MDS. The skilled worker can readily determine the effective amount for a given situation by routine experimentation.

As used herein, the terms "optional" or "optionally" mean that the subsequently described event or circumstance may occur or may not occur, and that the description includes instances where the event or circumstance occurs as well as instances in which it does not. For example, "optionally substituted alkyl" refers to the alkyl may be substituted as well as where the alkyl is not substituted.

It is understood that substituents and substitution patterns on the compounds of the present invention can be selected by one of ordinary skilled person in the art to result in chemically stable compounds which can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results.

As used herein, the term "optionally substituted" refers to the replacement of one to six hydrogen radicals in a given structure with the radical of a specified substituent including, but not limited to: hydroxyl, hydroxyalkyl, alkoxy, halogen, alkyl, nitro, silyl, acyl, acyloxy, aryl, cycloalkyl, heterocyclyl, amino, aminoalkyl, cyano, haloalkyl, haloalkoxy, -OCO-CH_2-O-alkyl, -OP(O)(O-alkyl)$_2$ or –CH_2-OP(O)(O-alkyl)$_2$. Preferably, "optionally substituted" refers to the replacement of one to four hydrogen radicals in a given structure with the substituents mentioned above. More preferably, one to three hydrogen radicals are replaced by the substituents as mentioned above. It is understood that the substituent can be further substituted.

As used herein, the term "alkyl" refers to saturated aliphatic groups, including but not limited to C_1-C_{10} straight-chain alkyl groups or C_1-C_{10} branched-chain alkyl groups. Preferably, the "alkyl" group refers to C_1-C_6 straight-chain alkyl groups or C_1-C_6 branched-chain alkyl groups. Most preferably, the "alkyl" group refers to C_1-C_4 straight-chain alkyl groups or C_1-C_4 branched-chain alkyl groups. Examples of "alkyl" include, but are not limited to, methyl, ethyl, 1-propyl, 2-propyl, n-butyl, sec-butyl, tert-butyl, 1-pentyl, 2-pentyl, 3-pentyl, neo-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 1-octyl, 2-octyl, 3-octyl or 4-octyl and the like. The "alkyl" group may be optionally substituted.

The term "acyl" is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)-, preferably alkylC(O)-.

The term "acylamino" is art-recognized and refers to an amino group substituted with an acyl group and may be represented, for example, by the formula hydrocarbylC(O)NH-.

The term "acyloxy" is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)O-, preferably alkylC(O)O-.

The term "alkoxy" refers to an alkyl group having an oxygen attached thereto. Representative alkoxy groups include methoxy, ethoxy, propoxy, tert-butoxy and the like.

The term "alkoxyalkyl" refers to an alkyl group substituted with an alkoxy group and may be represented by the general formula alkyl-O-alkyl.

The term "alkyl" refers to saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl-substituted cycloalkyl groups, and cycloalkyl-substituted alkyl groups. In preferred embodiments, a

straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C_{1-30} for straight chains, C_{3-30} for branched chains), and more preferably 20 or fewer.

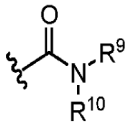
Moreover, the term "alkyl" as used throughout the specification, examples, and claims is intended to include both unsubstituted and substituted alkyl groups, the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone, including haloalkyl groups such as trifluoromethyl and 2,2,2-trifluoroethyl, etc.

The term "C_{x-y}" or "C_x-C_y", when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups that contain from x to y carbons in the chain. C_0alkyl indicates a hydrogen where the group is in a terminal position, a bond if internal. A C_{1-6}alkyl group, for example, contains from one to six carbon atoms in the chain.

The term "alkylamino", as used herein, refers to an amino group substituted with at least one alkyl group.

The term "alkylthio", as used herein, refers to a thiol group substituted with an alkyl group and may be represented by the general formula alkylS-.

The term "amide", as used herein, refers to a group



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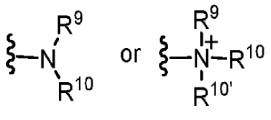
wherein R^9 and R^{10} each independently represent a hydrogen or hydrocarbyl group, or R^9 and R^{10} taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines and salts thereof, e.g., a moiety that can be represented by



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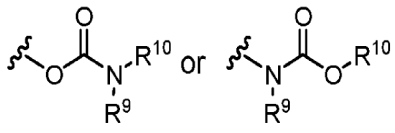
wherein R^9, R^{10}, and $R^{10'}$ each independently represent a hydrogen or a hydrocarbyl group, or R^9 and R^{10} taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

The term "aminoalkyl", as used herein, refers to an alkyl group substituted with an amino group.

The term "aralkyl", as used herein, refers to an alkyl group substituted with an aryl group.

The term "aryl" as used herein include substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon. Preferably the ring is a 5- to 7-membered ring, more preferably a 6-membered ring. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline, and the like.

The term "carbamate" is art-recognized and refers to a group



wherein R^9 and R^{10} independently represent hydrogen or a hydrocarbyl group.

The term "carbocyclylalkyl", as used herein, refers to an alkyl group substituted with a carbocycle group.

The term "carbocycle" includes 5-7 membered monocyclic and 8-12 membered bicyclic rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated and aromatic rings. Carbocycle includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term "fused carbocycle" refers to a bicyclic carbocycle in which each of the rings shares two adjacent atoms with the other ring. Each ring of a fused carbocycle may be selected from saturated, unsaturated and aromatic rings. In an exemplary embodiment, an aromatic ring, e.g., phenyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene. Any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits, is included in the definition of carbocyclic. Exemplary "carbocycles" include cyclopentane, cyclohexane, bicyclo[2.2.1]heptane, 1,5-cyclooctadiene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]oct-3-ene, naphthalene and adamantane. Exemplary fused carbocycles include decalin, naphthalene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]octane, 4,5,6,7-tetrahydro-1H-indene and bicyclo[4.1.0]hept-3-ene. "Carbocycles" may be substituted at any one or more positions capable of bearing a hydrogen atom.

The term "carbocyclylalkyl", as used herein, refers to an alkyl group substituted with a carbocycle group.

The term "carbonate" is art-recognized and refers to a group $-OCO_2-$.

The term "carboxy", as used herein, refers to a group represented by the formula $-CO_2H$.

The term "cycloalkyl" includes substituted or unsubstituted non-aromatic single ring structures, preferably 4- to 8-membered rings, more preferably 4- to 6-membered rings. The term "cycloalkyl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is cycloalkyl and the substituent (e.g., R^{100}) is attached to the cycloalkyl ring, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrazine, pyridazine, pyrimidine, denzodioxane, tetrahydroquinoline, and the like.

The term "ester", as used herein, refers to a group $-C(O)OR^9$ wherein R^9 represents a hydrocarbyl group.

The term "ether", as used herein, refers to a hydrocarbyl group linked through an oxygen to another hydrocarbyl group. Accordingly, an ether substituent of a hydrocarbyl group may be hydrocarbyl-O-. Ethers may be either symmetrical or unsymmetrical. Examples of ethers include, but are not limited to, heterocycle-O-heterocycle and aryl-O-heterocycle. Ethers include "alkoxyalkyl" groups, which may be represented by the general formula alkyl-O-alkyl.

The terms "halo" and "halogen" as used herein means halogen and includes chloro, fluoro, bromo, and iodo.

The terms "hetaralkyl" and "heteroaralkyl", as used herein, refers to an alkyl group substituted with a hetaryl group.

The terms "heteroaryl" and "hetaryl" include substituted or unsubstituted aromatic single ring structures, preferably 5- to 7-membered rings, more preferably 5- to 6-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms "heteroaryl" and "hetaryl" also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is

heteroaromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like.

The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, and sulfur.

The term "heterocyclylalkyl", as used herein, refers to an alkyl group substituted with a heterocycle group.

The terms "heterocyclyl", "heterocycle", and "heterocyclic" refer to substituted or unsubstituted non-aromatic ring structures, preferably 3- to 10-membered rings, more preferably 3- to 7-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms "heterocyclyl" and "heterocyclic" also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heterocyclic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heterocyclyl groups include, for example, piperidine, piperazine, pyrrolidine, morpholine, lactones, lactams, and the like.

The term "hydrocarbyl", as used herein, refers to a group that is bonded through a carbon atom that does not have a =O or =S substituent, and typically has at least one carbon-hydrogen bond and a primarily carbon backbone, but may optionally include heteroatoms. Thus, groups like methyl, ethoxyethyl, 2-pyridyl, and even trifluoromethyl are considered to be hydrocarbyl for the purposes of this application, but substituents such as acetyl (which has a =O substituent on the linking carbon) and ethoxy (which is linked through oxygen, not carbon) are not. Hydrocarbyl groups include, but are not limited to aryl, heteroaryl, carbocycle, heterocycle, alkyl, alkenyl, alkynyl, and combinations thereof.

The term "hydroxyalkyl", as used herein, refers to an alkyl group substituted with a hydroxy group.

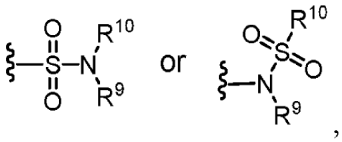
The term "lower" when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups where there are ten or fewer atoms in the substituent, preferably six or fewer. A "lower alkyl", for example, refers to an alkyl group that contains ten or fewer carbon atoms, preferably six or fewer. In certain

embodiments, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy substituents defined herein are respectively lower acyl, lower acyloxy, lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy, whether they appear alone or in combination with other substituents, such as in the recitations hydroxyalkyl and aralkyl (in which case, for example, the atoms within the aryl group are not counted when counting the carbon atoms in the alkyl substituent).

The terms "polycyclyl", "polycycle", and "polycyclic" refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls) in which two or more atoms are common to two adjoining rings, e.g., the rings are "fused rings". Each of the rings of the polycycle can be substituted or unsubstituted. In certain embodiments, each ring of the polycycle contains from 3 to 10 atoms in the ring, preferably from 5 to 7.

The term "sulfate" is art-recognized and refers to the group $-OSO_3H$, or a pharmaceutically acceptable salt thereof.

The term "sulfonamide" is art-recognized and refers to the group represented by the general formulae



wherein R^9 and R^{10} independently represents hydrogen or hydrocarbyl.

The term "sulfoxide" is art-recognized and refers to the group–S(O)-.

The term "sulfonate" is art-recognized and refers to the group SO_3H, or a pharmaceutically acceptable salt thereof.

The term "sulfone" is art-recognized and refers to the group $-S(O)_2$-.

The term "substituted" refers to moieties having substituents replacing a hydrogen on one or more carbons of the backbone. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds.

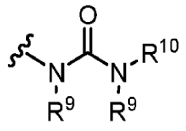
The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate.

The term "thioalkyl", as used herein, refers to an alkyl group substituted with a thiol group.

The term "thioester", as used herein, refers to a group $-C(O)SR^9$ or $-SC(O)R^9$ wherein R^9 represents a hydrocarbyl.

The term "thioether", as used herein, is equivalent to an ether, wherein the oxygen is replaced with a sulfur.

The term "urea" is art-recognized and may be represented by the general formula



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wherein R^9 and R^{10} independently represent hydrogen or a hydrocarbyl.

The term "modulate" as used herein includes the inhibition or suppression of a function or activity (such as cell proliferation) as well as the enhancement of a function or activity.

The phrase "pharmaceutically acceptable" is art-recognized. In certain embodiments, the term includes compositions, excipients, adjuvants, polymers and other materials and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

"Pharmaceutically acceptable salt" or "salt" is used herein to refer to an acid addition salt or a basic addition salt which is suitable for or compatible with the treatment of patients.

The term "pharmaceutically acceptable acid addition salt" as used herein means any non-toxic organic or inorganic salt of any base compounds represented by Formula I, Ia – Ih, IIa – Iif, and IIIa - IIIf. Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulfuric and phosphoric acids, as well as metal salts such as sodium monohydrogen orthophosphate and potassium hydrogen sulfate. Illustrative organic acids that form suitable salts include mono-, di-, and tricarboxylic acids such as glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, benzoic, phenylacetic, cinnamic and salicylic acids, as well as sulfonic acids such as p-toluene sulfonic and methanesulfonic acids. Either the mono or di-acid salts can be formed, and such salts may exist in either a hydrated, solvated or substantially anhydrous form. In general, the acid addition salts of compounds of Formula I, Ia – Ih, IIa – Iif, and IIIa - IIIf are more soluble in water and various hydrophilic organic solvents, and generally demonstrate higher melting points in comparison to their free base forms. The selection of the appropriate salt will be known to one skilled in the art. Other non-pharmaceutically acceptable salts, e.g., oxalates, may be used, for example, in the isolation of compounds of Formula I, Ia – Ih, IIa – Iif, and IIIa - IIIf for laboratory use, or for subsequent conversion to a pharmaceutically acceptable acid addition salt.

The term "pharmaceutically acceptable basic addition salt" as used herein means any non-toxic organic or inorganic base addition salt of any acid compounds represented by Formula I, Ia – Ih, IIa – Iif, and IIIa - IIIf or any of their intermediates. Illustrative inorganic bases which form suitable salts include lithium, sodium, potassium, calcium, magnesium, or barium hydroxide. Illustrative organic bases which form suitable salts include aliphatic, alicyclic, or aromatic organic amines such as methylamine, trimethylamine and picoline or ammonia. The selection of the appropriate salt will be known to a person skilled in the art.

Many of the compounds useful in the methods and compositions of this disclosure have at least one stereogenic center in their structure. This stereogenic center may be present in a R or a S configuration, said R and S notation is used in correspondence with the rules described in Pure Appl. Chem. (1976), 45, 11-30. The disclosure contemplates all stereoisomeric forms such as enantiomeric and diastereoisomeric forms of the compounds,

salts, prodrugs or mixtures thereof (including all possible mixtures of stereoisomers). See, e.g., WO 01/062726.

Furthermore, certain compounds which contain alkenyl groups may exist as Z (zusammen) or E (entgegen) isomers. In each instance, the disclosure includes both mixture and separate individual isomers.

Some of the compounds may also exist in tautomeric forms. Such forms, although not explicitly indicated in the formulae described herein, are intended to be included within the scope of the present disclosure.

"Prodrug" or "pharmaceutically acceptable prodrug" refers to a compound that is metabolized, for example hydrolyzed or oxidized, in the host after administration to form the compound of the present disclosure (e.g., compounds of formula I). Typical examples of prodrugs include compounds that have biologically labile or cleavable (protecting) groups on a functional moiety of the active compound. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, or dephosphorylated to produce the active compound. Examples of prodrugs using ester or phosphoramidate as biologically labile or cleavable (protecting) groups are disclosed in U.S. Patents 6,875,751, 7,585,851, and 7,964,580, the disclosures of which are incorporated herein by reference. The prodrugs of this disclosure are metabolized to produce a compound of Formula I. The present disclosure includes within its scope, prodrugs of the compounds described herein. Conventional procedures for the selection and preparation of suitable prodrugs are described, for example, in "Design of Prodrugs" Ed. H. Bundgaard, Elsevier, 1985.

The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filter, diluent, excipient, solvent or encapsulating material useful for formulating a drug for medicinal or therapeutic use.

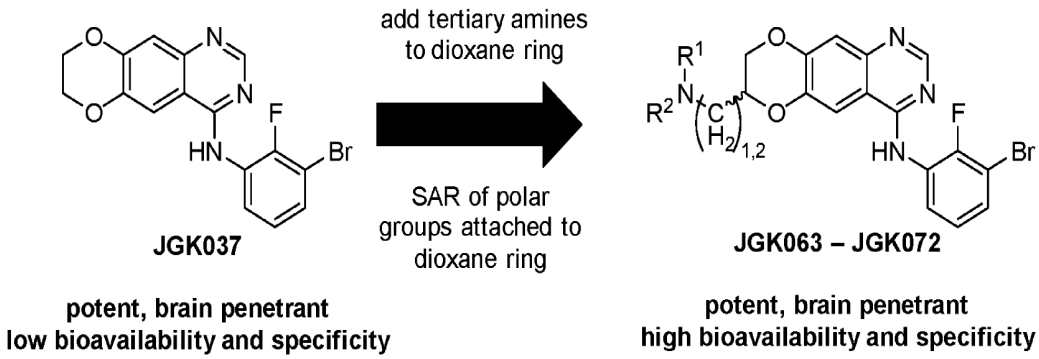
The term "Log of solubility", "LogS" or "logS" as used herein is used in the art to quantify the aqueous solubility of a compound. The aqueous solubility of a compound significantly affects its absorption and distribution characteristics. A low solubility often goes along with a poor absorption. LogS value is a unit stripped logarithm (base 10) of the solubility measured in mol/liter.

EXAMPLES

The invention now being generally described, it will be more readily understood by reference to the following examples which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

Example 1: Exemplary Design Rational for Certain Compounds of the JGK Series

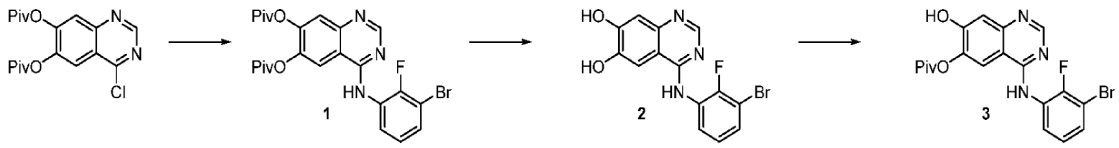
Certain Compounds of the present disclosure were designed according to Scheme 1.



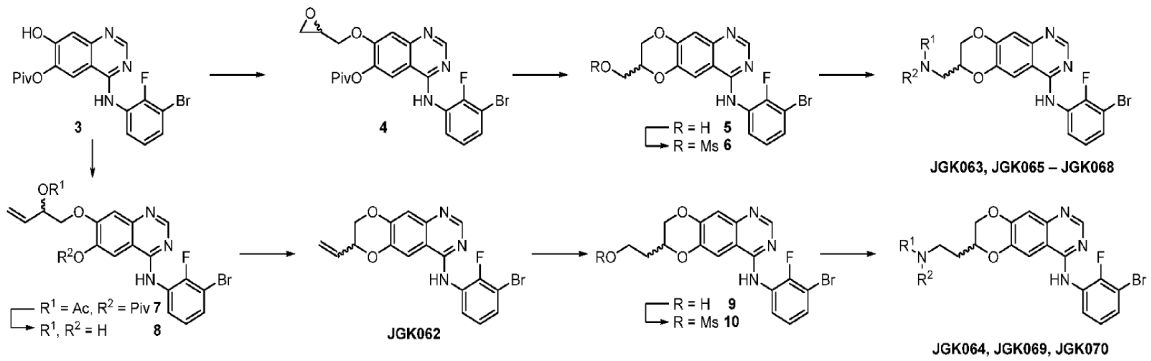
Scheme 1.

Example 2: Preparation of Exemplary Compounds of the JGK Series

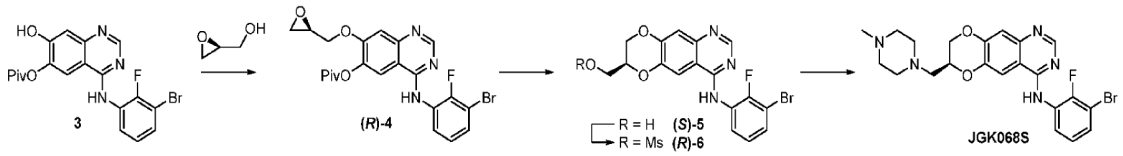
Exemplary compounds of the present disclosure were prepared according to the following methods.



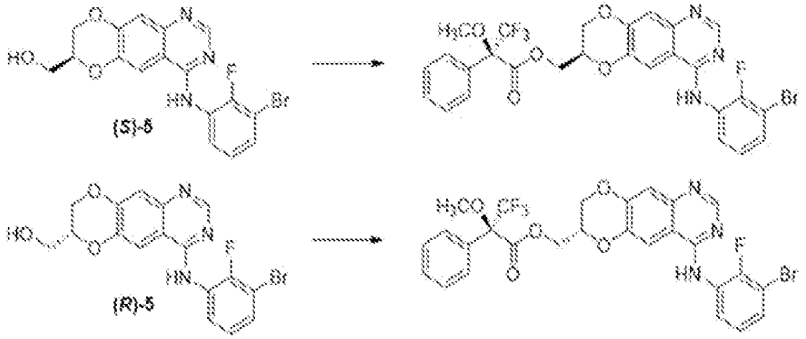
Scheme 1. Synthesis of monoprotected quinazoline intermediate **3**.



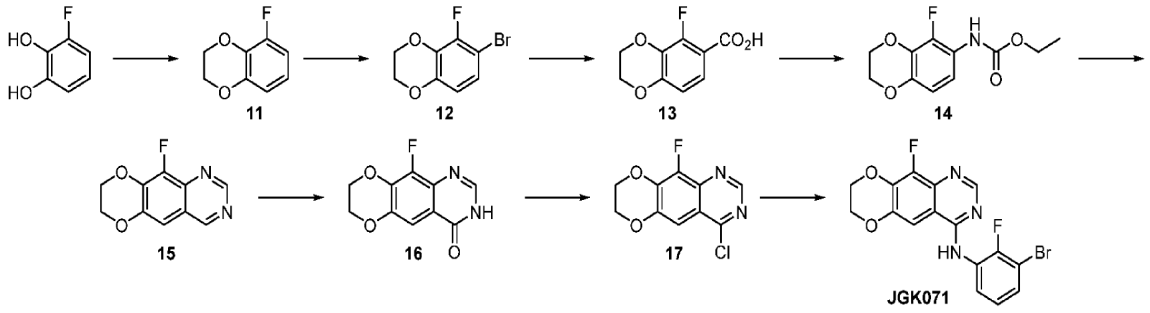
Scheme 2. Synthesis of JGK063 – JGK070.



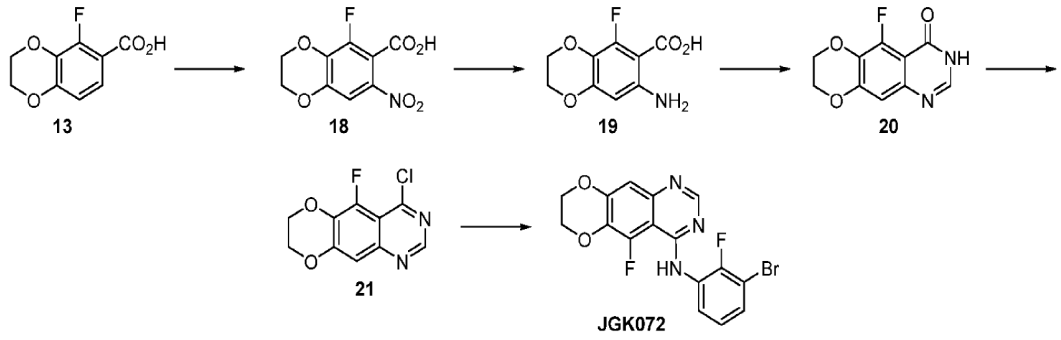
Scheme 3. Synthesis of **JGK068S** ((*S*)-**JGK068**). The synthesis was performed in the same way as for the racemic sample of **JGK068** ((±)-**JGK068**), but with enantiomerically pure (*S*)-(−)-glycidol. The other enantiomer **JGK068R** ((*R*)-**JGK068**) was prepared using (*R*)-(+)-glycidol (not shown).



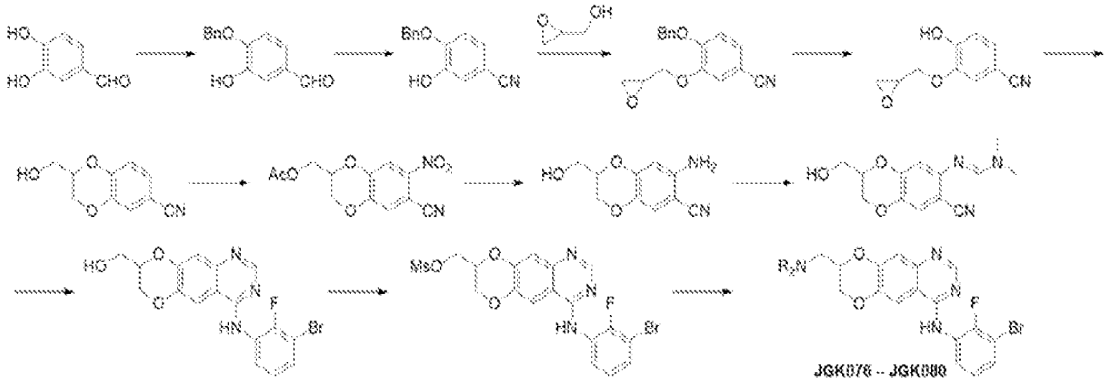
Scheme 4. The enantiomeric purity of the synthetic intermediate **5** was determined by chiral SFC (Chiralpak AD-3 column, 40% MeOH) and by comparison of the ^{19}F NMR spectra of the Mosher ester derivatives of **5** (FIG. 1).



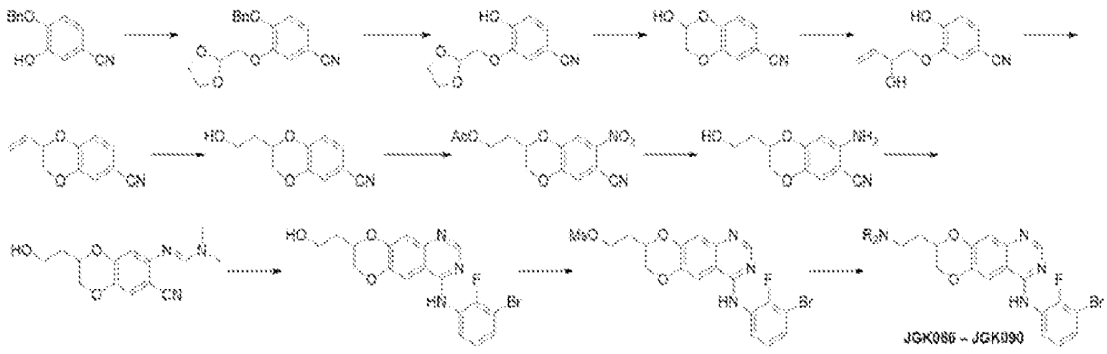
Scheme 5. Synthesis of **JGK071**.



Scheme 6. Synthesis of **JGK072**.



Scheme 7. Synthesis of **JGK076 – JGK080**.



Scheme 8. Synthesis of **JGK086-JGK090**.

General Chemistry Information

All chemicals, reagents, and solvents were purchased from commercial sources when available and were used as received. When necessary, reagents and solvents were purified and dried by standard methods. Air- and moisture-sensitive reactions were carried out under an inert atmosphere of argon in oven-dried glassware. Microwave-irradiated reactions were carried out in a single mode reactor CEM Discover microwave synthesizer. Room temperature (RT) reactions were carried out at ambient temperature (approximately 23 °C). All reactions were monitored by thin layer chromatography (TLC) on precoated Merck 60

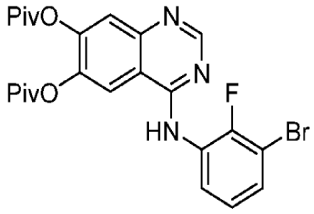
F_{254} silica gel plates with spots visualized by UV light (λ = 254, 365 nm) or by using an alkaline $KMnO_4$ solution. Flash column chromatography (FC) was carried out on SiO_2 60 (particle size 0.040–0.063 mm, 230–400 mesh). Preparative thin-layer chromatography (PTLC) was carried out with Merck 60 F_{254} silica gel plates (20 x 20 cm, 210–270 mm) or Analtech Silica Gel GF TLC plates (20 x 20 cm, 1000 mm). Concentration under reduced pressure (in vacuo) was performed by rotary evaporation at 23–50 °C. Purified compounds were further dried under high vacuum or in a desiccator. Yields correspond to purified compounds, and were not further optimized. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Bruker spectrometers (operating at 300, 400, or 500 MHz). Carbon NMR (^{13}C NMR) spectra were recorded on Bruker spectrometers (either at 400 or 500 MHz). NMR chemical shifts (δ ppm) were referenced to the residual solvent signals. ^{1}H NMR data are reported as follows: chemical shift in ppm; multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet/complex pattern, td = triplet of doublets, ddd = doublet of doublet of doublets, br = broad signal); coupling constants (J) in Hz, integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift, and if applicable coupling constants. High resolution mass (HRMS) spectra were recorded on a Thermo Fisher Scientific Exactive Plus with IonSense ID-CUBE DART source mass spectrometer, or on a Waters LCT Premier mass spectrometer with ACQUITY UPLC with autosampler.

General Procedures (GP). *GP-1: Nucleophilic Substitution of Quinazolinyl Mesylates with Secondary Amines.* A mixture of quinazolinyl mesylate (1 equiv) in DMF (0.05 M) was treated with the secondary amine (5 equiv) and triethylamine (2 equiv), and the mixture was stirred at 85 °C for 24 h. The mixture was cooled to 23 °C, and evaporated. The residue was dissolved in EtOAc (20 mL), washed with 10 mM NaOH (4 x 5 mL), brine (5 mL), dried (Na_2SO_4), filtered, and evaporated. Purification by FC or PTLC afforded the desired products typically as off-white, friable foams.

GP-2: Nucleophilic Aromatic Substitution of 4-Chloroquinazoline with Anilines. A mixture of 4-chloroquinazoline (1 equiv) in acetonitrile (0.1 M) was treated with aniline (2 equiv), and with a 4 M solution of HCl in dioxane (1 equiv). The mixture was heated at 80 °C under microwave irradiation for 30 min. The mixture was either concentrated under reduced pressure, or the precipitated 4-anilinoquinazoline hydrochloride salt was isolated by filtration (washings with Et_2O). The residue was suspended in sat. aq. $NaHCO_3$, and extracted with

CH_2Cl_2 (3x). The combined organic extracts were washed with water, brine, dried (Na_2SO_4), filtered, and concentrated. Purification by FC (elution with a gradient of CH_2Cl_2/EtOAc or hexanes/EtOAc) afforded the desired products typically as white to off-white, or pale-yellow solids.

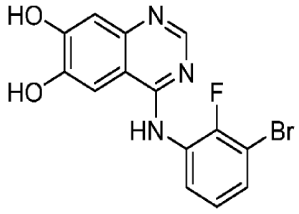
*4-(3-Bromo-2-fluoroanilino)quinazoline-6,7-diyl bis(2,2-dimethylpropanoate) (**1**).*



A mixture of 4-chloroquinazoline-6,7-diyl bis(2,2-dimethylpropanoate)[1] (41.08 g, 113 mmol) in *i*PrOH (450 mL) was treated with 3-bromo-2-fluoroaniline (17.05 mL, 152 mmol) and stirred at 80 °C for 3.5 h. The mixture was cooled to 23 °C and evaporated. The residue was several times resuspended in hexanes (50 mL) and concentrated, and then dried under HV. The residue was recrystallized from EtOH to give a yellow solid, which was suspended in sat. aq. $NaHCO_3$ (1 L), and extracted with DCM (3 x 550 mL). The combined organics were washed with water (400 mL), brine (400 mL), dried ($MgSO_4$), filtered, and evaporated to afford the title compound **1** (35.057 g, 60%) as a yellow friable foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.76 (s, 1H), 8.46 (t, J = 7.5 Hz, 1H), 7.72 (s, 1H), 7.68 (s, 1H), 7.56 (br, 1H), 7.32 (ddd, J = 8.0, 6.4, 1.5 Hz, 1H), 7.11 (td, J = 8.2, 1.5 Hz, 1H), 1.40 (s, 9H), 1.39 ppm (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.13, 175.55, 156.71, 154.96, 150.69 (d, J_{CF} = 243.7 Hz), 148.75, 147.83, 142.45, 128.27, 127.86 (d, J_{CF} = 10.8 Hz), 125.29 (d, J_{CF} = 4.7 Hz), 122.70, 122.51, 114.43, 113.21, 108.84 (d, J_{CF} = 19.4 Hz), 39.54, 39.51, 27.40, 27.32 ppm. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{24}H_{26}BrFN_3O_4^+$, 518.1085; found, 518.1072.

*4-(3-Bromo-2-fluoroanilino)quinazoline-6,7-diol (**2**).*

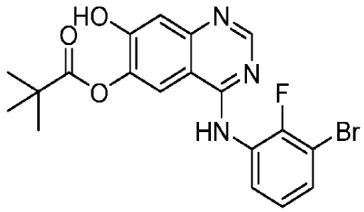


A stirred slurry of **1** (34.988 g, 67.5 mmol) was treated at 0 °C with 7 M solution of NH_3 in MeOH (241 mL, 1.69 mol). The mixture was stirred at 0 °C for 15 min, and then at 23

°C for 4.5 h. The mixture was evaporated, and the residue suspended in water (400 mL), stirred overnight, and filtered. The residue was washed with water (500 mL), acetonitrile (100 mL), DCM (4 x 150 mL), Et_2O (2 x 150 mL), and dried in a desiccator to afford the title compound **2** (23.68 g, quant.) as a pale-yellow powder.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.18 (s, 1H), 7.59 – 7.47 (m, 2H), 7.51 (s, 1H), 7.16 (t, J = 8.0 Hz, 1H), 6.87 ppm (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 156.43, 156.12, 153.06 (d, J_{CF} = 246.7 Hz), 151.34, 148.39, 146.80, 129.23, 129.01, 127.12, 125.23 (d, J_{CF} = 4.3 Hz), 108.47, 108.32, 107.09, 103.04 ppm. HRMS (DART): m/z $[M + H]^+$ calcd for $C_{14}H_{10}BrFN_3O_2^+$, 349.9935; found, 349.9923.

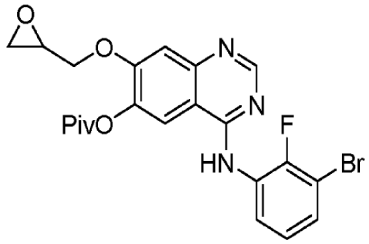
4-(3-Bromo-2-fluoroanilino)-7-hydroxyquinazolin-6-yl 2,2-dimethylpropanoate (3).



A stirred suspension of **2** (3500 mg, 10.0 mmol) in DMF (52.6 mL) was treated with Et_3N (5.57 mL, 40.0 mmol), cooled to –40 °C, and treated dropwise with Piv_2O (3.14 mL, 15.5 mmol). The mixture was stirred at –40 °C for 1 h, after which the cooling bath was removed, and stirring was continued for 2.5 h. The reaction mixture was diluted with DCM (500 mL), washed with 10% citric acid (2 x 50 mL), dried (Na_2SO_4), filtered, and evaporated. FC (DCM/EtOAc 1:1 → 0:1) afforded a solid, which was redissolved in EtOAc (750 mL), and washed with half-sat. aq. NH_4Cl (4 x 75 mL), dried (Na_2SO_4), filtered, and evaporated to afford the title compound **3** (2.844 g, 66%) as a beige-yellow solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.00 (br, 1H), 9.70 (s, 1H), 8.39 (s, 1H), 8.14 (s, 1H), 7.59 (ddd, J = 8.0, 6.2, 1.6 Hz, 1H), 7.53 (ddd, J = 8.3, 7.1, 1.6 Hz, 1H), 7.21 (td, J = 8.1, 1.2 Hz, 1H), 7.17 (s, 1H), 1.36 ppm (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 175.93, 157.68, 154.61, 154.53, 153.34 (d, J_{CF} = 247.3 Hz), 149.80, 139.65, 130.14, 127.92 (d, J_{CF} = 12.9 Hz), 127.62, 125.47 (d, J_{CF} = 4.4 Hz), 116.36, 111.00, 108.55 (d, J = 20.0 Hz), 107.77, 38.64, 26.93 ppm. HRMS (DART): m/z $[M + H]^+$ calcd for $C_{19}H_{18}BrFN_3O_3^+$, 434.0510; found, 434.0489.

*(±)-4-(3-Bromo-2-fluoroanilino)-7-[(oxiran-2-yl)methoxy]quinazolin-6-yl 2,2-dimethylpropanoate ((±)-**4**).*

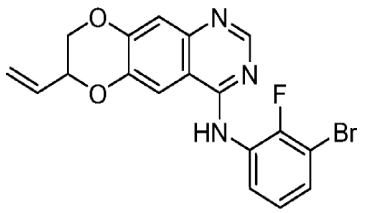


A mixture of **3** (1350 mg, 3.11 mmol) and PPh_3 (2038 mg, 7.77 mmol) in THF (21 mL) was treated with glycidol (495 µL, 7.46 mmol), cooled to 0 °C, and treated with DIAD (1.47 mL, 7.46 mmol) during 10 min. The mixture was stirred at 23 °C for 2.5 h, and concentrated. FC (DCM/EtOAc 9:1 → 4:6) afforded the title compound (±)-**4** (848 mg, 56%) as an off-white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.73 (s, 1H), 8.54 (ddd, J = 8.6, 7.3, 1.6 Hz, 1H), 7.54 (s, 1H), 7.45 (br, 1H), 7.30 (ddd, J = 8.2, 6.4, 1.5 Hz, 1H), 7.28 (s, 1H), 7.11 (td, J = 8.2, 1.6 Hz, 1H), 4.34 (dd, J = 10.8, 3.0 Hz, 1H), 3.99 (dd, J = 10.8, 6.2 Hz, 1H), 3.35 (ddt, J = 6.2, 4.1, 2.8 Hz, 1H), 2.92 (dd, J = 4.8, 4.1 Hz, 1H), 2.74 (dd, J = 4.8, 2.6 Hz, 1H), 1.45 ppm (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.87, 156.46, 155.10, 154.93, 150.41 (d, J_{CF} = 243.3 Hz), 150.27, 140.99, 128.25 (d, J_{CF} = 10.5 Hz), 127.75, 125.28 (d, J_{CF} = 4.7 Hz), 122.22, 114.02, 109.72, 109.49, 108.74 (d, J_{CF} = 19.1 Hz), 70.05, 49.55, 44.56, 39.45, 27.38 ppm. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{22}H_{22}BrFN_3O_4^+$, 490.0772; found, 490.0764.

(±)-N-(3-Bromo-2-fluorophenyl)-7-ethenyl-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4-amine

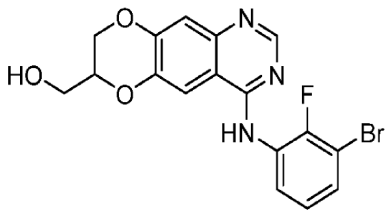
*((±)-**JGK062**).*



A solution of PPh_3 (832 mg, 3.17 mmol) and DIAD (624 µL, 3.17 mmol) in THF (23 mL) was stirred at 0 °C for 15 min, and then added dropwise to a solution of (±)-**8** (1149 mg, 2.73 mmol) in THF (27 mL) during 10 min at 0 °C. The mixture was stirred at 0 ° for 2 h, and evaporated. FC (hexanes/EtOAc 9:1 → 4:6) followed by another FC (DCM/EtOAc 1:0 → 6:4) afforded the title compound (±)-**JGK062** (1115 mg, quant.) as an off-white friable foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.68 (s, 1H), 8.65 (ddd, J = 8.2, 7.3, 1.5 Hz, 1H), 7.40 (s, 1H), 7.37 (br, 1H), 7.35 (s, 1H), 7.27 (ddd, J = 8.0, 6.4, 1.5 Hz, 1H), 7.10 (td, J = 8.2, 1.6 Hz, 1H), 5.95 (ddd, J = 17.3, 10.7, 5.8 Hz, 1H), 5.60 (dt, J = 17.3, 1.2 Hz, 1H), 5.48 (dt, J = 10.7, 1.1 Hz, 1H), 4.82 – 4.74 (m, 1H), 4.42 (dd, J = 11.5, 2.5 Hz, 1H), 4.09 ppm (dd, J = 11.6, 8.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.90, 153.38, 150.14 (d, J = 242.4 Hz), 149.12, 146.70, 144.12, 131.48, 128.64 (d, J = 10.3 Hz), 127.24, 125.30 (d, J = 4.7 Hz), 121.76, 120.43, 114.29, 110.69, 108.58 (d, J = 19.3 Hz), 106.06, 74.03, 67.84 ppm. HRMS (DART): m/z $[M + H]^+$ calcd for $C_{18}H_{14}BrFN_3O_2^+$, 402.0248; found, 402.0233.

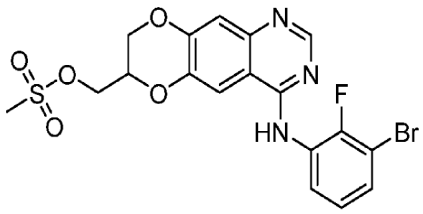
*(±)-[4-(3-Bromo-2-fluoroanilino)-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-7-yl]methanol ((±)-**5**).*



A mixture of (±)-**4** (842 mg, 1.72 mmol) in MeOH (31 mL) was treated with K_2CO_3 (482 mg, 3.49 mmol), stirred at 23 °C for 10.5 h, and concentrated. The residue was suspended in half-sat. aq. NH_4Cl (130 mL), and extracted with EtOAc (3 x 20 mL). The combined organics were washed with water (20 mL), brine (20 mL), dried (Na_2SO_4), filtered, and concentrated to afford the title compound (±)-**5** (720 mg, quant.) as a yellow solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.59 (s, 1H), 8.34 (s, 1H), 7.95 (s, 1H), 7.59 (ddd, J = 8.0, 6.2, 1.6 Hz, 1H), 7.55 (ddd, J = 8.4, 7.0, 1.6 Hz, 1H), 7.24 – 7.18 (m, 1H), 7.21 (s, 1H), 5.16 (t, J = 5.6 Hz, 1H), 4.49 (dd, J = 11.5, 2.4 Hz, 1H), 4.34 (dtd, J = 7.6, 5.2, 2.3 Hz, 1H), 4.21 (dd, J = 11.5, 7.4 Hz, 1H), 3.76 – 3.64 ppm (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 157.20, 153.35 (d, J_{CF} = 247.5 Hz), 153.10, 148.88, 145.95, 143.39, 130.11, 128.05 (d, J_{CF} = 13.0 Hz), 127.73, 125.44 (d, J_{CF} = 4.4 Hz), 112.33, 109.79, 108.56 (d, J_{CF} = 20.0 Hz), 108.37, 73.78, 65.50, 59.78 ppm. HRMS (DART): m/z $[M + H]^+$ calcd for $C_{17}H_{14}BrFN_3O_3^+$, 406.0197; found, 406.0185.

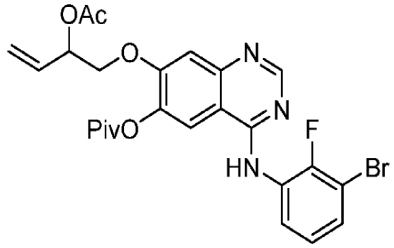
*(±)-[4-(3-Bromo-2-fluoroanilino)-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-7-yl]methyl methanesulfonate ((±)-**6**).*



A solution of (±)-**5** (688 mg, 1.69 mmol) in THF (14 mL) was treated with Et_3N (357 µL, 2.56 mmol), cooled to 0 °C, and treated dropwise with MsCl (174 µL, 2.24 mmol). The mixture was stirred at 23 °C for 16 h, cooled to 0 °C, treated with sat. aq. $NaHCO_3$ (120 mL), and extracted with DCM (3 x 120 mL). The combined organics were washed with water (100 mL), brine (100 mL), dried (Na_2SO_4), filtered and evaporated. FC (DCM/EtOAc 8:2 → 3:7) afforded the title compound (±)-**6** (496 mg, 61%) as an off-white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.69 (s, 1H), 8.60 (ddd, J = 8.5, 7.2, 1.4 Hz, 1H), 7.43 (s, 1H), 7.39 (br, 1H), 7.37 (s, 1H), 7.29 (ddd, J = 8.1, 6.5, 1.5 Hz, 1H), 7.11 (td, J = 8.2, 1.5 Hz, 1H), 4.63 (dtd, J = 7.2, 4.9, 2.5 Hz, 1H), 4.52 (dd, J = 4.9, 0.9 Hz, 2H), 4.49 (dd, J = 11.8, 2.5 Hz, 1H), 4.29 (dd, J = 11.8, 7.1 Hz, 1H), 3.13 ppm (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.02, 153.66, 150.28 (d, J_{CF} = 242.9 Hz), 148.65, 146.80, 143.09, 128.43 (d, J_{CF} = 10.4 Hz), 127.54, 125.32 (d, J_{CF} = 4.7 Hz), 122.01, 114.77, 110.90, 108.66 (d, J_{CF} = 19.4 Hz), 106.44, 71.10, 66.46, 64.77, 38.02 ppm. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{18}H_{15}BrFN_3O_5S^+$, 483.9973; found, 483.9950.

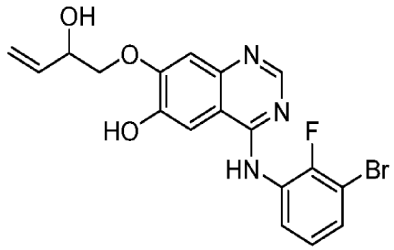
(±)-4-(3-Bromo-2-fluoroanilino)-7-{[2-(acetoxy)but-3-en-1-yl]oxy}quinazolin-6-yl 2,2-dimethylpropanoate ((±)-7).



A mixture of **3** (2639 mg, 6.08 mmol) and PPh_3 (3986 mg, 15.2 mmol) in THF (41 mL) was treated with racemic 1-hydroxybut-3-en-2-yl acetate[2] (1.7 mL, 13.7 mmol), cooled to 0 °C, and treated dropwise with DIAD (2.7 mL, 13.7 mmol). The mixture was stirred at 23 °C for 3 h, and concentrated. FC (DCM/EtOAc 1:0 → 6:4) afforded the crude (±)-**7** (5.508 g, estimated yield 60%) as an off-white solid, which was contaminated with remaining Ph_3PO. The material was used in the next step without any further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (s, 1H), 8.53 (t, J = 7.9 Hz, 1H), 7.53 (s, 1H), 7.45 (br, 1H), 7.33 (s, 1H), 7.30 (t, J = 7.7 Hz, 1H), 7.11 (t, J = 8.0 Hz, 1H), 5.90 (ddd, J = 17.0, 10.6, 6.2 Hz, 1H), 5.65 (q, J = 6.0 Hz, 1H), 5.49 – 5.29 (m, 2H), 4.31 – 4.08 (m, 2H), 2.11 (s, 3H), 1.41 ppm (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.51, 170.08, 156.49, 155.24, 154.88, 150.46 (d, J_{CF} = 243.2 Hz), 150.17, 140.90, 132.16, 128.18 (d, J_{CF} = 11.0 Hz), 127.86, 125.31 (d, J_{CF} = 4.8 Hz), 122.27, 119.64, 114.00, 109.56, 109.39, 108.76 (d, J_{CF} = 19.4 Hz), 72.18, 69.81, 39.34, 27.33, 21.19 ppm. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{25}H_{26}BrFN_3O_5^+$, 546.1034; found, 546.1018.

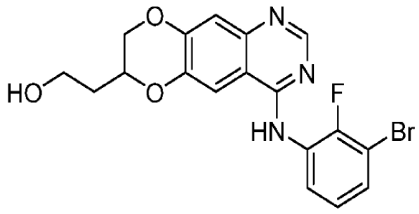
*(±)-4-(3-Bromo-2-fluoroanilino)-7-[(2-hydroxybut-3-en-1-yl)oxy]quinazolin-6-ol ((±)-**8**).*



A mixture of crude (±)-**7** (5508 mg, contaminated with remaining Ph_3PO from the last step) in MeOH (61 mL) was treated with K_2CO_3 (4198 mg, 30.4 mmol), stirred at 23 °C for 1 h, and concentrated. The residue was suspended in half-sat. aq. NH_4Cl (1 L), and extracted with EtOAc (3 x 600 mL). The combined organics were dried (Na_2SO_4), filtered, and evaporated. FC (DCM/EtOAc 1:1 → 0:1) afforded the title compound (±)-**8** (1154 mg, 45% over two steps) as an off-white solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.46 (s, 1H), 9.40 (br, 1H), 8.33 (s, 1H), 7.71 (s, 1H), 7.59 – 7.52 (m, 2H), 7.203 (s), 7.197 (td, J = 8.1, 1.1 Hz, 1H), 6.01 (ddd, J = 17.4, 10.7, 4.9 Hz, 1H), 5.42 (dt, J = 17.3, 1.9 Hz, 1H), 5.36 (br, 1H), 5.20 (dt, J = 10.6, 1.8 Hz, 1H), 4.49 (br, 1H), 4.20 (dd, J = 9.8, 3.8 Hz, 1H), 3.95 ppm (dd, J = 9.8, 7.5 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 156.77, 153.30 (d, J_{CF} = 244.9 Hz), 152.77, 152.31, 146.66, 146.11, 137.61, 129.75, 128.46 (d, J_{CF} = 13.0 Hz), 127.49, 125.38 (d, J_{CF} = 4.3 Hz), 115.58, 109.42, 108.50 (d, J_{CF} = 19.8 Hz), 107.68, 105.14, 72.56, 69.26 ppm. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{18}H_{16}BrFN_3O_3^+$, 420.0354; found, 420.0340.

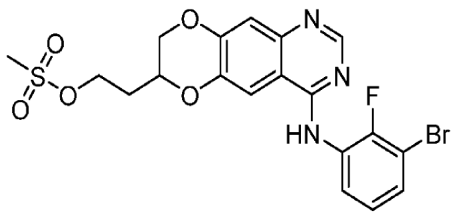
*(±)-2-[4-(3-Bromo-2-fluoroanilino)-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-7-yl]ethan-1-ol ((±)-**9**).*



A mixture of (±)-**JGK062** (480 mg, 1.19 mmol) in THF (4.8 mL) was treated with a 0.5 M solution of 9-BBN in THF (4.8 mL, 2.39 mmol), and the mixture was stirred at 68 °C for 16 h. The mixture was cooled to 0 °C, diluted with THF (2.4 mL), and treated with 3 N NaOH (3 mL, 8.95 mmol), and 30% H_2O_2 (474 μL, 8.95 mmol), and stirred at 23 °C for 6 h. The mixture was concentrated to about half of the original volume of THF, diluted with water (100 mL) and brine (40 mL), and extracted with EtOAc (3 x 100 mL). The combined organics were washed with water (70 mL), brine (70 mL), dried (Na_2SO_4), filtered, and evaporated to afford the title compound (±)-**9** (912 mg) as a yellow foam, which was directly used in the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.66 (s, 1H), 8.62 (ddd, J = 8.8, 7.4, 1.6 Hz, 1H), 7.35 (s, 1H), 7.33 (br, 1H), 7.2 (ddd, J = 8.0, 6.5, 1.6 Hz, 1H), 7.16 (s, 1H), 7.09 (td, J = 8.2, 1.6 Hz, 1H), 4.50 (dtd, J = 8.4, 6.4, 2.3 Hz, 1H), 4.43 (dd, J = 11.5, 2.3 Hz, 1H), 4.09 (dd, J = 11.5, 8.2 Hz, 1H), 4.01 – 3.91 (m, 2H), 1.95 ppm (td, J = 6.5, 5.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.84, 153.28, 150.08 (d, J_{CF} = 242.6 Hz), 149.42, 146.47, 144.20, 128.51 (d, J_{CF} = 10.2 Hz), 127.31, 125.30 (d, J_{CF} = 4.7 Hz), 121.69, 113.95, 110.50, 108.58 (d, J_{CF} = 19.2 Hz), 105.83, 71.33, 68.49, 58.23, 33.61 ppm. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{16}BrFN_3O_3^+$, 420.0354; found, 420.0370.

*(±)-2-[4-(3-Bromo-2-fluoroanilino)-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-7-yl]ethyl methanesulfonate ((±)-**10**).*

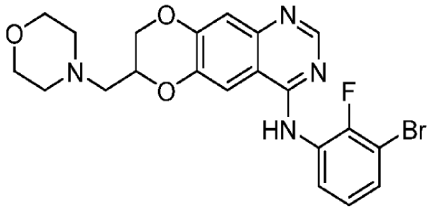


A solution of crude (±)-**9** (912 mg) in THF (11.9 mL) was treated with Et_3N (931 mL, 6.68 mmol), cooled to 0 °C, and treated dropwise with MsCl (462 μL, 5.97 mmol). The mixture was stirred at 0 °C for 15 min, and then at 23 °C for 21 h. The mixture was cooled to

0 °C, treated dropwise with sat. aq. $NaHCO_3$ (120 mL), and extracted with DCM (3 x 120 mL). The combined organics were washed with water (100 mL), brine (100 mL), dried (Na_2SO_4), filtered, and evaporated. FC (DCM/EtOAc 9:1 → 4:6) afforded the title compound (±)-**10** (112 mg, 19% over two steps) as an off-white, friable foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.68 (s, 1H), 8.60 (ddd, J = 8.6, 7.3, 1.5 Hz, 1H), 7.44 (br, 1H), 7.42 (s, 1H), 7.35 (s, 1H), 7.29 (ddd, J = 8.1, 6.5, 1.6 Hz, 1H), 7.11 (td, J = 8.2, 1.5 Hz, 1H), 4.60 – 4.48 (m, 3H), 4.44 (dd, J = 11.6, 2.4 Hz, 1H), 4.12 (dd, J = 11.6, 7.6 Hz, 1H), 3.08 (s, 3H), 2.24 – 2.10 ppm (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.03, 153.39, 150.31 (d, J_{CF} = 242.9 Hz), 149.11, 146.54, 143.60, 128.47 (d, J_{CF} = 10.5 Hz), 127.52, 125.32 (d, J_{CF} = 4.6 Hz), 122.02, 114.30, 110.68, 108.66 (d, J_{CF} = 19.2 Hz), 106.32, 69.78, 67.82, 65.05, 37.75, 30.90 ppm. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{18}BrFN_3O_5S^+$, 498.0129; found, 498.0144.

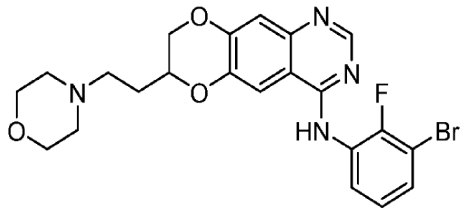
*(±)-N-(3-Bromo-2-fluorophenyl)-7-[(morpholin-4-yl)methyl]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4-amine ((±)-**JGK063**).*



Following general procedure **GP-1**, compound (±)-**JGK063** was prepared from (±)-**6** (20 mg, 0.04 mmol) and morpholine (18 µL, 0.21 mmol) in DMF (826 µL). PTLC (DCM/EtOAc 1:9) afforded (±)-**JGK063** (15 mg, 76%) as an off-white, friable foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.67 (s, 1H), 8.63 (ddd, J = 8.6, 7.3, 1.5 Hz, 1H), 7.38 (s, 1H), 7.37 (br, 1H), 7.31 (s, 1H), 7.27 (ddd, J = 8.0, 6.3, 1.5 Hz, 1H), 7.10 (td, J = 8.2, 1.5 Hz, 1H), 4.50 – 4.41 (m, 2H), 4.21 – 4.12 (m, 1H), 3.75 (t, J = 4.7 Hz, 4H), 2.77 (dd, J = 13.4, 5.9 Hz, 1H), 2.69 – 2.54 ppm (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.89, 153.36, 150.15 (d, J_{CF} = 242.5 Hz), 149.35, 146.66, 144.02, 128.60 (d, J_{CF} = 10.4 Hz), 127.27, 125.30 (d, J_{CF} = 4.6 Hz), 121.80, 114.29, 110.63, 108.58 (d, J_{CF} = 19.5 Hz), 106.06, 71.61, 67.18, 67.01, 58.94, 54.56 ppm. HRMS (ESI): *m/z* $[M - H]^-$ calcd for $C_{21}H_{19}BrFN_4O_3^-$, 473.0630; found, 473.0630.

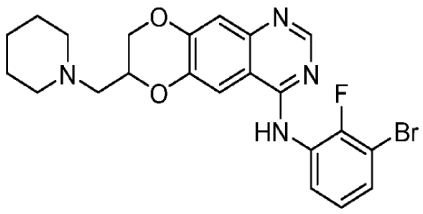
*(±)-N-(3-Bromo-2-fluorophenyl)-7-[2-(morpholin-4-yl)ethyl]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4-amine ((±)-**JGK064**).*



Following general procedure **GP-1**, compound (±)-**JGK064** was prepared from (±)-**10** (35 mg, 0.07 mmol) and morpholine (31 μL, 0.35 mmol) in DMF (1.4 mL). PTLC (EtOAc, 0.5% acetonitrile, 1.5% aq. NH_4OH) followed by another PTLC (EtOAc) afforded (±)-**JGK064** (25 mg, 73%) as an off-white, friable foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.68 (s, 1H), 8.65 (ddd, J = 8.3, 7.4, 1.5 Hz, 1H), 7.39 (s, 1H), 7.36 (br, 1H), 7.28 (s, 1H), 7.30 – 7.25 (m, 1H), 7.11 (td, J = 8.2, 1.5 Hz, 1H), 4.44 (dd, J = 11.3, 2.3 Hz, 1H), 4.43 – 4.37 (m, 1H), 4.10 (dd, J = 11.3, 7.7 Hz, 1H), 3.73 (t, J = 4.7 Hz, 4H), 2.62 (ddt, J = 12.5, 8.4, 3.9 Hz, 2H), 2.57 – 2.42 (m, 4H), 2.00 – 1.82 ppm (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.86, 153.31, 150.13 (d, J_{CF} = 242.3 Hz), 149.40, 146.67, 144.33, 128.66 (d, J_{CF} = 10.4 Hz), 127.22, 125.33 (d, J_{CF} = 4.6 Hz), 121.75, 114.21, 110.63, 108.58 (d, J_{CF} = 19.2 Hz), 105.87, 72.20, 68.33, 67.06, 54.23, 53.86, 28.15 ppm. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{23}BrFN_4O_3^+$, 489.0932; found, 489.0935.

*(±)-N-(3-Bromo-2-fluorophenyl)-7-[(piperidin-1-yl)methyl]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4-amine ((±)-**JGK065**).*

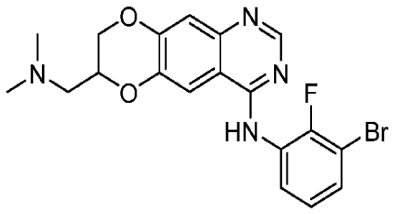


Following general procedure **GP-1**, compound (±)-**JGK065** was prepared from (±)-**6** (40 mg, 0.08 mmol) and piperidine (41 μL, 0.41 mmol) in DMF (1.65 mL). PTLC (EtOAc) afforded (±)-**JGK065** (24 mg, 61%) as an off-white, friable foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.66 (s, 1H), 8.63 (ddd, J = 8.7, 7.3, 1.5 Hz, 1H), 7.369 (s, 1H), 7.368 (br, 1H), 7.30 (s, 1H), 7.26 (ddd, J = 8.1, 6.5, 1.5 Hz, 1H), 7.09 (td, J = 8.2, 1.5 Hz, 1H), 4.46 (dd, J = 11.3, 2.3 Hz, 1H), 4.43 (ddd, J = 8.3, 5.8, 2.0 Hz, 1H), 4.12 (dd, J = 11.2, 7.5 Hz, 1H), 2.71 (dd, J = 13.3, 5.9 Hz, 1H), 2.58 (dd, J = 13.4, 6.2 Hz, 1H),

2.59 – 2.42 (m, 4H), 1.65 – 1.57 (m, 4H), 1.49 – 1.41 ppm (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.86, 153.26, 150.12 (d, J_{CF} = 242.6 Hz), 149.49, 146.62, 144.23, 128.65 (d, J_{CF} = 10.3 Hz), 127.18, 125.27 (d, J_{CF} = 4.5 Hz), 121.76, 114.16, 110.57, 108.56 (d, J_{CF} = 19.4 Hz), 106.00, 71.87, 67.46, 59.34, 55.59, 26.07, 24.20 ppm. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{23}BrFN_4O_2^+$, 473.0983; found, 473.0991.

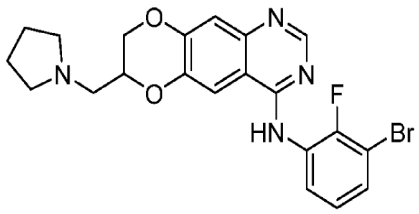
*(±)-N-(3-Bromo-2-fluorophenyl)-7-[(dimethylamino)methyl]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4-amine ((±)-**JGK066**).*



Following general procedure **GP-1**, compound (±)-**JGK066** was prepared from (±)-**6** (45 mg, 0.09 mmol) and a 2 M solution of Me_2NH in THF (232 µL, 0.46 mmol) in DMF (1.85 mL). PTLC (EtOAc, 0.5% acetonitrile, 1.5% aq. NH_4OH) afforded (±)-**JGK066** (39 mg, 97%) as an off-white, friable foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.680 (s, 1H), 8.675 (ddd, J = 8.2, 7.5, 1.5 Hz, 1H), 7.39 (s, 1H), 7.38 (s, 1H), 7.37 (br, 1H), 7.27 (ddd, *J* = 8.0, 6.4, 1.5 Hz, 1H), 7.10 (d, *J* = 1.6 Hz, 1H), 4.46 – 4.41 (m, 1H), 4.45 (dd, *J* = 11.8, 2.3 Hz, 1H), 4.12 (dd, *J* = 11.9, 8.1 Hz, 1H), 2.73 (dd, *J* = 13.2, 7.1 Hz, 1H), 2.55 (dd, *J* = 13.1, 5.0 Hz, 1H), 2.38 ppm (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.89, 153.34, 150.07 (d, J_{CF} = 242.3 Hz), 149.38, 146.67, 144.06, 128.70 (d, J_{CF} = 10.4 Hz), 127.16, 125.29 (d, J_{CF} = 4.7 Hz), 121.65, 114.27, 110.67, 108.56 (d, J_{CF} = 19.4 Hz), 106.15, 71.70, 67.20, 59.78, 46.41 ppm. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{19}BrFN_4O_2^+$, 433.0670; found, 433.0677.

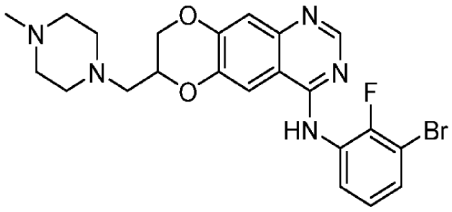
*(±)-N-(3-Bromo-2-fluorophenyl)-7-[(pyrrolidin-1-yl)methyl]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4-amine ((±)-**JGK067**).*



Following general procedure **GP-1**, compound (±)-**JGK067** was prepared from (±)-**6** (35 mg, 0.07 mmol) and pyrrolidine (30 µL, 0.36 mmol) in DMF (1.45 mL). PTLC (EtOAc, 1.5% *i*PrOH, 1.5% aq. NH_4OH) afforded (±)-**JGK067** (31 mg, 93%) as an off-white, friable foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.68 (s, 1H), 8.67 (ddd, J = 8.7, 7.5, 1.6 Hz, 2H), 7.39 (s, 1H), 7.36 (br, 1H), 7.35 (s, 1H), 7.27 (ddd, J = 8.0, 6.4, 1.5 Hz, 2H), 7.10 (td, J = 8.2, 1.5 Hz, 1H), 4.49 – 4.42 (m, 1H), 4.48 (dd, J = 11.6, 2.0 Hz, 1H), 4.15 (dd, J = 11.7, 8.0 Hz, 1H), 2.88 (dd, J = 12.9, 6.5 Hz, 1H), 2.80 (dd, J = 12.6, 5.5 Hz, 1H), 2.72 – 2.60 (m, 4H), 1.90 – 1.79 ppm (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.87, 153.32, 150.09 (d, J_{CF} = 242.6 Hz), 149.45, 146.68, 144.18, 128.71 (d, J_{CF} = 10.3 Hz), 127.15, 125.30 (d, J_{CF} = 4.7 Hz), 121.67, 114.26, 110.65, 108.56 (d, J_{CF} = 19.4 Hz), 106.06, 72.73, 67.35, 56.57, 55.15, 23.75 ppm. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{21}H_{21}BrFN_4O_2^+$, 459.0826; found, 459.0845.

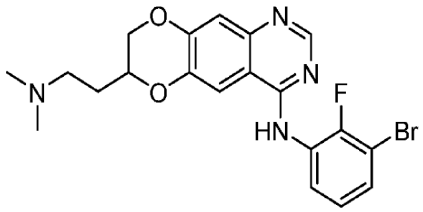
*(±)-N-(3-Bromo-2-fluorophenyl)-7-[(4-methylpiperazin-1-yl)methyl]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4-amine ((±)-**JGK068**).*



Following general procedure **GP-1**, compound (±)-**JGK068** was prepared from (±)-**6** (35 mg, 0.07 mmol) and 1-methylpiperazine (40 μL, 0.36 mmol) in DMF (1.45 mL). PTLC (EtOAc/*i*PrOH 85:15, 1.5% aq. NH_4OH) afforded (±)-**JGK068** (29 mg, 82%) as an off-white, friable foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.68 (s, 1H), 8.64 (ddd, J = 8.3, 7.3, 1.5 Hz, 1H), 7.39 (s, 1H), 7.36 (br d, J = 3.8 Hz, 1H), 7.32 (s, 1H), 7.27 (ddd, J = 8.0, 6.5, 1.6 Hz, 1H), 7.10 (td, J = 8.2, 1.5 Hz, 1H), 4.48 – 4.41 (m, 2H), 4.15 (dd, J = 11.5, 8.6 Hz, 1H), 2.78 (dd, J = 13.4, 6.0 Hz, 1H), 2.661 (dd, J = 13.4, 5.8 Hz, 1H), 2.656 (br, 4H), 2.51 (br, 4H), 2.32 ppm (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.89, 153.35, 150.15 (d, J_{CF} = 242.6 Hz), 149.40, 146.69, 144.11, 128.64 (d, J_{CF} = 10.3 Hz), 127.24, 125.30 (d, J_{CF} = 4.7 Hz), 121.78, 114.27, 110.63, 108.59 (d, J_{CF} = 19.2 Hz), 106.07, 71.80, 67.27, 58.43, 55.10, 53.96, 46.06 ppm. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{24}BrFN_5O_2^+$, 488.1092; found, 488.1109.

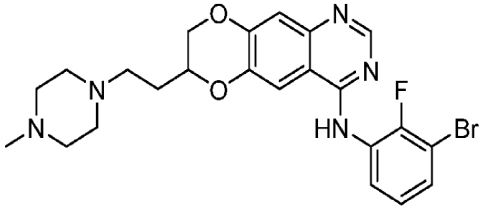
*(±)-N-(3-Bromo-2-fluorophenyl)-7-[2-(dimethylamino)ethyl]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4-amine ((±)-**JGK069**).*



Following general procedure **GP-1**, compound (±)-**JGK069** was prepared from (±)-**10** (32 mg, 0.06 mmol) and a 2 M solution of Me_2NH in THF (161 µL, 0.32 mmol) in DMF (1.3 mL). PTLC (EtOAc, 5% *i*PrOH, 1.5% aq. NH_4OH) afforded (±)-**JGK069** (19 mg, 66%) as an off-white friable foam.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.67 (s, 1H), 8.63 (ddd, J = 8.7, 7.4, 1.6 Hz, 1H), 7.373 (br, 1H), 7.371 (s, 1H), 7.28 (s, 1H), 7.28 – 7.24 (m, 1H), 7.10 (td, J = 8.2, 1.5 Hz, 1H), 4.42 (dd, J = 11.4, 2.3 Hz, 1H), 4.38 (tdd, J = 7.7, 5.1, 2.3 Hz, 1H), 4.08 (dd, J = 11.3, 7.8 Hz, 1H), 2.56 (t, J = 7.2 Hz, 2H), 2.29 (s, 6H), 1.93 (dq, J = 14.2, 7.4 Hz, 1H), 1.84 ppm (dtd, J = 14.2, 7.5, 5.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.86, 153.26, 150.14 (d, J_{CF} = 242.4 Hz), 149.42, 146.65, 144.36, 128.67 (d, J_{CF} = 10.5 Hz), 127.18, 125.30 (d, J_{CF} = 4.7 Hz), 121.77, 114.14, 110.60, 108.56 (d, J_{CF} = 19.2 Hz), 105.88, 72.19, 68.34, 55.06, 45.58, 29.16 ppm. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{21}BrFN_4O_2^+$, 447.0826; found, 447.0820.

*(±)-N-(3-Bromo-2-fluorophenyl)-7-[2-(4-methylpiperazin-1-yl)ethyl]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4-amine ((±)-**JGK070**).*

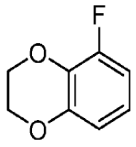


Following general procedure **GP-1**, compound (±)-**JGK070** was prepared from (±)-**10** (32 mg, 0.06 mmol) and 1-methylpiperazine (36 µL, 0.32 mmol) in DMF (1.3 mL). PTLC (EtOAc/*i*PrOH 8:2, 1.5% aq. NH_4OH) afforded (±)-**JGK070** (21 mg, 65%) as an off-white friable foam.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.66 (s, 1H), 8.62 (ddd, J = 8.5, 7.3, 1.5 Hz, 1H), 7.373 (br, 1H), 7.367 (s, 1H), 7.29 – 7.24 (m, 1H), 7.28 (s, 1H), 7.09 (td, J = 8.2, 1.5 Hz, 1H), 4.43 (dd, J = 11.4, 2.3 Hz, 1H), 4.37 (tdd, J = 7.7, 5.4, 2.3 Hz, 1H), 4.08 (dd, J = 11.4, 7.9 Hz, 1H), 2.68 – 2.54 (m, 2H), 2.50 (br, 8H), 2.30 (s, 3H), 1.94 (dtd, J = 13.6, 7.5, 6.0 Hz,

1H), 1.86 ppm (dtd, J = 14.2, 7.3, 5.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.86, 153.27, 150.16 (d, J_{CF} = 242.5 Hz), 149.41, 146.64, 144.37, 128.64 (d, J_{CF} = 10.3 Hz), 127.22, 125.28 (d, J_{CF} = 4.6 Hz), 121.81, 114.13, 110.60, 108.57 (d, J_{CF} = 19.4 Hz), 105.88, 72.38, 68.36, 55.20, 53.77, 53.25, 46.11, 28.50 ppm. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{26}BrFN_5O_2^+$, 502.1248; found, 502.1261.

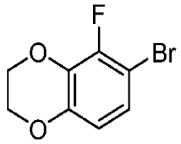
*5-Fluoro-2,3-dihydro-1,4-benzodioxine (**11**).*



A mixture of 3-fluorobenzene-1,2-diol (7233 mg, 56.5 mmol) in DMF (113 mL) was treated with K_2CO_3 (19514 mg, 141 mmol), stirred for 10 min at 23 °C, and treated with 1-bromo-2-chloroethane (9.4 mL, 113 mmol). The mixture was stirred at 23 °C for 1 h, and then at 95 °C for 16 h. The mixture was cooled to 23 °C, diluted with water (150 mL), and extracted with EtOAc (3 x 150 mL). The combined organics were washed with water (90 mL), brine (90 mL), dried (Na_2SO_4), filtered, and evaporated. FC (hexanes/EtOAc 30:1 → 10:1) afforded the title compound **11** (7973 mg, 92%) as a clear, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.78 – 6.63 (m, 3H), 4.34 – 4.26 ppm (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.05 (d, J_{CF} = 244.3 Hz), 145.27 (d, J_{CF} = 3.8 Hz), 132.78 (d, J_{CF} = 13.9 Hz), 120.02 (d, J_{CF} = 8.9 Hz), 112.74 (d, J_{CF} = 3.1 Hz), 108.52 (d, J_{CF} = 18.1 Hz), 64.50, 64.45 ppm. HRMS (DART): m/z $[M]^{\bullet+}$ calcd for $C_8H_7FO_2^{\bullet+}$, 154.0425; found, 154.0420.

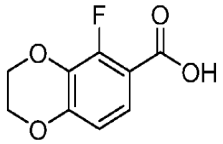
*6-Bromo-5-fluoro-2,3-dihydro-1,4-benzodioxine (**12**).*



A solution of **11** (7812 mg, 50.7 mmol) in MeOH (101 mL) was treated with NBS (9022 mg, 50.7 mmol), and heated at 70 °C for 30 min. The mixture was cooled to 23 °C, and concentrated. The residue was dissolved in DCM (700 mL), washed with water (300 mL), dried ($MgSO_4$), filtered, and evaporated. FC (hexanes/EtOAc 30:1 → 20:1) followed by drying under HV at 100 °C to remove any remaining starting material, afforded the title compound **12** (8807 mg, 75%, containing about 15% of the regioisomer) as a clear, colorless oil, which solidified in the freezer to give an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96 (dd, J = 9.0, 7.0 Hz, 1H), 6.59 (dd, J = 9.0, 2.0 Hz, 1H), 4.35 – 4.24 ppm (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.87 (d, J_{CF} = 245.1 Hz), 144.53 (d, J_{CF} = 3.5 Hz), 133.81 (d, J_{CF} = 14.6 Hz), 123.31, 113.39 (d, J_{CF} = 3.6 Hz), 109.17 (d, J_{CF} = 19.3 Hz), 64.51, 64.34 ppm. HRMS (DART): m/z $[M]^{\bullet+}$ calcd for $C_8H_6BrFO_2^{\bullet+}$, 231.9530; found, 231.9525.

*5-Fluoro-2,3-dihydro-1,4-benzodioxine-6-carboxylic acid (**13**).*



A mixture of **12** (7.0 g, 30.0 mmol) in THF (108 mL) was cooled to –78 °C, and treated dropwise with a 2.5 M solution of *n*BuLi in hexanes (12.02 mL, 30.0 mmol) during 10 min. The mixture was stirred at –78 °C for 30 min, and then transferred via cannula onto crushed dry ice (rinsed the cannula with 10 mL of THF). The mixture was allowed to warm to 23 °C, and concentrated. Water (200 mL) and 1 M NaOH (50 mL) were added to the residue, and the aq. phase was extracted with Et_2O (3 x 60 mL). The aq. phase was acidified with 6 M HCl (15 mL), and extracted with DCM (3 x 150 mL). The combined organics were washed with brine (150 mL), dried ($MgSO_4$), filtered, and evaporated. FC (hexanes/EtOAc 7:3 → 3:7) afforded the title compound **13** (3591 mg, 60%) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.90 (br, 1H), 7.33 (dd, J = 8.9, 7.7 Hz, 1H), 6.78 (dd, J = 8.9, 1.7 Hz, 1H), 4.39 – 4.29 ppm (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 164.65 (d, J_{CF} = 3.0 Hz), 151.21 (d, J_{CF} = 257.5 Hz), 148.50 (d, J_{CF} = 4.4 Hz), 132.68 (d, J_{CF} = 13.6 Hz), 122.44 (d, J_{CF} = 1.4 Hz), 112.12 (d, J_{CF} = 3.4 Hz), 111.97 (d, J_{CF} = 7.3 Hz), 64.42, 63.91 ppm. HRMS (DART): m/z $[M - H]^-$ calcd for $C_9H_6FO_4^-$, 197.0256; found, 197.0250.

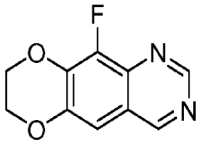
*Ethyl (5-fluoro-2,3-dihydro-1,4-benzodioxin-6-yl)carbamate (**14**).*

A mixture of **13** (650 mg, 3.28 mmol) in toluene (13.1 mL) was treated with Et_3N (1.4 mL, 9.84 mmol), and at 10 °C with DPPA (780 µL, 3.62 mmol). The mixture was stirred at 23 °C for 30 min, then at 85 °C for 1.5 h. The mixture was cooled to 23 °C, treated with EtOH (5 mL), stirred for 1.5 h at 23 °C, and concentrated. The residue was dissolved in Et_2O (150 mL), washed with sat. aq. $NaHCO_3$ (40 mL), water (40 mL), brine (40 mL), dried

($MgSO_4$), filtered, and evaporated. FC (hexanes/DCM 7:3 → 1:9) afforded the title compound **14** (512 mg, 65%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (br, 1H), 6.64 (dd, J = 9.2, 2.2 Hz, 1H), 6.56 (br, 1H), 4.32 – 4.24 (m, 4H), 4.22 (q, J = 7.1 Hz, 2H), 1.31 ppm (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.80, 142.61 (d, J_{CF} = 246.0 Hz), 140.82, 132.66 (d, J_{CF} = 12.4 Hz), 120.36 (d, J_{CF} = 6.9 Hz), 112.36, 111.81 (d, J_{CF} = 3.7 Hz), 64.72, 64.29, 61.61, 14.66 ppm. HRMS (DART): m/z $[M + H]^+$ calcd for $C_{11}H_{13}FNO_4^+$, 242.0823; found, 242.0816.

*10-Fluoro-7,8-dihydro[1,4]dioxino[2,3-g]quinazoline (**15**).*

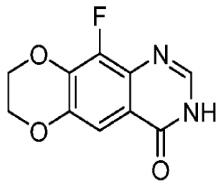


A mixture of **14** (450 mg, 1.87 mmol) and HMTA (263 mg, 1.87 mmol) in TFA (5.7 mL) was irradiated in the microwave at 110 °C for 10 min. The mixture was cooled to 23 °C, diluted with water (60 mL), treated with 6 M NaOH (12 mL), and extracted with DCM (3 x 60 mL). The combined organics were washed with water (50 mL), brine (50 mL), dried (Na_2SO_4), filtered, and evaporated to give a foamy, yellow oil.

A mixture of the oil in 10% KOH in dioxane/water 1:1 (15.5 mL) was treated with [$K_3Fe(CN)_6$] (614 mg, 1.87 mmol), and irradiated in the microwave at 100 °C for 10 min. This procedure was repeated a total of four times (4 cycles of addition of 1 equiv of potassium ferricyanide followed by microwave irradiation). The resulting mixture was diluted with water (160 mL), and extracted with DCM (3 x 120 mL). The combined organics were washed with water (100 mL), brine (100 mL), dried (Na_2SO_4), filtered, and evaporated to afford the title compound **15** (330 mg, 86%) as a yellow solid, which was used in the next step without any further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.21 (br, 1H), 9.19 (s, 1H), 7.18 (d, J = 2.0 Hz, 1H), 4.53 – 4.41 ppm (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.06 (d, J_{CF} = 2.9 Hz), 153.81 (d, J_{CF} = 1.8 Hz), 145.76 (d, J_{CF} = 2.9 Hz), 144.40 (d, J_{CF} = 256.1 Hz), 138.56 (d, J_{CF} = 11.0 Hz), 136.73 (d, J_{CF} = 10.1 Hz), 119.81 (d, J_{CF} = 2.7 Hz), 106.55 (d, J_{CF} = 4.3 Hz), 64.78, 64.34 ppm. HRMS (DART): m/z $[M + H]^+$ calcd for $C_{10}H_8FN_2O_2^+$, 207.0564; found, 207.0563.

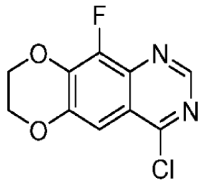
*10-Fluoro-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4(3H)-one (**16**).*



A solution of **15** (306 mg, 1.48 mmol) in AcOH (1 mL) was treated dropwise with a 0.833 M solution of CAN in water (7.12 mL, 5.94 mmol), and stirred at 23 °C for 15 min. The white precipitate was collected by filtration, and washed with water (2 x 2 mL), acetonitrile (2 x 2 mL), DCM (2 mL), and Et_2O (2 mL) to afford a first batch of the title compound. The aq. filtrate was neutralized to pH ~7 with 1 M NaOH, and the white precipitate was collected as before by filtration, followed by washings to afford a second batch of the title compound **16** (81 mg, 25%) as a white solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.19 (br, 1H), 7.98 (d, J = 3.3 Hz, 1H), 7.32 (s, 1H), 4.52 – 4.28 ppm (m, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 159.31, 144.58 (d, J_{CF} = 251.8 Hz), 144.28, 143.80 (d, J_{CF} = 3.4 Hz), 137.86 (d, J_{CF} = 11.1 Hz), 132.94 (d, J_{CF} = 8.9 Hz), 115.75, 106.62 (d, J_{CF} = 3.7 Hz), 64.57, 64.02 ppm. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{10}H_8FN_2O_3^+$, 223.0513; found, 223.0503.

*4-Chloro-10-fluoro-7,8-dihydro[1,4]dioxino[2,3-g]quinazoline (**17**).*

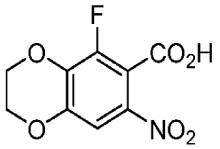


A stirred suspension of **16** (92 mg, 0.41 mmol) in toluene (1.2 mL) was treated with DIPEA (220 µL, 1.26 mmol), followed by dropwise addition of $POCl_3$ (103 µL, 1.12 mmol) at 10 °C. The mixture was stirred at 23 °C for 1 h, then at 90 °C for 5 h, and concentrated. The residue was treated with sat. aq. $NaHCO_3$ (10 mL) at 0 °C for 5 min, diluted with water (5 mL), and extracted with DCM (3 x 7 mL). The combined organics were washed with half-sat. aq. $NaHCO_3$ (7 mL), brine (7 mL), dried (Na_2SO_4), filtered, and evaporated to afford the title compound **17** (51 mg, 51%) as a light-brown solid, which was used in the next step without any further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.90 (s, 1H), 7.51 (d, J = 2.0 Hz, 1H), 4.55 – 4.43 ppm (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.48 (d, J_{CF} = 4.3 Hz), 152.31, 146.29 (d, J_{CF} = 3.3 Hz), 144.63 (d, J_{CF} = 256.2 Hz), 138.95 (d, J_{CF} = 11.3 Hz), 137.68 (d, J_{CF} = 10.2

Hz), 118.56 (d, J_{CF} = 2.4 Hz), 105.82 (d, J_{CF} = 4.2 Hz), 64.81, 64.41 ppm. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{10}H_7ClFN_2O_2^+$, 241.0175; found, 241.0174.

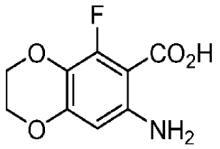
*5-Fluoro-7-nitro-2,3-dihydro-1,4-benzodioxine-6-carboxylic acid (**18**).*



A mixture of **13** (1500 mg, 7.57 mmol) in AcOH (7.5 mL) was treated dropwise with H_2SO_4 (2.02 mL) at 10 °C. The vigorously stirred mixture was treated dropwise with 65% HNO_3 (2.6 mL) at 0 °C during 10 min. The resulting mixture was stirred at 0 °C for 30 min, and then at 23 °C for 16 h. The mixture was poured into ice-water (40 mL), and the white precipitate was collected by filtration (washings with cold water, 40 mL), and dried in a desiccator to afford the title compound **18** (1280 mg, 70%) as a white solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 14.09 (br, 1H), 7.62 (d, J = 1.7 Hz, 1H), 4.52 – 4.40 ppm (m, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 162.71, 147.16 (d, J_{CF} = 248.7 Hz), 144.72 (d, J_{CF} = 5.1 Hz), 138.15 (d, J_{CF} = 13.7 Hz), 137.10 (d, J_{CF} = 6.6 Hz), 113.44 (d, J_{CF} = 20.3 Hz), 109.52 (d, J_{CF} = 2.3 Hz), 64.97, 64.48 ppm. HRMS (DART): *m/z* $[M - H]^-$ calcd for $C_9H_5FNO_6^-$, 242.0106; found, 242.0124.

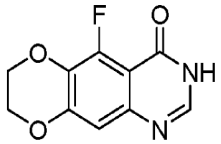
*7-Amino-5-fluoro-2,3-dihydro-1,4-benzodioxine-6-carboxylic acid (**19**).*



A mixture of **18** (500 mg, 2.06 mmol) and 5% Pd/C (223 mg, 0.10 mmol) in MeOH (21 mL) was stirred under an atmosphere of H_2 at 23 °C for 13.5 h. The mixture was filtered through Celite (washings with EtOH), and evaporated to give the title compound **19** (418 mg, 95%) as a grey solid, which did not seem to be very stable.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.35 (br, 2H), 6.04 (d, J = 1.9 Hz, 1H), 4.29 – 4.24 (m, 2H), 4.19 – 4.14 ppm (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 167.36 (d, J_{CF} = 2.9 Hz), 151.36 (d, J_{CF} = 252.0 Hz), 148.86 (d, J_{CF} = 7.0 Hz), 145.81 (d, J_{CF} = 5.7 Hz), 122.88 (d, J_{CF} = 15.4 Hz), 97.19 (d, J_{CF} = 2.9 Hz), 95.37 (d, J_{CF} = 10.9 Hz), 64.95, 63.58 ppm. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_9H_9FNO_4^+$, 214.0510; found, 214.0508.

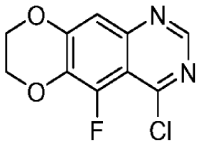
*5-Fluoro-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4(3H)-one (**20**).*



A mixture of **19** (417 mg, 1.96 mmol) in formamide (2.3 mL, 58.7 mmol) was stirred at 120–125 °C for 16 h. The mixture was cooled to 0 °C, and treated with water (4 mL), stirred for 30 min, diluted with water (4 mL), and filtered. The residue was washed with cold water (3 x 5 mL), and dried over Drierite under HV to afford the title compound **20** (249 mg, 57%) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.00 (br, 1H), 7.90 (d, J = 3.6 Hz, 1H), 6.93 (d, J = 1.9 Hz, 1H), 4.45 – 4.35 ppm (m, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 157.64 (d, J_{CF} = 3.0 Hz), 149.70 (d, J_{CF} = 6.0 Hz), 148.45 (d, J_{CF} = 261.3 Hz), 144.60, 142.99, 131.47 (d, J_{CF} = 12.7 Hz), 108.76 (d, J_{CF} = 3.5 Hz), 106.38 (d, J_{CF} = 3.8 Hz), 64.69, 63.98 ppm. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{10}H_8FN_2O_3^+$, 223.0513; found, 223.0510.

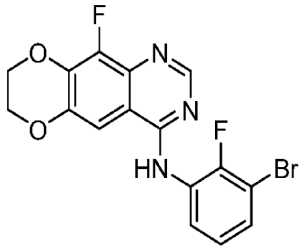
*4-Chloro-5-fluoro-7,8-dihydro[1,4]dioxino[2,3-g]quinazoline (**21**).*



A stirred suspension of **20** (90 mg, 0.41 mmol) in toluene (1.2 mL) was treated with DIPEA (215 µL, 1.24 mmol), followed by dropwise addition of $POCl_3$ (100 µL, 1.09 mmol) at 10 °C. The mixture was stirred at 23 °C for 1 h, then at 88 °C for 5 h, and concentrated. The residue was treated with sat. aq. $NaHCO_3$ (10 mL) at 0 °C, diluted with water (5 mL), and extracted with DCM (3 x 7 mL). The combined organics were washed with half-sat. aq. $NaHCO_3$ (7 mL), brine (7 mL), dried (Na_2SO_4), filtered, and evaporated to afford the title compound **21** (96 mg, 99%) as a light-orange solid, which was used in the next step without any further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.83 (s, 1H), 7.35 (d, J = 2.0 Hz, 1H), 4.51 – 4.45 ppm (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.76 (d, J_{CF} = 4.5 Hz), 152.70 (d, J_{CF} = 2.3 Hz), 151.66 (d, J_{CF} = 4.9 Hz), 146.08, 144.51 (d, J_{CF} = 261.8 Hz), 134.04 (d, J_{CF} = 14.0 Hz), 110.85 (d, J_{CF} = 7.7 Hz), 109.43 (d, J_{CF} = 4.0 Hz), 64.89, 64.37 ppm. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{10}H_7ClFN_2O_2^+$, 241.0175; found, 241.0176.

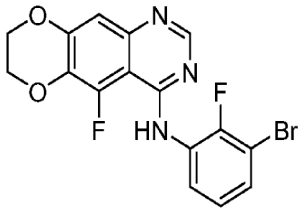
N-(3-Bromo-2-fluorophenyl)-10-fluoro-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4-amine ***(JGK071)***.



Following general procedure **GP-2**, compound **JGK071** was prepared from chloroquinazoline **17** (35 mg, 0.15 mmol) and 3-bromo-2-fluoroaniline. FC (DCM/EtOAc 1:0 → 8:2) afforded **JGK071** (44 mg, 77%) as a white solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.76 (s, 1H), 8.38 (s, 1H), 7.80 (d, J = 1.8 Hz, 1H), 7.62 (ddd, J = 8.0, 6.3, 1.6 Hz, 1H), 7.54 (ddd, J = 8.5, 7.1, 1.6 Hz, 1H), 7.22 (td, J = 8.0, 1.2 Hz, 1H), 4.53 – 4.40 ppm (m, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 156.93 (d, J_{CF} = 3.7 Hz), 153.44 (d, J_{CF} = 247.5 Hz), 153.12, 144.04 (d, J_{CF} = 250.0 Hz), 143.97 (d, J_{CF} = 3.2 Hz), 137.04 (d, J_{CF} = 10.9 Hz), 135.62 (d, J_{CF} = 9.9 Hz), 130.48, 127.89, 127.62 (d, J_{CF} = 13.1 Hz), 125.51 (d, J_{CF} = 4.5 Hz), 108.58 (d, J_{CF} = 23.4 Hz), 108.51, 103.25 (d, J_{CF} = 3.9 Hz), 64.63, 64.21 ppm. HRMS (DART): m/z $[M + H]^+$ calcd for $C_{16}H_{11}BrF_2N_3O_2^+$, 393.9997; found, 393.9999.

N-(3-Bromo-2-fluorophenyl)-5-fluoro-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4-amine ***(JGK072)***.

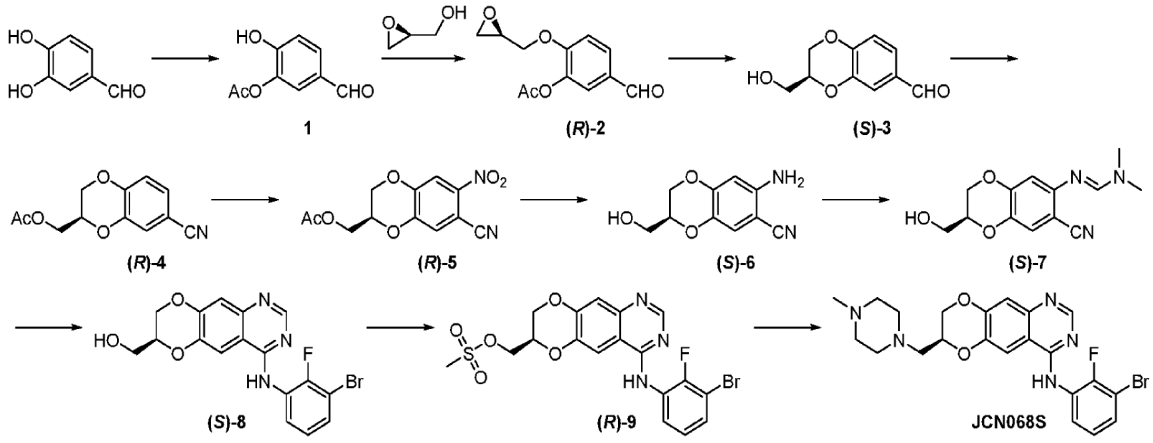


Following general procedure **GP-2**, compound **JGK072** was prepared from chloroquinazoline **21** (35 mg, 0.15 mmol) and 3-bromo-2-fluoroaniline. FC (DCM/EtOAc 1:0 → 8:2) afforded **JGK072** (47 mg, 82%) as a white solid.

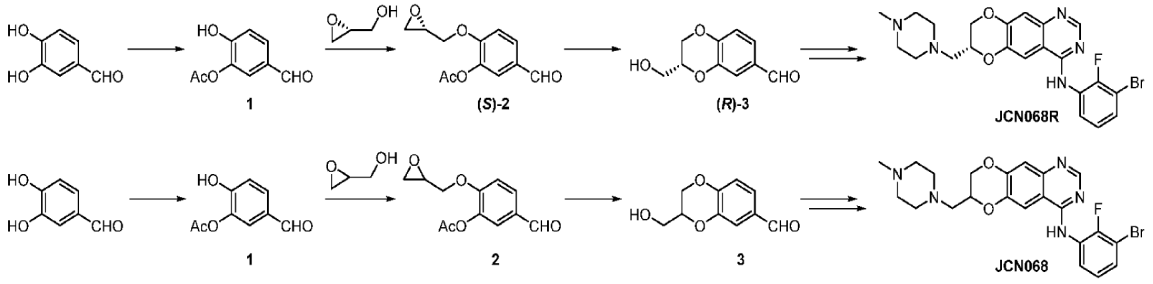
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.67 (ddd, J = 8.6, 7.2, 1.5 Hz, 1H), 8.62 (s, 1H), 8.52 (dd, J = 19.6, 2.2 Hz, 1H), 7.29 (ddd, J = 8.1, 6.4, 1.5 Hz, 1H), 7.23 (d, J = 2.0 Hz, 1H), 7.10 (td, J = 8.2, 1.6 Hz, 1H), 4.48 – 4.42 ppm (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.27 (d, J_{CF} = 5.2 Hz), 153.90, 150.34 (d, J_{CF} = 243.9 Hz), 149.93 (d, J_{CF} = 6.2 Hz), 145.75

(d, J_{CF} = 250.3 Hz), 144.78, 131.96 (d, J_{CF} = 15.6 Hz), 128.43 (d, J_{CF} = 10.4 Hz), 127.71, 125.20 (d, J_{CF} = 4.7 Hz), 122.48, 109.69 (d, J_{CF} = 3.3 Hz), 108.63 (d, J_{CF} = 19.2 Hz), 101.42 (d, J_{CF} = 7.2 Hz), 64.84, 64.48 ppm. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{16}H_{11}BrF_2N_3O_2^+$, 393.9997; found, 393.9996.

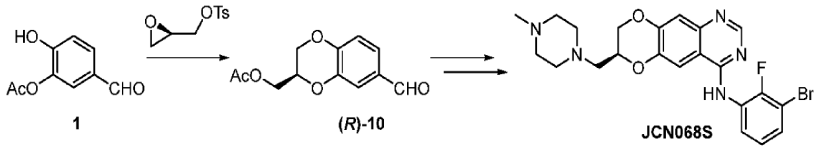
Example 3: Preparation of Further Exemplary Compounds of the JGK series



Scheme 1. Synthesis of **JGK068S**.

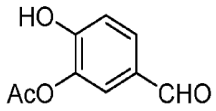


Scheme 2. The preparation of the (*R*)-enantiomer **JGK068R** or of racemic mixtures (**JGK068**) follows the same route as shown in Scheme 1, but employs (*R*)- or racemic glycidol, respectively.



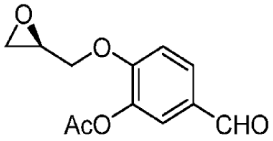
Scheme 3. Synthesis of benzodioxane carbaldehyde (*R*)-**10** in one step from benzaldehyde **1** with chiral glycidyl tosylate. This route avoids the Mitsunobu reaction in Scheme 1 (preparation of **2** from **1**). Compound (*R*)-**10** can be used in the route shown in Scheme 1 for the preparation of **JGK068S**.

*5-Formyl-2-hydroxyphenyl acetate (**1**).*



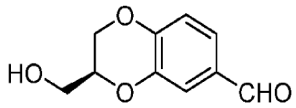
A mixture of 3,4-dihydroxybenzaldehyde (100 g, 0.724 mol) in THF (965 mL) was cooled to 0 °C, and treated with 10% aq. NaOH (724 mL, 1.81 mol) over 4–5 min. After the reaction mixture was stirred at 0 °C for 15 min, acetic anhydride (Ac_2O, 82.1 mL, 0.869 mol) was added dropwise over 20 min. The mixture was stirred for 30 min at the same temperature, and then poured into a mixture of EtOAc (1.25 L) and 2 M HCl (1.13 L) at 0 °C. The phases were separated, and the aq. phase was extracted with EtOAc (4 x 250 mL). The combined organics were washed with water (2 x 500 mL), brine (500 mL), dried (Na_2SO_4), filtered, and evaporated. The residue was treated with a small amount of *n*-heptane and evaporated (3x). Recrystallization from EtOAc (275 mL; crystals washed with Et_2O) gave a first crop of the title compound **1** (66.96 g, 51%) as light-brown crystals. Recrystallization of the mother liquor from EtOAc gave a second crop of the title compound **1** (29.436 g, 23%) as a light-brown solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.85 (s, 1H), 7.73 – 7.65 (m, 2H), 7.11 (d, J = 8.8 Hz, 1H), 6.34 (br, 1H), 2.39 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 190.40, 168.99, 152.96, 138.81, 130.24, 129.72, 124.13, 117.87, 21.09. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_9H_9O_4^+$, 181.0495; found, 181.0488.

*5-Formyl-2-{[(2R)-oxiran-2-yl]methoxy}phenyl acetate ((R)-**2**).*



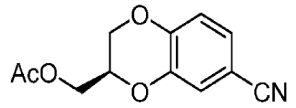
A mixture of **1** (32.5 g, 0.18 mol) and triphenylphosphine (PPh_3, 70.976g , 0.27 mol) in THF (905 mL) was treated with (*S*)-glycidol (17.95 mL, 0.27 mol), cooled to 0 °C, and treated dropwise with diisopropyl azodicarboxylate (DIAD, 56.8 mL, 0.289 mmol) over 30 min. The mixture was stirred for an additional 10 min at 0 °C, after which the cooling bath was removed, and stirring was continued at 23 °C for 15.5 h. All volatiles were evaporated, and crude (*R*)-**2**, obtained as a brown oil, was used without any further purification in the next step.

*(3S)-3-(Hydroxymethyl)-2,3-dihydro-1,4-benzodioxine-6-carbaldehyde ((S)-**3**).*



A mixture of crude (*R*)-**2** in MeOH (1.564 L) was treated with K_2CO_3 (49.87 g, 0.36 mol) and stirred at 23 °C for 18.5 h, and then the solvent was evaporated. The residue was suspended in half-sat. NH_4Cl (750 mL), and extracted with EtOAc (3 x 500 mL). The combined organics were washed with water (250 mL), brine (250 mL), dried (Na_2SO_4), filtered, and evaporated. The crude material was purified by several rounds of flash chromatography (hexanes/EtOAc 9:1 → 1:1) as well as by precipitation from hexanes/Et_2O 1:1 (to remove triphenylphospine oxide Ph_3PO), to afford the title compound (*S*)-**3** (17.322 g, 49% over two steps) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.81 (s, 1H), 7.43 (d, J = 1.8 Hz, 1H), 7.41 (dd, J = 8.1, 1.9 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 4.39 (dd, J = 11.4, 2.3 Hz, 1H), 4.31 – 4.25 (m, 1H), 4.20 (dd, J = 11.3, 7.9 Hz, 1H), 3.95 (dd, J = 12.1, 4.3 Hz, 1H), 3.87 (dd, J = 12.1, 4.9 Hz, 1H), 2.18 (br, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 190.79, 148.76, 143.46, 130.79, 124.46, 118.33, 117.70, 73.31, 65.61, 61.54. HRMS (DART): *m/z* [M + H]$^+$ calcd for $C_{10}H_{11}O_4^+$, 195.0652; found, 195.0650.

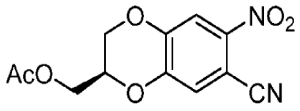
*[(2R)-7-Cyano-2,3-dihydro-1,4-benzodioxin-2-yl]methyl acetate ((R)-**4**).*



A mixture of (*S*)-**3** (17.322 g, 0.089 mol) in AcOH (189 mL) was treated with KOAc (22.944 g, 0.234 mol), stirred at 23 °C for 10 min, and then treated with NH_2OH•HCl (16.233 g, 0.234 mol). The resulting mixture was stirred at 120 – 125 °C for 18.5 h. The mixture was cooled to 23 °C, poured into water (1 L), and extracted with EtOAc (4 x 250 mL). The combined organics were treated with 3.5 M NaOH (400 mL) and sat. aq. $NaHCO_3$ (100 mL) to obtain a final pH of ~8, and the emulsion was stirred at 23 °C for 1 h. The organic layer was separated, and washed with sat. aq. $NaHCO_3$ (300 mL), water (300 mL), brine (300 mL), dried (Na_2SO_4), filtered, and evaporated. Purification by flash chromatography (hexanes/EtOAc 10:1 → 6:4) afforded the title compound (*R*)-**4** (13.513 g, 65%) as a clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, J = 2.0 Hz, 1H), 7.16 (dd, J = 8.4, 2.0 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 4.43 – 4.38 (m, 1H), 4.36 (dd, J = 11.6, 2.4 Hz, 1H), 4.34 (dd, J = 11.1, 4.5 Hz, 1H), 4.30 (dd, J = 11.6, 4.6 Hz, 1H), 4.11 (dd, J = 11.5, 7.2 Hz, 1H),

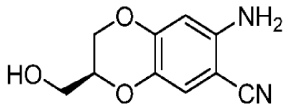
2.12 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.64, 147.13, 143.11, 126.28, 121.56, 118.85, 118.32, 105.13, 71.11, 65.45, 62.24, 20.83. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{12}H_{12}NO_4^+$, 234.0761; found, 234.0759.

*[(2R)-7-Cyano-6-nitro-2,3-dihydro-1,4-benzodioxin-2-yl]methyl acetate ((R)-**5**).*



A mixture of (*R*)-**4** (13.345 g, 57.2 mmol) in Ac_2O (74.3 mL) was treated with H_2SO_4 (3.05 mL, 57.2 mmol), cooled to 0 °C, and treated dropwise with 70% HNO_3 (19.63 mL, 286 mmol) at 0 °C over 35 min. The mixture was stirred for another 2 h at 0 °C, and then at 23 °C for 3.5 h. The mixture was poured into ice-water (850 mL), and the pH was adjusted to ~7 with 6 M NaOH (320 mL). Sat. aq. $NaHCO_3$ (200 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 x 500 mL). The combined organics were washed with sat. aq. $NaHCO_3$ (400 mL), water (400 mL), brine (400 mL), dried (Na_2SO_4), filtered, and evaporated to afford the title compound (*R*)-**5** (15.696 g, 99%) as a yellow oil, which was used in the next step without any further purification. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.96 (s, 1H), 7.80 (s, 1H), 4.73 – 4.67 (m, 1H), 4.58 (dd, J = 11.8, 2.6 Hz, 1H), 4.36 (dd, J = 12.5, 3.7 Hz, 1H), 4.31 (dd, J = 12.5, 5.7 Hz, 1H), 4.27 (dd, J = 11.8, 7.0 Hz, 1H), 2.05 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 170.11, 147.75, 146.26, 142.23, 123.77, 115.21, 115.17, 100.06, 72.00, 64.98, 61.72, 20.52. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{12}H_{11}N_2O_6^+$, 279.0612; found, 279.0601.

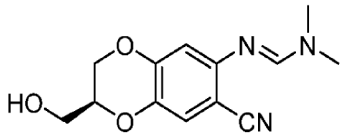
*(3S)-7-Amino-3-(hydroxymethyl)-2,3-dihydro-1,4-benzodioxine-6-carbonitrile ((S)-**6**).*



A suspension of (*R*)-**5** (15.591 g, 56 mmol) in water/ethanol 1:1 (250 mL) was treated with $Na_2S_2O_4$ (39.266 g, 185 mmol), and the mixture was stirred at 50 °C for 105 min, and then heated to 70 °C for 2 h while treated portionwise with conc. HCl (73.6 mL , 0.897 mol) during that time. The mixture was cooled to 23 °C, poured on ice, and the pH was adjusted to ~10 with 6 M NaOH (200 mL) and half-sat. $NaHCO_3$ (500 mL). The mixture was extracted with EtOAc (3 x 500 mL). The combined organics were washed with water (500 mL), brine (500 mL), dried (Na_2SO_4), filtered, and evaporated to afford crude (*S*)-**6** (9.483 g, 82%) as an orange-yellow solid, which was used in the next step without any further purification. ^{1}H

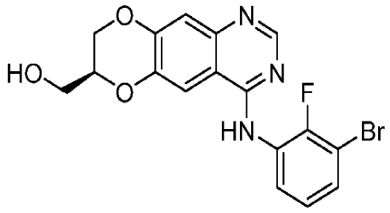
NMR (500 MHz, DMSO-d_6): δ 6.92 (s, 1H), 6.29 (s, 1H), 5.50 (br, 2H), 5.04 (t, J = 5.7 Hz, 1H), 4.32 (dd, J = 10.7, 1.6 Hz, 1H), 4.07 – 3.99 (m, 1H), 4.00 (dd, J = 11.2, 8.3 Hz, 1H), 3.64 – 3.51 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 148.50, 147.29, 134.39, 119.04, 118.04, 102.45, 86.72, 73.25, 65.92, 59.77. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{10}H_{10}N_2O_3^{\bullet+}$, 206.0686; found, 206.0685.

N'-[(2S)-7-Cyano-2-(hydroxymethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]-N,N-dimethylmethan-imidamide ((S)-7).



A mixture of (*S*)-**6** (9.38 g, 45.5 mmol) in toluene (117 mL) was treated with AcOH (143 µL, 2.5 mmol) and DMF-DMA (13.1 mL, 98.9 mmol), and the mixture was stirred at 105 °C for 3 h. The evaporated MeOH (~4 – 5 mL) was collected in a Dean-Stark trap to monitor the progress of the reaction. The mixture was cooled to 23 °C and evaporated to obtain crude (*S*)-**7** (14.243 g, quant.) as a viscous, brown oil, which was used in the next step without any further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.05 (s, 1H), 6.48 (s, 1H), 4.33 (dd, J = 11.2, 2.0 Hz, 1H), 4.23 – 4.17 (m, 1H), 4.13 (dd, J = 11.2, 8.1 Hz, 1H), 3.90 (dd, J = 12.1, 4.2 Hz, 1H), 3.83 (dd, J = 12.1, 4.8 Hz, 1H), 3.07 (s, 3H), 3.05 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.40, 153.78, 147.68, 138.63, 121.08, 118.64, 108.16, 99.31, 73.34, 65.83, 61.67, 40.51, 34.82. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{13}H_{16}N_3O_3^+$, 262.1186; found, 262.1183.

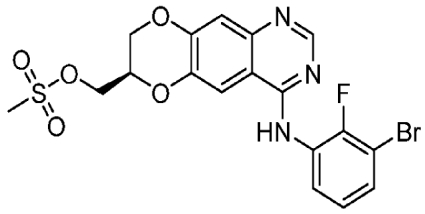
*[(7S)-4-(3-Bromo-2-fluoroanilino)-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-7-yl]methanol ((S)-**8**).*



A mixture of (*S*)-**7** in AcOH (152 mL) was treated with 3-bromo-2-fluoroaniline (6.63 mL, 59.1 mmol), and the mixture was stirred at 125 – 130 °C for 3 h. The mixture was cooled to 23 °C, poured into ice-water (500 mL), and the pH was adjusted to ~9 with sat. aq. NH_4OH (185 mL) and half-sat. aq. $NaHCO_3$ (200 mL). The mixture was extracted with EtOAc (3 x 400 mL), and the combined organics were washed with half-sat. aq. $NaHCO_3$ (400 mL),

water (400 mL), brine (400 mL), dried (Na_2SO_4), filtered, and evaporated. The residue was dissolved in MeOH (272 mL), and treated with K_2CO_3 (12.579 g, 91 mmol), stirred at 23 °C for 1 h, and evaporated. The residue was suspended in half-sat. aq. NH_4Cl (700 mL), and extracted with EtOAc (3 x 400 mL). The combined organics were washed with water (400 mL), brine (400 mL), dried (Na_2SO_4), filtered, and evaporated. The orange-yellow residue was suspended in EtOAc, warmed to 65 °C, and then let slowly cool down to 23 °C overnight. Filtration, and washing of the residue with cold hexanes (2 x 15 mL) and Et_2O (2 x 15 mL), and drying under high vacuum afforded the title compound (*S*)-**8** (9.407 g, 50.9% over two steps) as a fine, yellow powder. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.69 (s, 1H), 8.33 (s, 1H), 7.99 (s, 1H), 7.59 (ddd, J = 8.0, 6.2, 1.6 Hz, 1H), 7.54 (ddd, J = 8.4, 7.0, 1.6 Hz, 1H), 7.24 – 7.17 (m, 1H), 7.20 (s, 1H), 5.20 (t, J = 5.6 Hz, 1H), 4.49 (dd, J = 11.5, 2.4 Hz, 1H), 4.37 – 4.29 (m, 1H), 4.21 (dd, J = 11.6, 7.4 Hz, 1H), 3.76 – 3.64 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 157.22, 153.38 (d, J_{CF} = 247.0 Hz), 153.09, 148.87, 145.94, 143.37, 130.08, 128.09 (d, J_{CF} = 12.9 Hz), 127.75, 125.43 (d, J_{CF} = 4.5 Hz), 112.29, 109.81, 108.54 (d, J_{CF} = 20.0 Hz), 108.49, 73.77, 65.52, 59.76. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{17}H_{14}BrFN_3O_3^+$, 406.0197; found, 406.0185.

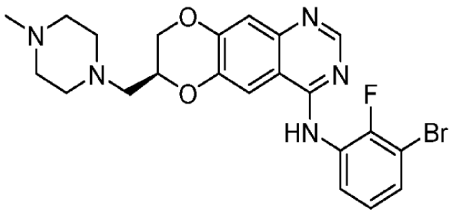
*[(7R)-4-(3-Bromo-2-fluoroanilino)-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-7-yl]methyl methanesulfonate ((R)-**9**).*



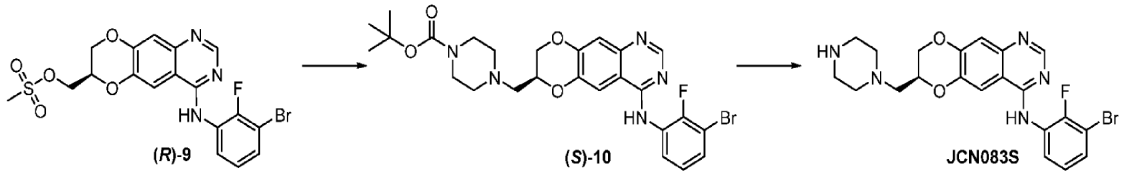
A mixture of (*S*)-**8** (9.01 g, 22.2 mmol) and Me_3N•HCl (234 mg, 2.45 mmol) in acetonitrile (148 mL) was treated with Et_3N (6.18 mL, 44.4 mmol), cooled to 0 – 5 °C, and treated dropwise with a solution of MsCl (2.57 mL, 33.2 mmol) in acetonitrile (17 mL; rinsed with 3 mL) over 10 min. The mixture was stirred at 0 °C for 1 h. Water (100 mL) was added, and most of the acetonitrile was evaporated in vacuo. Additional water (700 mL) was added, and the mixture was extracted with EtOAc (3 x 400 mL). The combined organics were washed with water (400 mL), brine (400 mL), dried (Na_2SO_4), filtered, and evaporated to afford the title compound (*R*)-**9** (10.33 g, 96%) as a yellow, friable foam, which was used in the next step without any further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.70 (s, 1H), 8.62 (ddd, J = 8.7, 7.3, 1.6 Hz, 1H), 7.44 (s, 1H), 7.362 (s, 1H), 7.360 (br, 1H), 7.29 (ddd, J =

8.1, 6.5, 1.5 Hz, 1H), 7.11 (td, *J* = 8.2, 1.6 Hz, 1H), 4.67 – 4.61 (m, 1H), 4.54 – 4.51 (m, 2H), 4.50 (dd, *J* = 11.7, 2.4 Hz, 1H), 4.29 (dd, *J* = 11.8, 7.1 Hz, 1H), 3.13 (s, 3H).

*(7S)-N-(3-Bromo-2-fluorophenyl)-7-[(4-methylpiperazin-1-yl)methyl]-7,8-dihydro[1,4]dioxino [2,3-g]quinazolin-4-amine (**JGK068S**).*

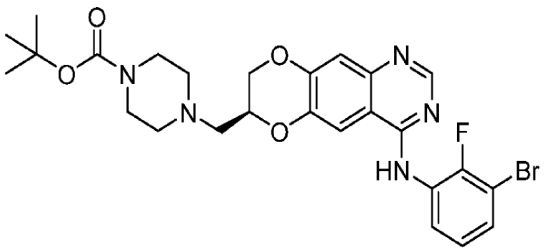


A mixture of (*R*)-**9** in DMF (427 mL) was treated with 1-methylpiperazine (11.83 mL, 107 mmol) and Et_3N (5.95 mL, 42.7 mmol), and the mixture was stirred at 85 °C for 24 h. The mixture was cooled to 23 °C, and evaporated. The residue was dissolved in EtOAc (1.2 L), and washed with 0.5 M NaOH (4 x 250 mL), brine (250 mL), dried (Na_2SO_4), filtered, and evaporated. Purification by flash chromatography (CH_2Cl_2/MeOH 1:0 → 8:2) afforded the title compound **JGK068S** (6.013 g, 58% over two steps) as an off-white, friable foam. ^1H NMR (500 MHz, $CDCl_3$): δ 8.67 (s, 1H), 8.63 (ddd, *J* = 8.7, 7.3, 1.6 Hz, 1H), 7.374 (s, 1H), 7.372 (br, 1H), 7.32 (s, 1H), 7.26 (ddd, *J* = 8.1, 6.5, 1.5 Hz, 1H), 7.09 (td, *J* = 8.2, 1.6 Hz, 1H), 4.48 – 4.40 (m, 2H), 4.14 (dd, *J* = 11.8, 8.0 Hz, 1H), 2.77 (dd, *J* = 13.4, 6.0 Hz, 1H), 2.653 (dd, *J* = 13.4, 5.8 Hz, 1H), 2.648 (br, 4H), 2.51 (br, 4H), 2.32 (s, 3H).



Scheme 4. Synthesis of JGK083S.

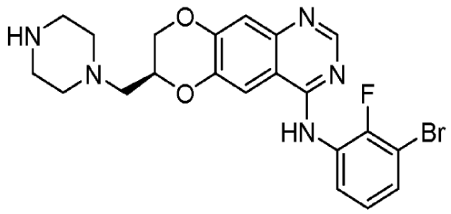
*tert-Butyl {[(7S)-4-(3-bromo-2-fluoroanilino)-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-7-yl]methyl}piperazine-1-carboxylate ((S)-**10**).*



Following general procedure **GP-1** of Example 16, compound (*S*)-**10** was prepared from *R*-**9** (91 mg, 0.188 mmol) and *tert*-butyl piperazine-1-carboxylate (175 mg, 0.94 mmol)

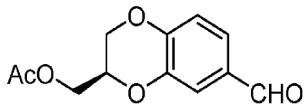
in DMF (3.8 mL), and stirred at 85 °C for 15 h. PTLC (CH_2Cl_2/EtOAc 4:6) afforded (*S*)-**10** (50 mg, 46%) as an off-white, friable foam. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (s, 1H), 8.65 (ddd, J = 8.3, 7.4, 1.5 Hz, 1H), 7.39 (s, 1H), 7.36 (br, 1H), 7.31 (s, 1H), 7.27 (ddd, J = 8.0, 6.5, 1.5 Hz, 1H), 7.11 (td, J = 8.2, 1.5 Hz, 1H), 4.50 – 4.42 (m, 2H), 4.17 (dd, J = 12.1, 8.2 Hz, 1H), 3.47 (t, J = 5.1 Hz, 4H), 2.78 (dd, J = 13.4, 5.9 Hz, 1H), 2.67 (dd, J = 13.5, 5.9 Hz, 1H), 2.62 – 2.47 (m, 4H), 1.47 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.89, 154.83, 153.39, 150.15 (d, J_{CF} = 242.4 Hz), 149.36, 146.72, 144.02, 128.63 (d, J_{CF} = 10.3 Hz), 127.27, 125.34, 121.78, 114.34, 110.66, 108.60 (d, J_{CF} = 19.5 Hz), 106.06, 79.97, 71.76, 67.18, 58.56, 53.96, 28.57, one carbon signal missing (probably due to overlapping peaks). HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{26}H_{30}BrFN_5O_4^+$, 574.1460; found, 574.1432.

*(7S)-N-(3-Bromo-2-fluorophenyl)-7-[(piperazin-1-yl)methyl]-7,8-dihydro[1,4]dioxino [2,3-g]quinazolin-4-amine (**JGK083S**).*



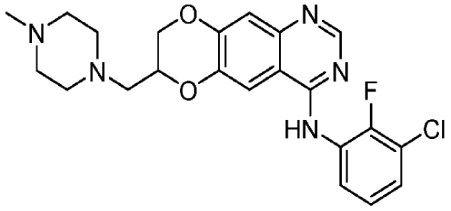
A mixture of (*S*)-**10** (42 mg, 0.073 mmol) in CH_2Cl_2 (500 µL) and TFA (250 µL) was stirred at 23 °C for 12 h. The mixture was diluted with 1 M HCl (20 mL), and washed with CH_2Cl_2 (3 x 7 mL). The aqueous phase was diluted with 6 M NaOH (4 mL) to pH >12, and extracted with EtOAc (3 x 8 mL). The combined organics were washed with brine (8 mL), dried (Na_2SO_4), filtered, and evaporated. Purification by PTLC (CH_2CL_2/MeOH 8:2) afforded the title compound **JGK083S** (18 mg, 52%) as a white, friable foam. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (s, 1H), 8.66 (ddd, J = 8.2, 7.3, 1.6 Hz, 1H), 7.39 (s, 1H), 7.35 (br d, J = 4.0 Hz, 1H), 7.32 (s, 1H), 7.27 (ddd, J = 8.1, 6.5, 1.6 Hz, 1H), 7.11 (td, J = 8.2, 1.5 Hz, 1H), 4.50 – 4.42 (m, 2H), 4.19 – 4.13 (m, 1H), 2.93 (t, J = 4.9 Hz, 4H), 2.76 (dd, J = 13.4, 5.9 Hz, 1H), 2.63 (dd, J = 13.4, 6.0 Hz, 1H), 2.63 – 2.50 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.88, 153.35, 150.12 (d, J_{CF} = 242.3 Hz), 149.45, 146.71, 144.17, 128.67 (d, J_{CF} = 10.4 Hz), 127.21, 125.32 (d, J_{CF} = 4.7 Hz), 121.74, 114.30, 110.64, 108.58 (d, J_{CF} = 19.3 Hz), 106.02, 71.70, 67.32, 59.19, 55.54, 46.23. HRMS (DART): *m/z* $[M - H]^-$ calcd for $C_{21}H_{20}BrFN_5O_2^-$, 472.0790; found, 472.0773.

*[(2R)-7-Formyl-2,3-dihydro-1,4-benzodioxin-2-yl]methyl acetate ((R)-**10**).*



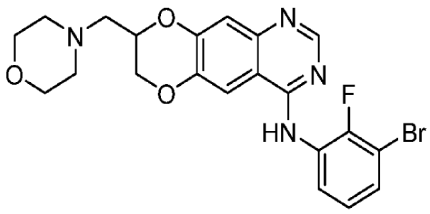
A mixture of **1** (150 mg, 0.833 mmol) and (2*R*)-glycidyl tosylate (203 mg, 0.891 mmol) in DMF (2 mL) was treated with K_2CO_3 (181 mg, 1.31 mmol), and the mixture was stirred at 60 °C for 15 h. The mixture was cooled to 23 °C, water (30 mL) was added, and the mixture was extracted with EtOAc (3 x 15 mL). The combined organics were washed with water (15 mL), brine (15 mL), dried (Na_2SO_4), filtered, and evaporated. Purification by preparative thin layer chromatography (hexanes/EtOAc 7:3) afforded the title compound (*R*)-**10** (111 mg, 56%) as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.82 (s, 1H), 7.44 (d, *J* = 1.8 Hz, 1H), 7.42 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 4.46 – 4.39 (m, 1H), 4.37 (dd, *J* = 11.5, 2.4 Hz, 1H), 4.35 (dd, *J* = 11.7, 4.9 Hz, 1H), 4.31 (dd, *J* = 11.9, 5.1 Hz, 1H), 4.13 (dd, *J* = 11.5, 7.1 Hz, 1H), 2.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 190.72, 170.67, 148.57, 143.22, 131.15, 124.38, 118.76, 117.85, 70.94, 65.54, 62.36, 20.83. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{12}H_{13}O_5^+$, 237.0757; found, 237.0745.

*(±)-N-(3-Chloro-2-fluorophenyl)-7-[(4-methylpiperazin-1-yl)methyl]-7,8-dihydro[1,4]dioxino [2,3-g]quinazolin-4-amine (**JGK075**).*



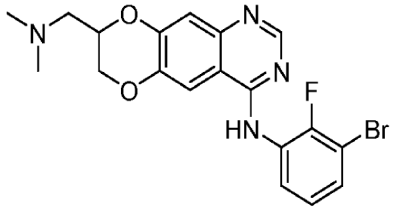
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (s, 1H), 8.61 (td, *J* = 7.3, 2.2 Hz, 1H), 7.39 (s, 1H), 7.35 (br d, *J* = 3.4 Hz, 1H), 7.32 (s, 1H), 7.16 (td, *J* = 8.1, 1.2 Hz, 1H), 7.13 (td, *J* = 8.2, 1.9 Hz, 1H), 4.49 – 4.41 (m, 2H), 4.15 (dd, *J* = 11.8, 8.1 Hz, 1H), 2.78 (dd, *J* = 13.4, 5.9 Hz, 1H), 2.66 (dd, *J* = 13.4, 5.9 Hz, 1H), 2.64 (br, 4H), 2.48 (br, 4H), 2.31 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.89, 153.35, 149.44, 149.30 (d, J_{CF} = 244.2 Hz), 146.72, 144.15, 128.76 (d, J_{CF} = 9.3 Hz), 124.71 (d, J_{CF} = 4.7 Hz), 124.45, 121.01, 120.85 (d, J_{CF} = 16.1 Hz), 114.30, 110.63, 106.05, 71.81, 67.31, 58.50, 55.17, 54.15, 46.19. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{22}H_{24}ClFN_5O_2^+$, 444.1597; found, 444.1582.

*(±)-N-(3-Bromo-2-fluorophenyl)-8-[(morpholin-4-yl)methyl]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4-amine (**JGK076**).*



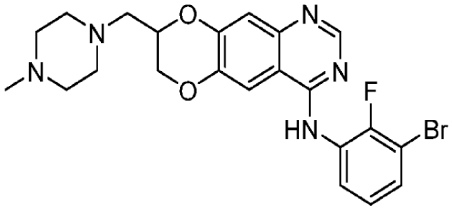
^{1}H NMR (500 MHz, DMSO-d_6): δ 9.62 (s, 1H), 8.33 (s, 1H), 7.94 (s, 1H), 7.59 (ddd, J = 8.0, 6.2, 1.6 Hz, 1H), 7.54 (ddd, J = 8.5, 7.1, 1.6 Hz, 1H), 7.21 (td, J = 8.1, 1.2 Hz, 1H), 7.19 (s, 1H), 4.63 – 4.56 (m, 1H), 4.46 (dd, J = 11.6, 2.5 Hz, 1H), 4.17 (dd, J = 11.6, 7.1 Hz, 1H), 3.59 (t, J = 4.6 Hz, 4H), 2.71 – 2.59 (m, 2H), 2.57 – 2.44 (m, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 157.22, 153.37 (d, J_{CF} = 247.3 Hz), 153.13, 148.75, 146.16, 143.28, 130.14, 128.02 (d, J_{CF} = 13.0 Hz), 127.74, 125.45 (d, J_{CF} = 4.7 Hz), 112.57, 109.61, 108.55 (d, J_{CF} = 19.9 Hz), 108.23, 71.41, 66.29, 66.18, 57.97, 53.89. HRMS (DART): m/z [M – H]$^-$ calcd for $C_{21}H_{19}BrFN_4O_3^-$, 473.0630; found, 473.0608.

*(±)-N-(3-Bromo-2-fluorophenyl)-8-[(dimethylamino)methyl]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4-amine (**JGK077**).*



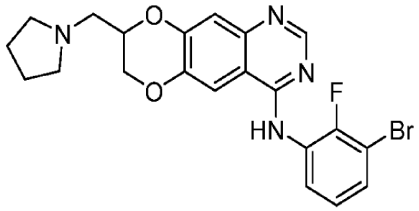
^{1}H NMR (500 MHz, DMSO-d_6): δ 9.62 (s, 1H), 8.33 (s, 1H), 7.94 (s, 1H), 7.59 (ddd, J = 8.0, 6.2, 1.6 Hz, 1H), 7.54 (ddd, J = 8.5, 7.1, 1.6 Hz, 1H), 7.21 (td, J = 8.1, 1.2 Hz, 1H), 7.17 (s, 1H), 4.57 – 4.51 (m, 1H), 4.44 (dd, J = 11.6, 2.5 Hz, 1H), 4.14 (dd, J = 11.7, 7.1 Hz, 1H), 2.58 (s, 1H), 2.57 (s, 1H), 2.25 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 157.22, 153.38 (d, J_{CF} = 247.4 Hz), 153.12, 148.78, 146.16, 143.29, 130.14, 128.02 (d, J_{CF} = 13.1 Hz), 127.75, 125.45 (d, J_{CF} = 4.4 Hz), 112.54, 109.59, 108.55 (d, J_{CF} = 19.8 Hz), 108.20, 71.76, 66.31, 58.73, 45.92. HRMS (DART): m/z [M – H]$^-$ calcd for $C_{19}H_{17}BrFN_4O_2^-$, 431.0524; found, 431.0503.

*(±)-N-(3-Bromo-2-fluorophenyl)-8-[(4-methylpiperazin-1-yl)methyl]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4-amine (**JGK078**).*



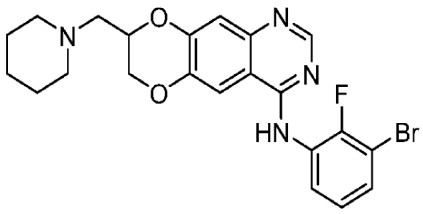
^{1}H NMR (500 MHz, DMSO-d_6): δ 9.61 (s, 1H), 8.33 (s, 1H), 7.94 (s, 1H), 7.59 (ddd, J = 8.0, 6.2, 1.6 Hz, 1H), 7.54 (ddd, J = 8.5, 7.1, 1.6 Hz, 1H), 7.21 (td, J = 8.1, 1.2 Hz, 1H), 7.19 (s, 1H), 4.60 – 4.53 (m, 1H), 4.44 (dd, J = 11.6, 2.5 Hz, 1H), 4.14 (dd, J = 11.7, 7.1 Hz, 1H), 2.68 – 2.59 (m, 2H), 2.53 (br, 4H), 2.34 (br, 4H), 2.16 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 157.22, 153.38 (d, J_{CF} = 247.4 Hz), 153.12, 148.78, 146.15, 143.29, 130.13, 128.02 (d, J_{CF} = 13.1 Hz), 127.74, 125.45 (d, J_{CF} = 4.5 Hz), 112.55, 109.60, 108.55 (d, J_{CF} = 19.8 Hz), 108.22, 71.57, 66.34, 57.52, 54.68, 53.29, 45.72. HRMS (DART): m/z $[M - H]^-$ calcd for $C_{22}H_{22}BrFN_5O_2^-$, 486.0946; found, 486.0928.

*(±)-N-(3-Bromo-2-fluorophenyl)-8-[(pyrrolidin-1-yl)methyl]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4-amine (**JGK079**).*



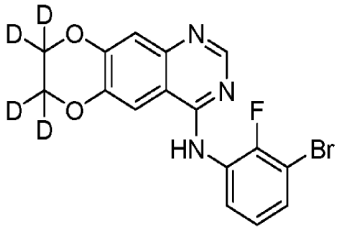
^{1}H NMR (500 MHz, DMSO-d_6): δ 9.61 (s, 1H), 8.33 (s, 1H), 7.94 (s, 1H), 7.59 (ddd, J = 8.0, 6.3, 1.6 Hz, 1H), 7.54 (ddd, J = 8.5, 7.1, 1.6 Hz, 1H), 7.21 (td, J = 8.0, 1.2 Hz, 1H), 7.19 (s, 1H), 4.57 – 4.49 (m, 1H), 4.46 (dd, J = 11.6, 2.5 Hz, 1H), 4.16 (dd, J = 11.6, 7.1 Hz, 1H), 2.80 (dd, J = 12.8, 6.0 Hz, 1H), 2.73 (dd, J = 12.8, 6.2 Hz, 1H), 2.62 – 2.48 (m, 4H), 1.74 – 1.66 (m, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 157.22, 153.37 (d, J_{CF} = 247.5 Hz), 153.12, 148.79, 146.17, 143.29, 130.13, 128.02 (d, J_{CF} = 12.9 Hz), 127.74, 125.45 (d, J_{CF} = 4.5 Hz), 112.54, 109.58, 108.55 (d, J_{CF} = 20.0 Hz), 108.19, 72.65, 66.32, 55.42, 54.31, 23.23. HRMS (DART): m/z $[M - H]^-$ calcd for $C_{21}H_{19}BrFN_4O_2^-$, 457.0681; found, 457.0660.

*(±)-N-(3-Bromo-2-fluorophenyl)-8-[(piperidin-1-yl)methyl]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4-amine (**JGK080**).*



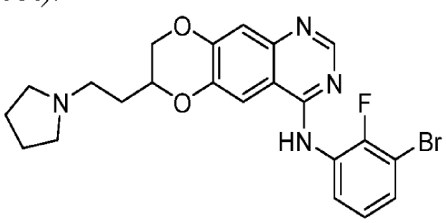
^{1}H NMR (500 MHz, DMSO-d_6): δ 9.61 (s, 1H), 8.33 (s, 1H), 7.94 (s, 1H), 7.59 (ddd, J = 8.0, 6.3, 1.6 Hz, 1H), 7.54 (ddd, J = 8.4, 7.0, 1.6 Hz, 1H), 7.21 (td, J = 8.1, 1.2 Hz, 1H), 7.18 (s, 1H), 4.59 – 4.52 (m, 1H), 4.44 (dd, J = 11.6, 2.5 Hz, 1H), 4.14 (dd, J = 11.7, 7.1 Hz, 1H), 2.65 – 2.54 (m, 2H), 2.53 – 2.37 (m, 4H), 1.55 – 1.47 (m, 4H), 1.43 – 1.34 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 157.21, 153.37 (d, J_{CF} = 247.1 Hz), 153.11, 148.83, 146.15, 143.32, 130.12, 128.03 (d, J_{CF} = 13.1 Hz), 127.73, 125.45 (d, J_{CF} = 4.5 Hz), 112.53, 109.57, 108.55 (d, J_{CF} = 19.8 Hz), 108.19, 71.63, 66.42, 58.35, 54.74, 25.61, 23.83. HRMS (DART): m/z [M – H]$^-$ calcd for $C_{22}H_{21}BrFN_4O_2^-$, 471.0837; found, 471.0814.

*N-(3-Bromo-2-fluorophenyl)(7,7,8,8-$^2H_4$)-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4-amine (**JGK081**).*



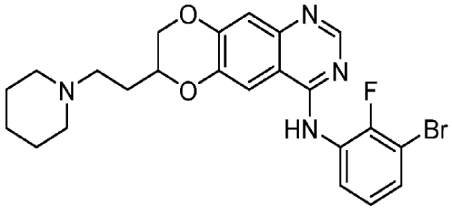
^{1}H NMR (500 MHz, DMSO-d_6): δ 9.61 (s, 1H), 8.33 (s, 1H), 7.93 (s, 1H), 7.59 (ddd, J = 7.9, 6.3, 1.6 Hz, 1H), 7.54 (ddd, J = 8.4, 7.1, 1.6 Hz, 1H), 7.21 (td, J = 8.1, 1.2 Hz, 1H), 7.19 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 157.19, 153.37 (d, J_{CF} = 247.2 Hz), 153.10, 149.27, 146.03, 143.67, 130.12, 128.03 (d, J_{CF} = 13.0 Hz), 127.74, 125.44 (d, J_{CF} = 4.2 Hz), 112.47, 109.63, 108.55 (d, J_{CF} = 19.9 Hz), 108.35. HRMS (DART): m/z [M + H]$^+$ calcd for $C_{16}H_8D_4BrFN_3O_2^+$, 380.0342; found, 380.0327.

*(±)-N-(3-Bromo-2-fluorophenyl)-7-[2-(pyrrolidin-1-yl)ethyl]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4-amine (**JGK084**).*



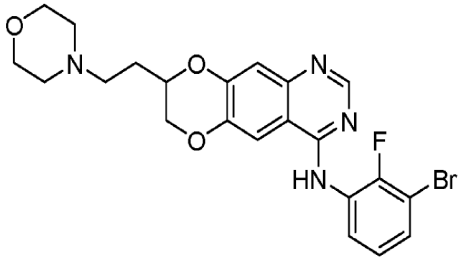
^{1}H NMR (500 MHz, DMSO-d_6): δ 9.60 (s, 1H), 8.33 (s, 1H), 7.95 (s, 1H), 7.58 (ddd, J = 8.0, 6.2, 1.6 Hz, 1H), 7.53 (ddd, J = 8.4, 7.0, 1.6 Hz, 1H), 7.21 (td, J = 8.1, 1.1 Hz, 2H), 7.20 (s, 1H), 4.50 (dd, J = 11.5, 2.3 Hz, 1H), 4.42 – 4.36 (m, 1H), 4.12 (dd, J = 11.5, 7.7 Hz, 1H), 2.70 – 2.56 (m, 2H), 2.49 – 2.40 (m, 4H), 1.89 – 1.78 (m, 2H), 1.73 – 1.64 (m, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 157.21, 153.33 (d, J_{CF} = 247.5 Hz), 153.13, 148.95, 146.02, 143.37, 130.08, 128.07 (d, J_{CF} = 13.1 Hz), 127.64, 125.48 (d, J_{CF} = 4.6 Hz), 112.26, 109.78, 108.58 (d, J_{CF} = 19.8 Hz), 108.44, 71.76, 67.78, 53.63, 51.03, 29.53, 23.16. HRMS (DART): m/z [M + H]$^+$ calcd for $C_{22}H_{23}BrFN_4O_2^+$, 473.0983; found, 473.0976.

*(±)-N-(3-Bromo-2-fluorophenyl)-7-[2-(piperidin-1-yl)ethyl]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4-amine (**JGK085**).*



^{1}H NMR (500 MHz, DMSO-d_6): δ 9.60 (s, 1H), 8.33 (s, 1H), 7.94 (s, 1H), 7.58 (ddd, J = 8.0, 6.2, 1.6 Hz, 1H), 7.53 (ddd, J = 8.4, 7.1, 1.6 Hz, 1H), 7.204 (td, J = 8.2, 1.3 Hz, 1H), 7.198 (s, 1H), 4.51 (dd, J = 11.5, 2.4 Hz, 1H), 4.39 – 4.33 (m, 1H), 4.11 (dd, J = 11.6, 7.8 Hz, 1H), 2.50 – 2.44 (m, 2H), 2.42 – 2.27 (m, 4H), 1.90 – 1.76 (m, 2H), 1.55 – 1.45 (m, 4H), 1.42 – 1.34 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 157.20, 153.33 (d, J_{CF} = 247.4 Hz), 153.12, 148.95, 146.02, 143.39, 130.08, 128.07 (d, J_{CF} = 13.1 Hz), 127.64, 125.48 (d, J_{CF} = 4.5 Hz), 112.25, 109.77, 108.58 (d, J_{CF} = 20.0 Hz), 108.43, 71.97, 67.80, 54.08, 53.96, 27.69, 25.61, 24.12. HRMS (DART): m/z [M + H]$^+$ calcd for $C_{23}H_{25}BrFN_4O_2^+$, 487.1139; found, 487.1137.

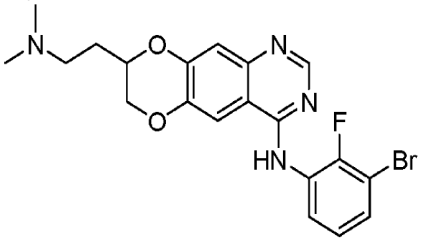
*(±)-N-(3-Bromo-2-fluorophenyl)-8-[2-(morpholin-4-yl)ethyl]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4-amine (**JGK086**).*



^{1}H NMR (500 MHz, DMSO-d_6): δ 9.63 (s, 1H), 8.32 (s, 1H), 7.93 (s, 1H), 7.58 (ddd, J = 8.0, 6.3, 1.5 Hz, 1H), 7.53 (t, J = 7.0 Hz, 1H), 7.21 (td, J = 8.1, 1.2 Hz, 1H), 4.50 (dd, J =

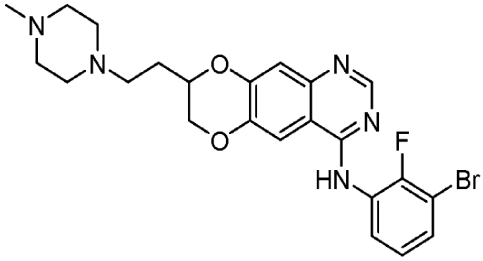
11.5, 2.4 Hz, 1H), 4.47 – 4.40 (m, 1H), 4.10 (dd, *J* = 11.6, 7.4 Hz, 1H), 3.58 (t, *J* = 4.7 Hz, 4H), 2.55 – 2.46 (m, 2H), 2.45 – 2.33 (m, 4H), 1.92 – 1.79 (m, 2H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$): *δ* 157.20, 153.33 (d, J_{CF} = 248.3 Hz), 153.06, 148.94, 146.06, 143.26, 130.03, 128.12 (d, J_{CF} = 9.8 Hz), 127.69, 125.44 (d, J_{CF} = 4.4 Hz), 112.47, 109.64, 108.55 (d, J_{CF} = 19.9 Hz), 108.18, 72.30, 67.35, 66.22, 53.53, 53.28, 27.25. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{22}H_{23}BrFN_4O_3^+$, 489.0932; found, 489.0926.

*(±)-N-(3-Bromo-2-fluorophenyl)-8-[2-(dimethylamino)ethyl]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4-amine (**JGK087**).*



^{1}H NMR (500 MHz, DMSO-*d*$_6$): *δ* 9.61 (s, 1H), 8.33 (s, 1H), 7.93 (s, 1H), 7.59 (t, *J* = 6.9 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 8.1 Hz, 1H), 7.18 (s, 1H), 4.49 (dd, *J* = 11.6, 2.3 Hz, 1H), 4.45 – 4.38 (m, 1H), 4.09 (dd, *J* = 11.6, 7.5 Hz, 1H), 2.47 – 2.38 (m, 2H), 2.17 (s, 6H), 1.86 – 1.78 (m, 2H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$): *δ* 157.20, 153.37 (d, J_{CF} = 247.6 Hz), 153.08, 148.99, 146.14, 143.29, 130.10, 128.07 (d, J_{CF} = 15.6 Hz), 127.72, 125.44 (d, J_{CF} = 4.4 Hz), 112.50, 109.58, 108.54 (d, J_{CF} = 19.7 Hz), 108.13, 72.30, 67.36, 54.43, 45.17, 28.27. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{20}H_{21}BrFN_4O_2^+$,447.0826; found, 447.0818.

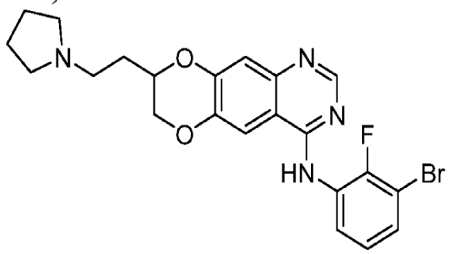
*(±)-N-(3-Bromo-2-fluorophenyl)-8-[2-(4-methylpiperazin-1-yl)ethyl]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4-amine (**JGK088**).*



^{1}H NMR (500 MHz, DMSO-*d*$_6$): *δ* 9.62 (s, 1H), 8.33 (s, 1H), 7.93 (s, 1H), 7.59 (t, *J* = 7.1 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.17 (s, 1H), 4.49 (dd, *J* = 11.5, 2.4 Hz, 1H), 4.45 – 4.38 (m, 1H), 4.10 (dd, *J* = 11.6, 7.4 Hz, 1H), 2.48 – 2.21 (m, 10H), 2.14 (s, 3H), 1.91 – 1.76 (m, 2H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$): *δ* 157.20, 153.36 (d, J_{CF} = 246.9 Hz), 153.08, 148.98, 146.13, 143.28, 130.09, 128.05 (d, J_{CF} = 11.7 Hz), 127.72, 125.44

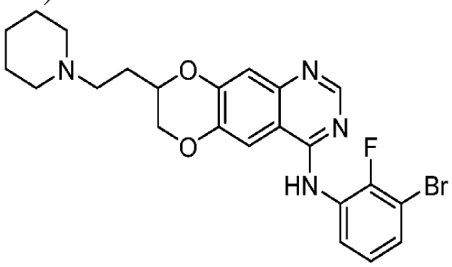
(d, J_{CF} = 4.3 Hz), 112.50, 109.58, 108.55 (d, J_{CF} = 19.8 Hz), 108.13, 72.40, 67.37, 54.78, 53.11, 52.65, 45.76, 27.61. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{23}H_{26}BrFN_5O_2^+$, 502.1248; found, 502.1240.

(±)-N-(3-Bromo-2-fluorophenyl)-8-[2-(pyrrolidin-1-yl)ethyl]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4-amine (**JGK089**).



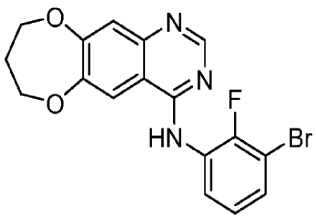
^{1}H NMR (500 MHz, DMSO-d_6): δ 9.62 (s, 1H), 8.33 (s, 1H), 7.93 (s, 1H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.17 (s, 1H), 4.49 (dd, *J* = 11.5, 2.4 Hz, 1H), 4.47 – 4.41 (m, 1H), 4.10 (dd, *J* = 11.5, 7.4 Hz, 1H), 2.68 – 2.53 (m, 2H), 2.50 – 2.40 (m, 4H), 1.89 – 1.81 (m, 2H), 1.73 – 1.65 (m, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 157.20, 153.36 (d, J_{CF} = 246.9 Hz), 153.07, 148.98, 146.13, 143.28, 130.07, 128.10, 127.71, 125.44 (d, J_{CF} = 4.6 Hz), 112.48, 109.60, 108.55 (d, J_{CF} = 19.8 Hz), 108.15, 72.31, 67.37, 53.57, 50.97, 29.58, 23.14. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{22}H_{23}BrFN_4O_2^+$, 473.0983; found, 473.0976.

*(±)-N-(3-Bromo-2-fluorophenyl)-8-[2-(piperidin-1-yl)ethyl]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-4-amine (**JGK090**).*



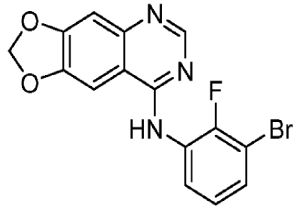
^{1}H NMR (500 MHz, DMSO-d_6): δ 9.62 (s, 1H), 8.32 (s, 1H), 7.93 (s, 1H), 7.59 (t, *J* = 7.1 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.21 (td, *J* = 8.0, 1.2 Hz, 1H), 7.17 (s, 1H), 4.49 (dd, *J* = 11.5, 2.4 Hz, 1H), 4.44 – 4.37 (m, 1H), 4.10 (dd, *J* = 11.6, 7.4 Hz, 1H), 2.48 – 2.43 (m, 2H), 2.41 – 2.27 (m, 4H), 1.90 – 1.77 (m, 2H), 1.54 – 1.45 (m, 4H), 1.42 – 1.34 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 157.19, 153.34 (d, J_{CF} = 246.7 Hz), 153.07, 149.00, 146.11, 143.29, 130.07, 128.10, 127.71, 125.44 (d, J_{CF} = 4.3 Hz), 112.48, 109.60, 108.55 (d, J_{CF} = 19.9 Hz), 108.14, 72.50, 67.40, 54.02, 53.87, 27.70, 25.63, 24.13. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{23}H_{25}BrFN_4O_2^+$, 487.1139; found, 487.1133.

*N-(3-Bromo-2-fluorophenyl)-8,9-dihydro-7H-[1,4]dioxepino[2,3-g]quinazolin-4-amine (**JGK091**).*



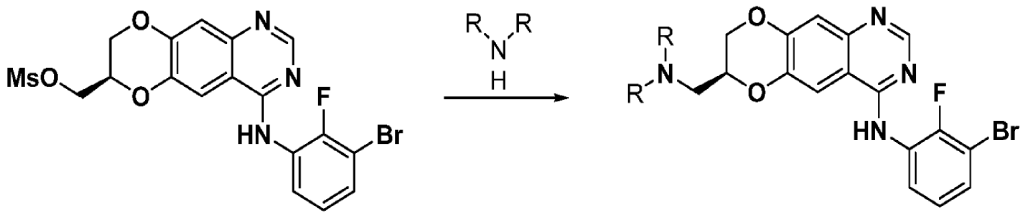
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.71 (s, 1H), 8.65 (ddd, J = 8.3, 7.3, 1.5 Hz, 1H), 7.48 (s, 1H), 7.43 (s, 1H), 7.39 (br, 1H), 7.28 (ddd, J = 8.1, 6.5, 1.5 Hz, 1H), 7.11 (td, J = 8.2, 1.6 Hz, 1H), 4.41 (t, J = 5.7 Hz, 1H), 4.38 (t, J = 5.8 Hz, 1H), 2.32 (p, J = 5.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.06, 156.08, 153.93, 151.62, 150.19 (d, J_{CF} = 242.7 Hz), 147.83, 128.53 (d, J_{CF} = 10.4 Hz), 127.39, 125.32 (d, J_{CF} = 4.7 Hz), 121.84, 119.15, 111.47, 110.85, 108.62 (d, J_{CF} = 19.3 Hz), 70.86, 70.51, 31.03. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{17}H_{14}BrFN_3O_2^+$, 390.0248; found, 390.0236.

*N-(3-Bromo-2-fluorophenyl)-2H-[1,3]dioxolo[4,5-g]quinazolin-8-amine (**JGK092**).*

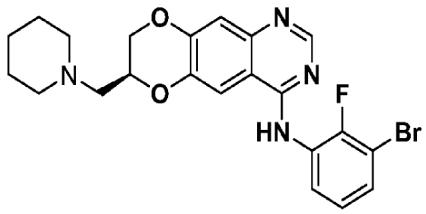


^{1}H NMR (500 MHz, $CDCl_3$): δ 8.69 (s, 1H), 8.58 (ddd, J = 8.3, 7.3, 1.5 Hz, 1H), 7.28 (ddd, J = 8.1, 6.5, 1.6 Hz, 1H), 7.25 (br, 1H), 7.14 (s, 1H), 7.11 (td, J = 8.2, 1.6 Hz, 1H), 6.17 (s, 2H), signal of one proton missing (probably hidden by the chloroform signal). ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.10, 153.37, 153.22, 150.22 (d, J_{CF} = 242.3 Hz), 149.37, 148.43, 128.67 (d, J_{CF} = 10.4 Hz), 127.28, 125.30 (d, J_{CF} = 4.7 Hz), 121.84, 110.75, 108.64 (d, J_{CF} = 19.4 Hz), 106.29, 102.48, 96.49. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{15}H_{10}BrFN_3O_2^+$, 361.9935; found, 361.9925.

General reaction scheme:

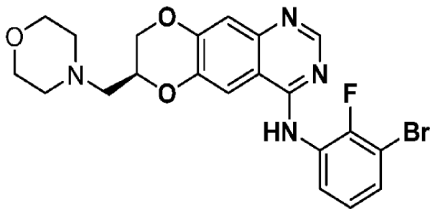


(S)-N-(3-bromo-2-fluorophenyl)-7-(piperidin-1-ylmethyl)-7,8-dihydro-[1,4]dioxino[2,3-g]quinazolin-4-amine **JCN065S**



To a solution of (*R*)-(4-((3-bromo-2-fluorophenyl)amino)-7,8-dihydro-[1,4] dioxino[2,3-*g*]quinazolin-7-yl)methyl methanesulfonate (300 mg, 0.619 mmol) in DMA (1.5 mL) was added piperidine (263 mg, 3.08 mmol), followed by the addition of triethylamine (TEA) (152 mg, 1.23 mmol). The resulting mixture was stirred for 30 min and then was heated to 85 °C and stirred overnight, after which it was cooled to room temperature (RT), water was added and the resulting mixture was extracted with ethyl acetate (EtOAc). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated to provide a crude product that was further purified by combiflash chromatography by elution with 0-10% MeOH-DCM to give the title compound (200 mg, 68%). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 9.58 (s; 1 H); 8.33 (s; 1 H); 7.96 (s; 1 H); 7.51-7.59 (m; 2 H); 7.19 (t; J = 8.32 Hz; 2 H); 4.44-4.51 (m; 2 H); 4.14 (dd; J = 11.49; 7.48 Hz; 1 H); 2.59 (d; J = 5.53 Hz; 2 H); 2.44 (m, 4H); 1.50 (d; J = 6.31 Hz; 4 H); 1.38 (s; 2 H). MS (ESI): *m/z* $[M+2H]^{2+}$ Calculated for $C_{22}H_{24}BrFN_4O_2^{2+}$: 237.05, Found: 237.1

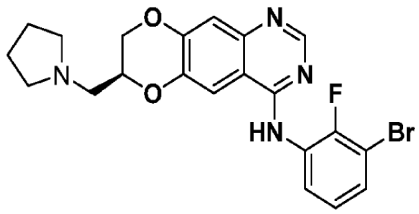
(S)-N-(3-bromo-2-fluorophenyl)-7-(morpholinomethyl)-7,8-dihydro-[1,4]dioxino[2,3-g]quinazolin-4-amine **JCN063S**



To a solution of (*R*)-(4-((3-bromo-2-fluorophenyl)amino)-7,8-dihydro-[1,4] dioxino[2,3-*g*]quinazolin-7-yl)methyl methanesulfonate (**S-8**) (250 mg, 0.516 mmol) in DMA (1 mL) was added morpholine (225 mg, 2.58 mmol), followed by the addition of TEA (104 mg, 1.03 mmol). The resulting mixture was stirred for 30 min and then was heated to 85 °C and stirred overnight, after which it was cooled to room temperature (RT), water was added and the resulting mixture was extracted with ethyl acetate (EtOAc). The combined organic

phases were dried over Na_2SO_4, filtered, and concentrated to provide a crude product that was further purified by combiflash chromatography by elution with 0-3% MeOH-DCM to give the title compound (180 mg, 73%). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 9.58 (s; 1 H); 8.33 (s; 1 H); 7.97 (s; 1 H); 7.51-7.59 (m; 2 H); 7.19 (t; J = 7.95 Hz; 2 H); 4.54 (d; J = 6.86 Hz; 1 H); 4.47 (d; J = 11.63 Hz; 1 H); 4.17 (dd; J = 11.55; 7.53 Hz; 1 H); 3.59 (t; J = 4.49 Hz; 4 H); 2.64 (d; J = 5.77 Hz; 6 H). MS (ESI): *m/z* $[M+2H]^{2+}$ Calculated for $C_{21}H_{22}BrFN_4O_2^{2+}$: 238.04, Found: 238.1.

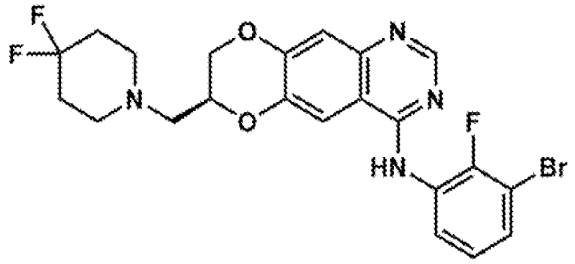
(S)-N-(3-bromo-2-fluorophenyl)-7-(pyrrolidin-1-ylmethyl)-7,8-dihydro-[1,4]dioxino[2,3-g]quinazolin-4-amine **JCN067S**



To a solution of (*R*)-(4-((3-bromo-2-fluorophenyl)amino)-7,8-dihydro-[1,4] dioxino[2,3-*g*]quinazolin-7-yl)methyl methanesulfonate (**S-8**) (300 mg, 0.619 mmol) in DMA (1.5 mL) was added pyrrolidine (220 mg, 3.09 mmol), followed by the addition of TEA (125 mg, 1.238 mmol). The resulting mixture was stirred for 30 min and then was heated to 85 °C and stirred overnight, after which it was cooled to room temperature (RT), water was added and the resulting mixture was extracted with ethyl acetate (EtOAc). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated to provide a crude product that was further purified by combiflash chromatography by elution with 0-3% MeOH-DCM to give the title compound (170 mg, 60%). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 9.57 (s; 1 H); 8.33 (s; 1 H); 7.97 (s; 1 H); 7.52-7.60 (m; 2 H); 7.20 (t; J = 8.12 Hz; 2 H); 4.48 (d; J = 9.67 Hz; 2 H); 4.17 (dd; J = 11.88; 7.82 Hz; 1 H); 2.53-2.82 (m; 6 H); 1.70 (s; 4 H). MS (ESI): *m/z* $[M+2H]^{2+}$ Calculated for $C_{21}H_{22}BrFN_4O_2^{2+}$: 230.04, Found: 230.1.

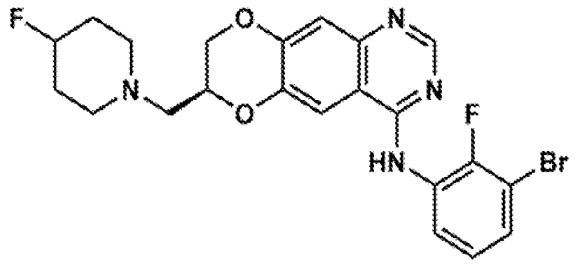
The below compounds were prepared using the route described for the synthesis of (±)-**JGK065** from (±)-6.

*(S)-N-(3-bromo-2-fluorophenyl)-7-((4,4-difluoropiperidin-1-yl)methyl)-7,8-dihydro-[1,4]dioxino[2,3-g]quinazolin-4-amine (**JGK093S**).*



^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (s, 1H), 8.60 (t, *J* = 7.6 Hz, 1H), 7.42 (s, 1H), 7.37 (s, 1H), 7.28 (t, *J* = 6.7 Hz, 1H), 7.10 (t, *J* = 8.2 Hz, 1H), 4.55 (m, 1H), 4.50 (dd, *J* = 11.7, 2.2 Hz, 1H), 4.31 (dd, *J* = 11.9, 7.0 Hz, 1H), 3.82 (dd, *J* = 11.8, 5.0 Hz, 1H), 3.76 (dd, *J* = 11.7, 6.8 Hz, 1H), 2.10 - 1.90 (m, 4H), 1.79 - 1.54 (m, 2H), 0.91 - 0.76 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.9, 153.4, 150.1 (d, *J* = 242.4 Hz), 148.8, 146.6, 143.2, 128.4 (d, *J* = 10.5 Hz), 127.3, 125.2 (d, *J* = 4.7 Hz), 121.9, 114.4, 110.7, 108.5 (d, *J* = 19.1 Hz), 106.2, 72.6, 65.5, 42.4 (t, *J* = 5.6 Hz), 41.4, 36.2 (t, *J* = 5.5 Hz), 34.7 (t, *J* = 23.8 Hz), 33.3 (t, *J* = 23.6 Hz), 29.7; HRMS *m/z* calculated for $C_{22}H_{21}BrF_3N_4O_2$, $[M + H]^+$ 509.0794, found 509.0787.

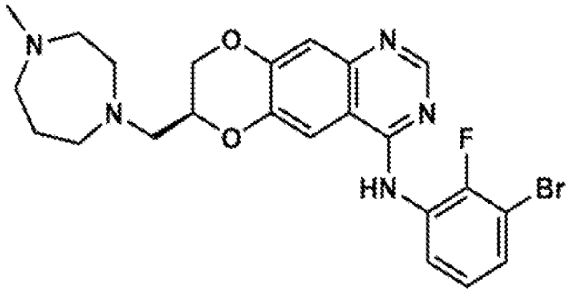
*(S)-N-(3-bromo-2-fluorophenyl)-7-((4-fluoropiperidin-1-yl)methyl)-7,8-dihydro-[1,4]dioxino[2,3-g]quinazolin-4-amine (**JGK094S**).*



^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (s, 1H), 8.61 (t, *J* = 7.8 Hz, 1H), 7.42 (s, 1H), 7.36 (s, 1H), 7.29 (m, 1H), 7.10 (t, *J* = 8.2 Hz, 1H), 4.55 (m, 1H), 4.50 (dd, *J* = 11.7, 2.1 Hz, 1H), 4.31 (dd, *J* = 11.6, 6.8 Hz, 1H), 3.82 (dd, *J* = 11.8, 5.0 Hz, 1H), 3.76 (dd, *J* = 11.7, 6.8 Hz), 1.97 - 1.74 (m, 3H), 1.32 - 1.17 (m, 4H), 0.91 - 0.78 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.9, 153.4, 150.1 (d, *J* = 242.6 Hz), 148.8, 146.6, 143.2, 128.4 (d, *J* = 10.4 Hz), 127.3, 125.2 (d, *J* = 4.6 Hz), 121.8, 114.4, 110.7, 108.5 (d, *J* = 19.4 Hz), 106.2, 73.2 (d, *J* =

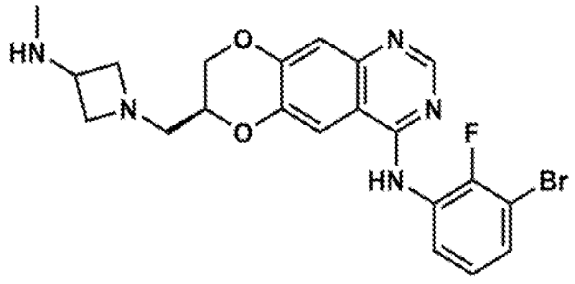
160.6 Hz), 65.5, 41.4 (d, J = 20.1 Hz), 35.4, 30.4, 29.7; HRMS *m/z* calculated for $C_{22}H_{22}BrF_2N_4O_2$, $[M + H]^+$ 491.0889, found 491.0880.

*(S)-N-(3-bromo-2-fluorophenyl)-7-((4-methyl-1,4-diazepan-1-yl)methyl)-7,8-dihydro-[1,4]dioxino[2,3-g]quinazolin-4-amine (**JGK095S**).*



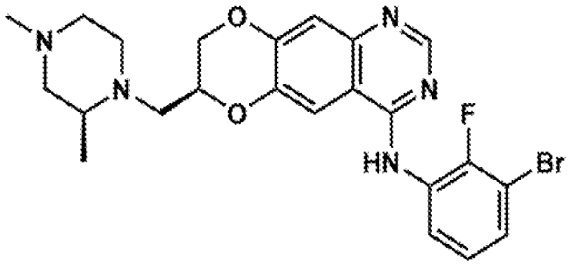
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.66 (s, 1H), 8.60 (t, J = 7.4 Hz, 1H), 7.39 (s, 1H), 7.28 (m, 2H), 7.09 (t, J = 7.8 Hz, 1H), 4.45 (m, 1H), 4.40 (m, 1H), 4.29 (m, 1H), 4.11 (q, J = 7.1 Hz), 3.99 (dd, J = 12.2, 4.2 Hz, 1H), 3.93 (dd, J = 12.1, 4.9 Hz, 1H), 2.23 - 2.08 (m, 2H), 2.04 (s, 3H), 1.73 - 1.49 (m, 2H), 1.35 - 1.21 (m, 4H), 0.91 - 0.77 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.8, 153.2, 150.0 (d, J = 242.5 Hz), 149.1, 146.3, 143.9, 128.4 (d, J = 10.8 Hz), 127.3, 125.2 (d, J = 4.6 Hz), 121.7, 114.0, 110.5, 108.5 (d, J = 19.1 Hz), 105.9, 73.8, 65.5, 61.4, 60.4, 30.0, 29.7, 29.4, 21.1, 14.2; HRMS *m/z* calculated for $C_{23}H_{26}BrFN_5O_2$, $[M + H]^+$ 502.1248, found 502.1235.

*(S)-N-(3-bromo-2-fluorophenyl)-7-((3-(methylamino)azetidin-1-yl)methyl)-7,8-dihydro-[1,4]dioxino[2,3-g]quinazolin-4-amine (**JGK096S**).*



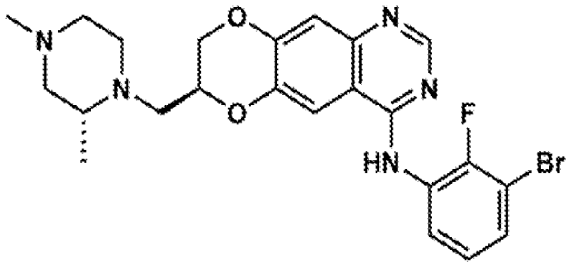
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.67 (m, 1H), 8.58 (m, 1H), 7.43 (s, 1H), 7.37 (m, 1H), 7.28 (m, 1H), 7.10 (m, 1H), 4.28 (m, 1H), 4.11 (m, 1H), 3.96 (m, 1H), 3.11 (m, 2H), 2.30 - 2.08 (m, 2H), 2.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 153.5, 153.2, 149.2 (d, J = 243.6 Hz), 148.6, 146.5, 143.9, 128.3 (d, J = 10.1 Hz), 127.5, 125.2 (d, J = 4.6 Hz), 122.0, 114.5, 110.7, 108.5 (d, J = 19.4 Hz), 106.3, 71.0, 66.3, 64.6, 60.4, 37.9, 29.7; HRMS *m/z* calculated for $C_{21}H_{22}BrFN_5O_2$, $[M + H]^+$ 474.0935, found 474.0919.

*(S)-N-(3-bromo-2-fluorophenyl)-7-(((S)-2,4-dimethylpiperazin-1-yl)methyl)-7,8-dihydro-[1,4]dioxino[2,3-g]quinazolin-4-amine (**JGK097S**).*



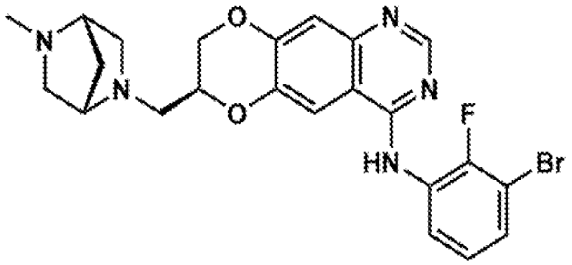
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.67 (s, 1H), 8.60 (m, 1H), 7.40 (s, 1H), 7.36 (m, 2H), 7.10 (m, 1H), 4.55 (m, 1H), 4.50 (m, 1H), 4.40 (m, 1H), 4.30 (m, 1H), 4.11 (m, 1H), 3.96 (m, 1H), 3.11 (m, 2H), 2.30 - 1.99 (m, 4H), 2.04 (s, 3H), 1.26 (d, J = 7.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.8, 153.3, 150.0 (d, J = 242.0 Hz), 149.1, 146.5, 143.9, 128.4 (d, J = 10.8 Hz), 127.2, 125.2 (d, J = 4.6 Hz), 121.7, 114.2, 110.5, 108.5 (d, J = 19.0 Hz), 105.9, 73.8, 71.0, 65.5, 64.6, 61.5, 60.4, 42.5, 29.7, 28.4; HRMS *m/z* calculated for $C_{23}H_{26}BrFN_5O_2$, $[M + H]^+$ 502.1248, found 502.1237.

*(S)-N-(3-bromo-2-fluorophenyl)-7-(((R)-2,4-dimethylpiperazin-1-yl)methyl)-7,8-dihydro-[1,4]dioxino[2,3-g]quinazolin-4-amine (**JGK098S**).*



^{1}H NMR (500 MHz, $CDCl_3$): δ 8.67 (s, 1H), 8.60 (m, 1H), 7.40 (s, 1H), 7.36 (m, 2H), 7.10 (m, 1H), 4.55 (m, 1H), 4.50 (m, 1H), 4.40 (m, 1H), 4.30 (m, 1H), 4.11 (m, 1H), 3.96 (m, 1H), 3.11 (m, 2H), 2.09 - 1.60 (m, 4H), 2.04 (s, 3H), 1.45 (d, J = 7.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.8, 153.3, 150.0 (d, J = 242.4 Hz), 149.1, 146.5, 143.9, 128.4 (d, J = 10.7 Hz), 127.2, 125.2 (d, J = 4.9 Hz), 121.7, 114.2, 110.5, 108.5 (d, J = 19.0 Hz), 105.9, 73.8, 71.0, 65.5, 64.6, 61.5, 60.4, 37.9, 29.7, 28.4; HRMS *m/z* calculated for $C_{23}H_{26}BrFN_5O_2$, $[M + H]^+$ 502.1248, found 502.1239.

*(S)-N-(3-bromo-2-fluorophenyl)-7-(((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)methyl)-7,8-dihydro-[1,4]dioxino[2,3-g]quinazolin-4-amine (**JGK099S**).*



^{1}H NMR (500 MHz, $CDCl_3$): δ ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.64 (m, 2H), 7.38 (m, 2H), 7.10 (m, 1H), 6.95 (m, 1H), 4.47 (m, 2H), 4.29 (m, 2H), 4.11 (m, 1H), 3.96 (m, 2H), 3.12 (m, 1H), 2.50 - 2.11 (m, 4H), 2.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.8, 153.5, 150.1 (d, J = 242.5 Hz), 149.0, 146.5, 144.0, 128.3 (d, J = 10.8 Hz), 127.4, 125.2 (d, J = 4.6 Hz), 121.7, 114.2, 110.5, 108.4 (d, J = 19.7 Hz), 105.9, 73.8, 70.9, 66.3, 65.5, 61.5, 60.4, 37.9, 30.0 29.7; HRMS *m/z* calculated for $C_{23}H_{24}BrFN_5O_2$, $[M + H]^+$ 500.1092, found 500.1077.

Example 4: Biological Activity of Exemplary Compounds of the Disclosure

PC-9 cells were purchased from Sigma, and HCC827 cells were purchased from ATCC. Each cell line was maintained at ≤passage 10 at 37 °C in a humidified incubator with 5% CO_2. Cells were plated in 96-well optical bottom plates (Corning #3903; Corning, NY) at a cell density of 5,000 cells/well, allowed to adhere for minimally 16 hours, and subsequently treated with the test compounds using an 11-point serial dilution (1:3) in duplicate using an HP D300 digital 4 dispenser (Tecan, Morrisville, NC). 72 hours after addition of the test compounds, Cell Titer Glo reagent (Promega, Madison, WI) was added to the plate according to manufacturer's protocol and luminescence measured using a Spectramax M5 (Molecular Devices, San Jose, CA). IC_{50}s were calculated using the 4-parameter variable slope curve fit using the equation below where, Y and X are variables plotted, Top and Bottom are plateaus in the units of the Y axis, LogIC_{50} is the Log transformation of the IC_{50} value and HillSlope is the Hill Slope for the curve and describes curve steepness (GraphPad Prism, version 6.07, GraphPad Software, Inc.). Y=Bottom + (Top-Bottom)/(1+10((LogIC50-X)*HillSlope)))

Example #	Structure	Cellular IC_{50} Data (EGFR exon 19 deletion)	
		PC-9 IC_{50} (nM)	HCC827 IC_{50} (nM)
JCN065S		53.9	49.5
JCN063S		21.7	12.7
JCN067S		36.2	25.7

Example 5: Brain Penetration of Exemplary Compounds of the Disclsoure

Disclosed in table 5 Brain to plasma percentages and unbound ratios of drugs in brain to plasma of indicated drugs in non-tumor bearing mice

Table 5: Brain Penetration of Exemplary Compounds of the Disclsoure

Compound	Brain Penetration (% of plasma)	Kpuu (Avg)
Erlotinib	8.50	0.051
JGK005	64.8	0.491
JGK038	84.3	0.575
JGK028	106.2	1.037
JGK010	106.4	1.045

JGK037	212.1	1.301
JGK042	167.6	1.033
JGK063	72.5	0.341
JGK066	274.3	1.175
JGK068	354.5	1.184
JGK068S	378.3	1.181
JGK074	166.2	n.d.
JGK083S	231.3	0.798

Example 6: Metabolic Studies of Exemplary Compounds of the JGK series

Exemplary compounds (10 mM) were incubated in human, dog, mouse, or rat liver microsomes (1 mg/mL) for up to 90 minutes at 37°C. Reactions were stopped by the addition of acetonitrile. Controls (compound free) microsome studies were run in parallel. LCMS Studies were performed on a Waters Xevo G2 QTof equipped with a Luna Omega Polar C18, 1.6 m, 2.1 x 30 mm column. Strcutures of exmplrary metabolites are decpited in FIG. 9.

Modification	Human (%)	Dog (%)	Mouse (%)	Rat (%)
1. Parent	**67.0**	3.5	59.9	70.2
2. Hydroxylation	6.0	0.0	0.0	4.8
3. N-demethylation	13.7	0.9	5.4	8.2
4. Hydroxylation	4.2	61.9	22.0	21.9
5. Hydroxylation	0.7	0.0	0.0	0.6
6. N-dealkylation	6.5	0.0	1.3	2.7

INCORPORATION BY REFERENCE

All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

EQUIVALENTS

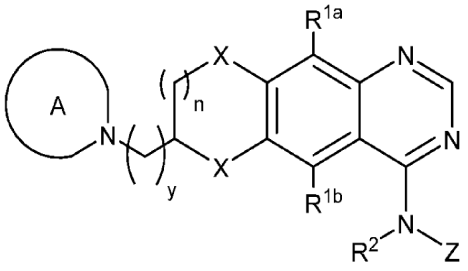
While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims below.

The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

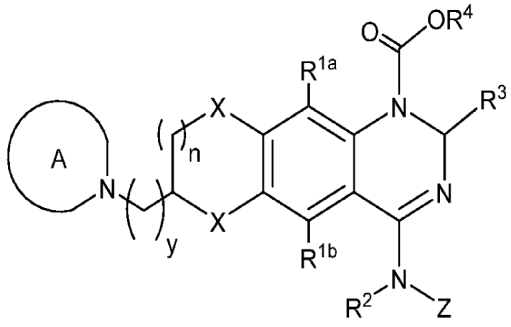
CLAIMS

We claim:

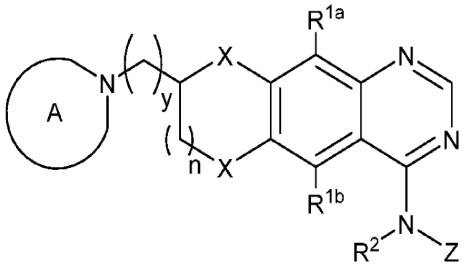
1. A compound having a structure represented by Formula Ia, Ib, Ic, or Id:



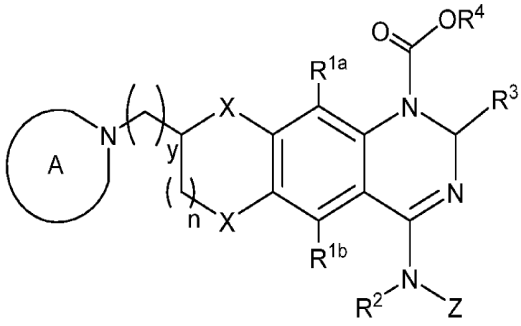
Ia



Ib



Ic



Id

or a pharmaceutically acceptable salt thereof, wherein:

A is a heterocyclyl;

Z is aryl or heteroaryl;

each X is independently selected from O, S, and NH;

R^{1a} and R^{1b} are each independently selected from hydrogen, alkyl, halo, CN, and NO_2;

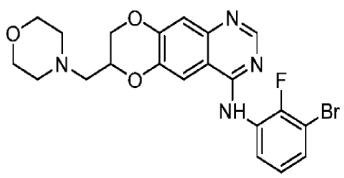
R^2 is hydrogen, alkyl, or acyl;

R^3 is alkoxy;

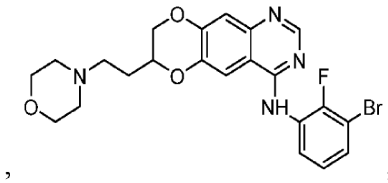
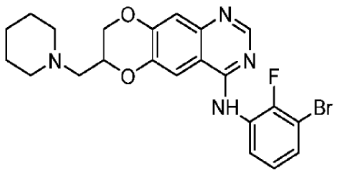
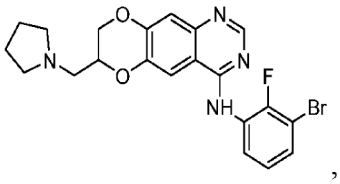
R^4 is alkyl;

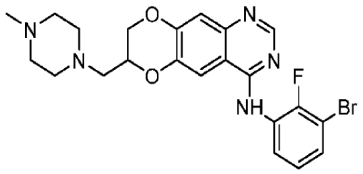
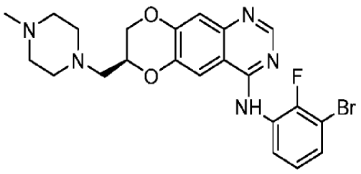
n is 1-3; and

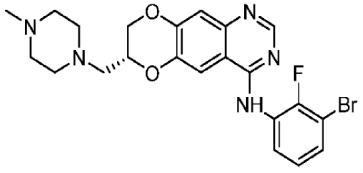
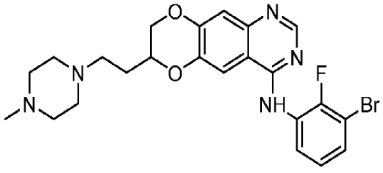
y is 1-3.

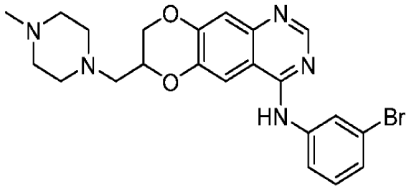
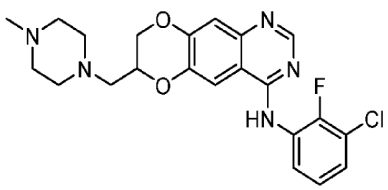


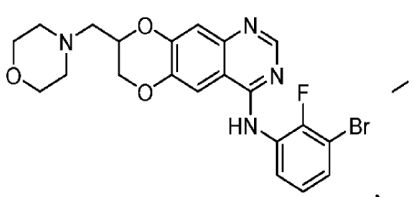
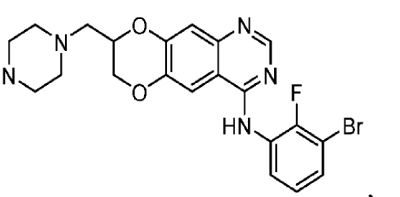
2. The compound of claim 1, wherein the compound is not

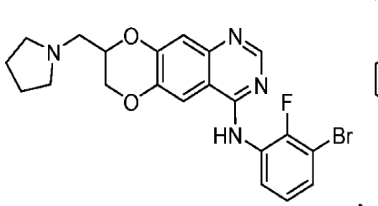
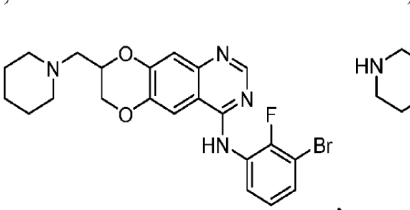
 ,  ,  ,

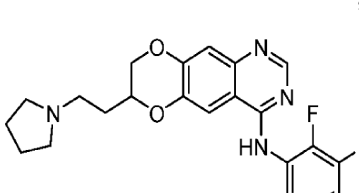
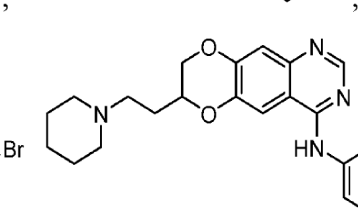
 ,  ,

 ,  ,

 ,  ,

 ,  ,

 ,  ,

 ,  ,  ,

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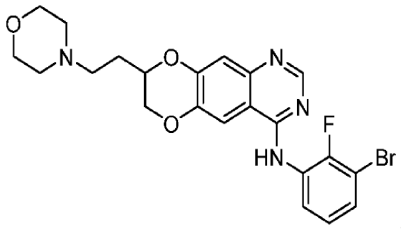
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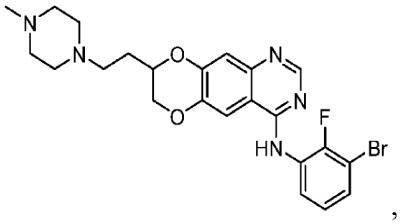
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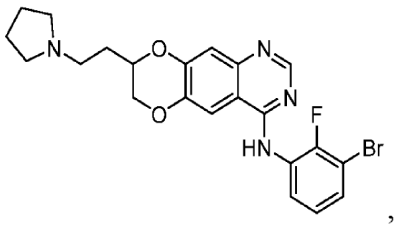
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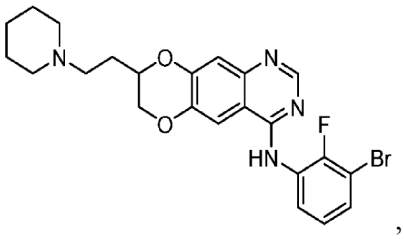
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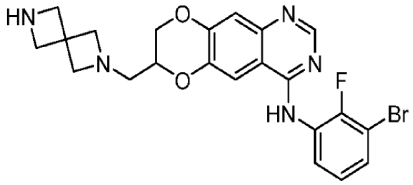
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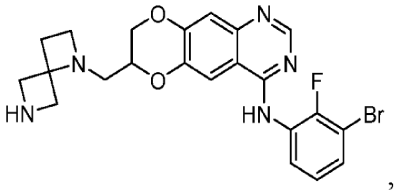
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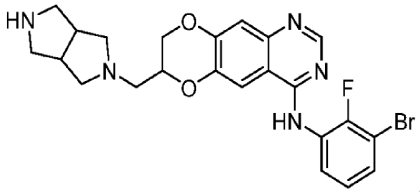
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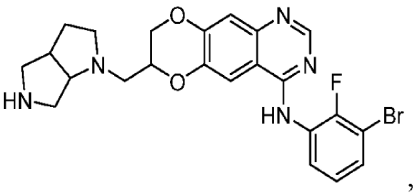
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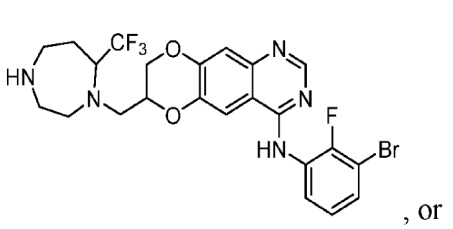
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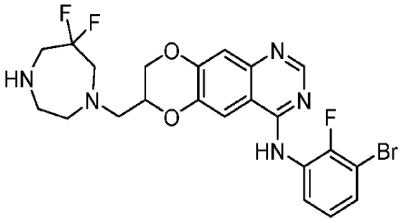
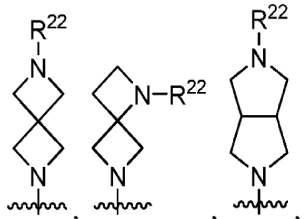
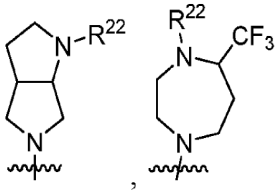
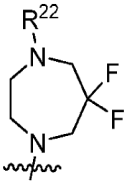

; or a pharmaceutically acceptable salt thereof.

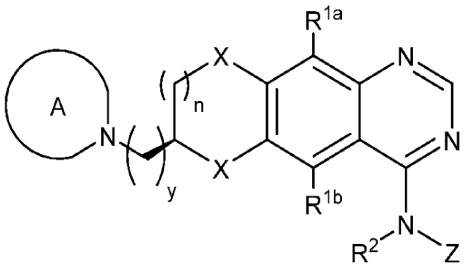
3. The compound of claim 1 or 2, wherein A is not diazepanyl substituted with fluoro (e.g., 6,6-difluorodiazepanyl).

4. The compound of any one of claims 1-3, wherein A is not a bicycle (e.g., a spirocycle).

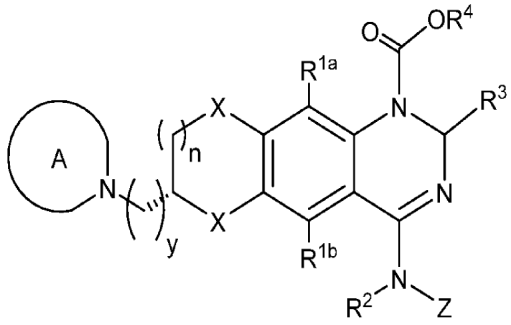
5. The compound of any one of claims 1-3, wherein A is not  ,  ,  , and ; and

R^{22} is selected from C_1-C_6 alkyl and C_3-C_6 cycloalkyl, each of which is optionally substituted with one or more halogen, or a pharmaceutically acceptable salt thereof.

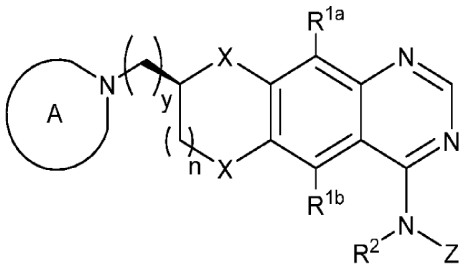
6. The compound of any one of claims 1-5, wherein the compound has a structure represented by Formula Ie, If, Ig, or Ih:



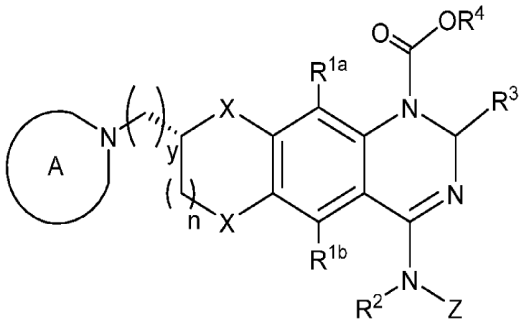
Ie



If



Ig



Ih

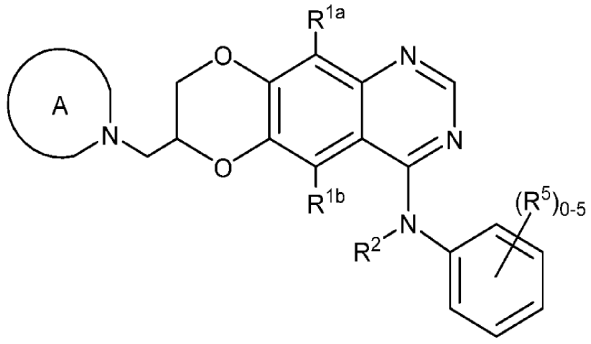
or a pharmaceutically acceptable salt thereof.

7. The compound of any one of claims 1-6, wherein if R^{1a} is hydrogen, then R^{1b} is selected from alkyl, halo, CN, and NO_2.

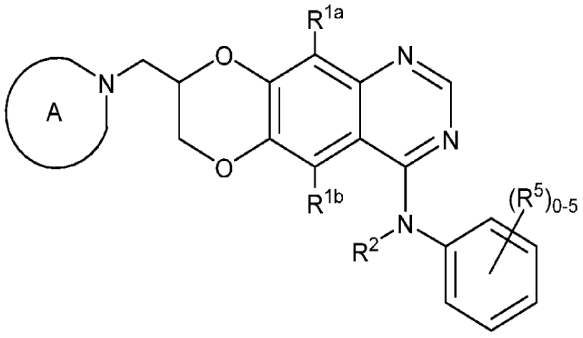
8. The compound of any one of claims 1-6, wherein if R^{1b} is hydrogen, then R^{1a} is selected from alkyl, halo, CN, and NO_2.

9. The compound of any one of claims 1-8, wherein R^{1a} or R^{1b} is selected from alkyl, halo, CN, and NO_2.

10. The compound of any one of claims 1-9, wherein the compound has a structure represented by Formula IIa or IIb:



IIa

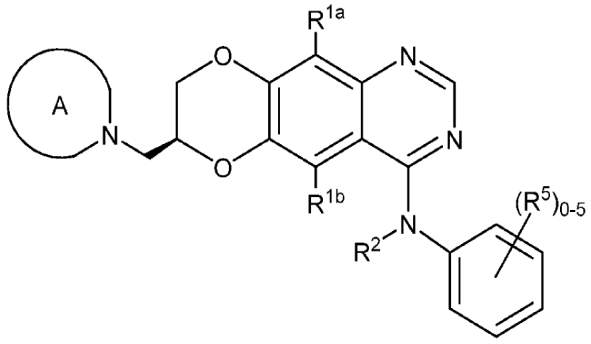


IIb

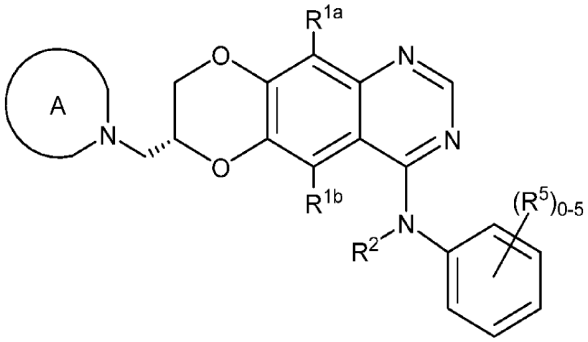
or a pharmaceutically acceptable salt thereof, wherein

each instance of R^5 is independently selected from alkyl, alkenyl, alkynyl, halo, hydroxyl, carboxyl, acyl, acetyl, ester, thioester, alkoxy, phosphoryl, amino, amide, cyano, nitro, azido, alkylthio, alkenyl, alkynyl, cycloalkyl, heterocyclylalkyl, heteroaralkyl, sulfonamide, aryl, heteroaryl, heterocyclyl, and aralkyl.

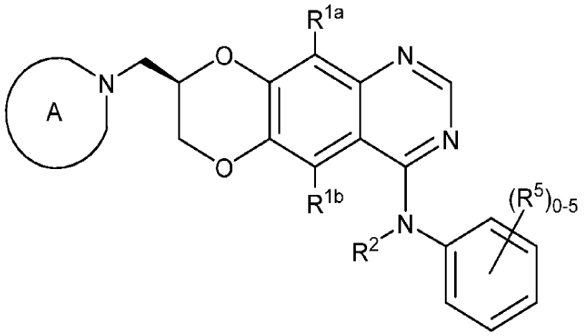
11. The compound of claim 10, wherein the compound has a structure represented by Formula IIc, IId, IIe, or IIf:



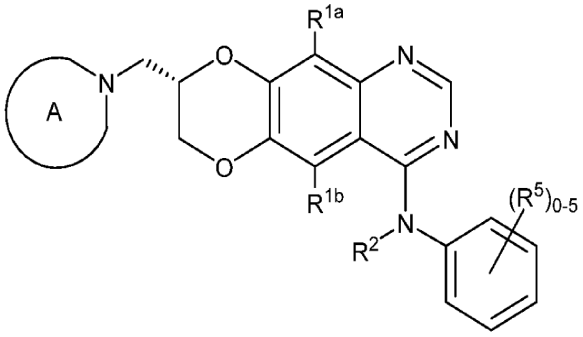
IIc



IId



IIe



IIf

or a pharmaceutically acceptable salt thereof.

12. The compound of any one of claims 1-11, wherein R^2 is hydrogen.

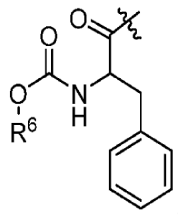
13. The compound of any one of claims 1-11, wherein R^2 is acyl.

14. The compound of claim 13, wherein R^2 is alkylacyl.

15. The compound of claim 13, wherein R^2 is alkyloxyacyl.

16. The compound of claim 13, wherein R^2 is acyloxyalkyl.

17. The compound of claim 13, wherein R^2 is



; and

R^6 is alkyl.

18. The compound of any one of claims 1-17, wherein Z is 2-fluoro-3-chlorophenyl, 2-fluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,4,6-trifluorophenyl, pentafluorophenyl, 2-fluoro-3-bromophenyl, 2-fluoro-3-ethynylphenyl, and 2-fluoro-3-(trifluoromethyl)phenyl.

19. The compound of any one of claims 1-17, wherein Z is 3-ethynylphenyl.

20. The compound of any one of claims 1-17, wherein Z is 3-chloro-4-((3-fluorobenzyl)oxy)benzene.

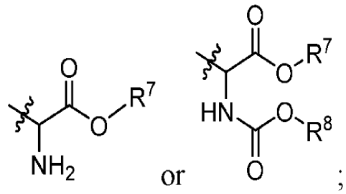
21. The compound of any one of claims 1-17, wherein Z is 3-chloro-2-(trifluoromethyl)phenyl.

22. The compound of any one of claims 1-17, wherein Z is 2-fluoro-3-bromophenyl.

23. The compound of any one of claims 1-17, wherein Z is 2-fluoro-5-bromophenyl.

24. The compound of any one of claims 1-17, wherein Z is 2,6-difluoro-5-bromophenyl.

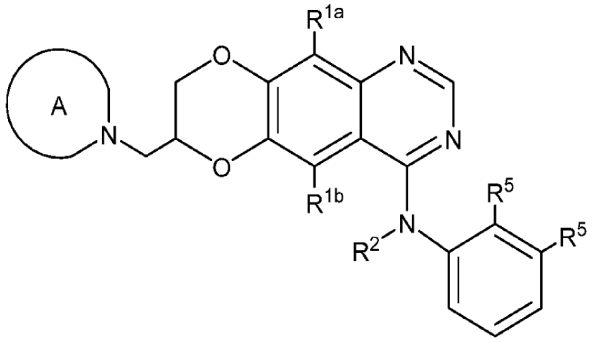
25. The compound of any one of claims 1-17, wherein:
Z is substituted with one R^5 selected from



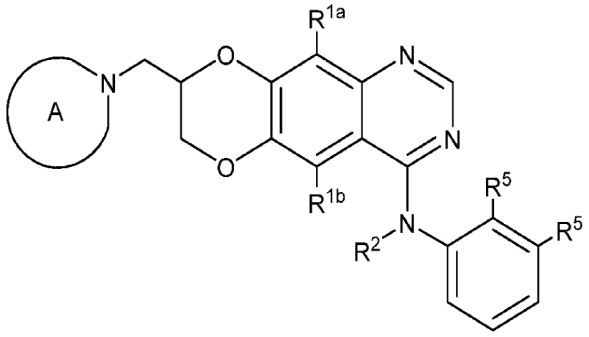
or ; and

R^7 and R^8 are independently selected from alkyl.

26. The compound of any one of claims 1-25, wherein the compound has a structure represented by Formula IIIa or IIIb:



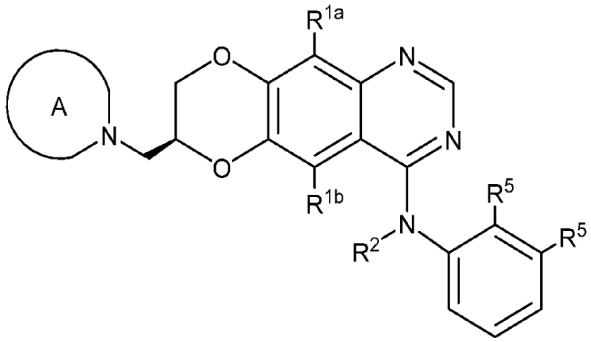
IIIa



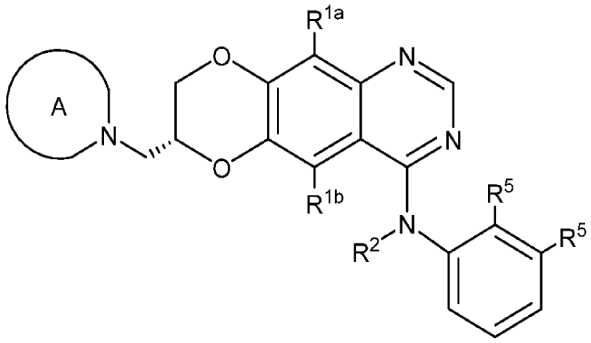
IIIb

or a pharmaceutically acceptable salt thereof.

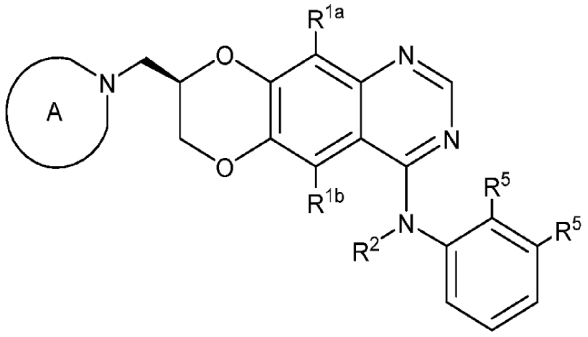
27. The compound of claim 26, wherein the compound has a structure represented by formula IIIc, IIId, IIIe, or IIIf:



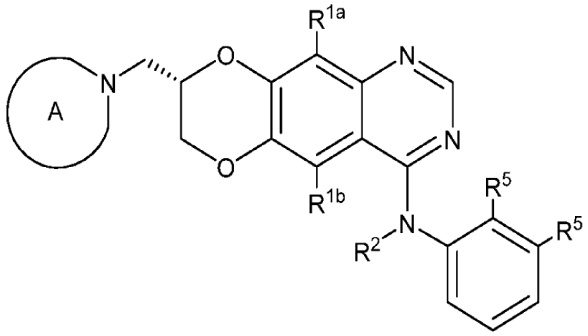
IIIc



IIId



IIIe



IIIf

or a pharmaceutically acceptable salt thereof.

28. The compound of any one of claims 1-27, wherein R^{1a} is hydrogen.

29. The compound of any one of claims 1-27, wherein R^{1a} is halo (e.g., fluoro).

30. The compound of any one of claims 1-29, wherein R^{1b} is hydrogen.

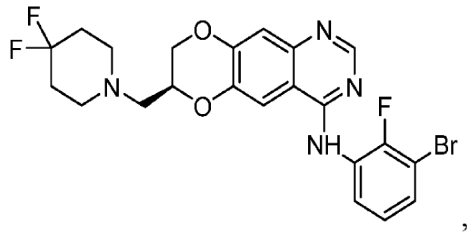
31. The compound of any one of claims 1-29, wherein R^{1b} is halo (e.g., fluoro).

32. The compound of any one of claims 1-31, wherein A is azetidinyl (e.g., methylaminoazetidinyl or acetylaminoazetidinyl), piperidinyl (e.g., fluoro- or difluoropiperidinyl or methyl- or dimethylpiperidinyl), piperazinyl (e.g., trifluoromethylpiperazinyl), diazepanyl (e.g., methyldiazepanyl), or diazabicycloheptanyl (e.g., methyldiazabicycloheptanyl).

33. The compound of any one of claims 1-32, wherein A is substituted with alkyl, alkenyl, alkynyl, halo, hydroxyl, carboxyl, acyl, acetyl, ester, thioester, alkoxy, phosphoryl, amino, amide, cyano, nitro, azido, alkylthio, alkenyl, alkynyl, cycloalkyl, heterocyclylalkyl, heteroaralkyl, sulfonamide, aryl, heteroaryl, heterocyclyl, and aralkyl.

34. The compound of any one of claims 1-33, wherein A is substituted with alkyl (e.g., methyl or trifluoromethyl), amino (e.g., alkylamino, such as methylamino or trifluoromethylamino; or acylamino, such as acetylamino), or halo (e.g., fluoro).

35. A compound selected from: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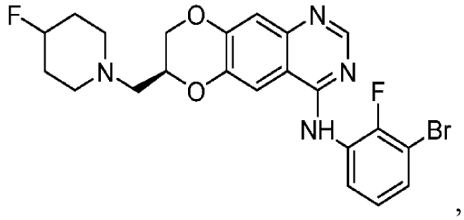
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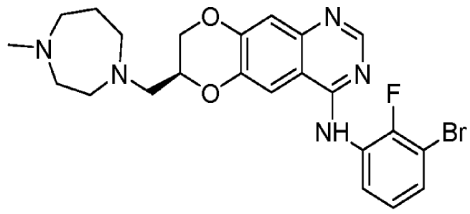
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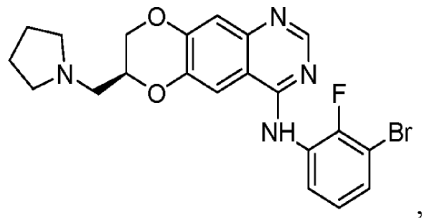
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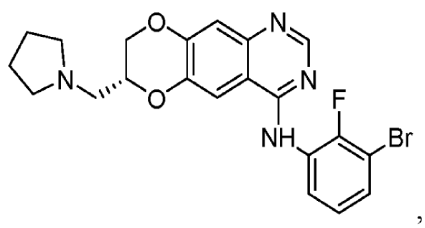
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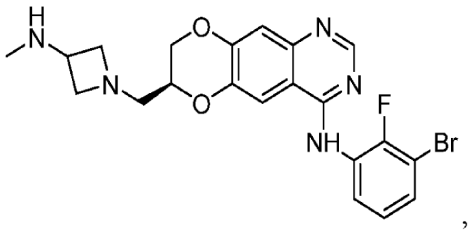
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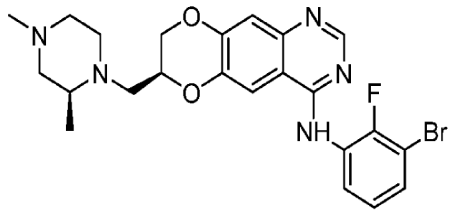
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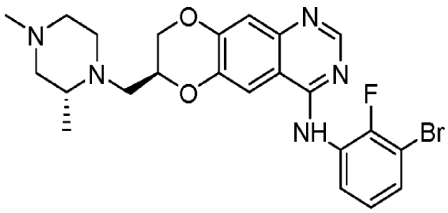
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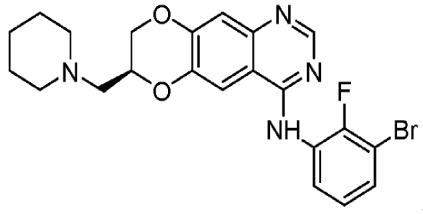
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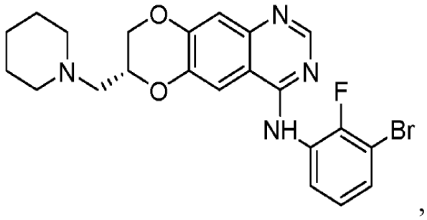
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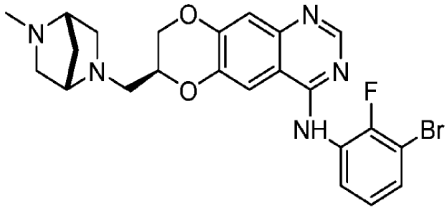
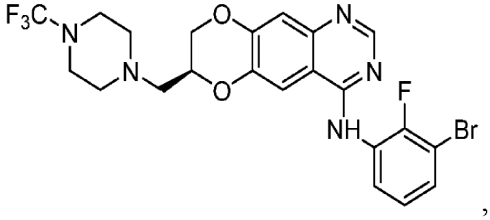
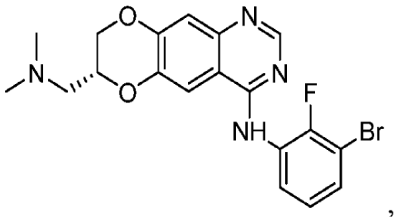
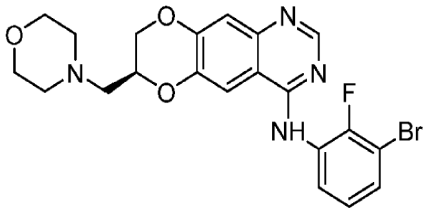
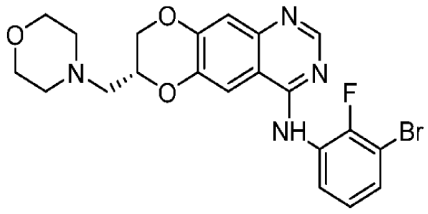
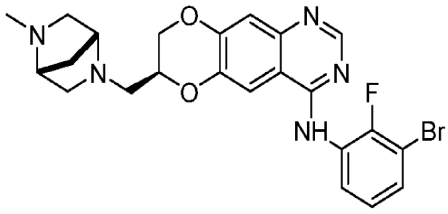
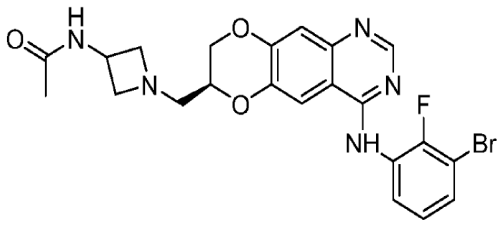

,

,

,

,

,

, and

; or a pharmaceutically acceptable salt thereof.

36. A pharmaceutical composition comprising the compound of any one of the preceding claims and a pharmaceutically acceptable excipient.

37. A method of inhibiting EGFR or a variant thereof, such as ΔEGFR, EGFR extracellular mutants, EGFR A289, EGFR T263, and/or EGFR activating mutants, for example ex19 deletion, comprising administering to a subject a compound or composition of any one of claims 1-36.

38. A method of treating cancer, comprising of administering to a subject in need of a treatment for cancer a compound or composition of any one of claims 1-36.

39. The method of claim 38, wherein the cancer is bladder cancer, bone cancer, brain cancer, breast cancer, cardiac cancer, cervical cancer, colon cancer, colorectal cancer, esophageal cancer, fibrosarcoma, gastric cancer, gastrointestinal cancer, head, spine and neck

cancer, Kaposi's sarcoma, kidney cancer, leukemia, liver cancer, lymphoma, melanoma, multiple myeloma, pancreatic cancer, penile cancer, testicular germ cell cancer, thymoma carcinoma, thymic carcinoma, lung cancer, ovarian cancer, or prostate cancer.

40. The method of claim 38, wherein the cancer is glioma, astrocytoma or glioblastoma.

41. A method of treating cancer in a subject, the method comprising administering to the subject a glucose metabolism inhibitor and an additional agent, wherein the glucose metabolism inhibitor is a compound of any one of claims 1-36 or a pharmaceutically acceptable salt thereof and the additional agent is a cytoplasmic p53 stabilizer.

42. The method of claim 41, wherein the cancer is bladder cancer, bone cancer, brain cancer, breast cancer, cardiac cancer, cervical cancer, colon cancer, colorectal cancer, esophageal cancer, fibrosarcoma, gastric cancer, gastrointestinal cancer, head, spine and neck cancer, Kaposi's sarcoma, kidney cancer, leukemia, liver cancer, lymphoma, melanoma, multiple myeloma, pancreatic cancer, penile cancer, testicular germ cell cancer, thymoma carcinoma, thymic carcinoma, lung cancer, ovarian cancer, or prostate cancer.

43. The method of claim 41, where the cancer is glioblastoma multiforme, glioma, low-grade astrocytoma, mixed oligoastrocytoma, pilocytic astrocytoma, pleomorphic xanthoastrocytoma, subependymal giant cell astrocytoma, anaplastic astrocytoma, CNS cancer, non-CNS cancer, or CNS metastases or lung cancer.

44. The method of claim 41, wherein the cancer is glioma, astrocytoma or glioblastoma.

45. The method of any one of claims 37-44, wherein the method reduces cancer cell proliferation.

46. The method of any one of claims 37-45, wherein the subject has been determined to have cancer that is susceptible to glucose metabolism inhibitors.

47. The method of claim 46, wherein the subject has been determined to be susceptible to the glucose metabolism inhibitor by a method comprising:

a. obtaining a first blood sample from the subject;
b. placing the subject on a ketogenic diet;
c. obtaining a second blood sample from the subject after being placed on a ketogenic diet for a period of time;
d. measuring glucose level in the first and in the second blood sample;
e. comparing the glucose level in the second blood sample with the glucose level in the first blood sample; and
f. determining that the subject is susceptible if the glucose level in the second blood sample is reduced as compared to glucose levels in the first blood sample.

48. The method of claim 47, wherein the reduction in the glucose level between the second blood sample and the first blood sample is about or greater than 0.15 mM.

49. The method of claim 47, wherein the reduction in the glucose level between the second blood sample and the first blood sample is about or greater than 0.20 mM.

50. The method of claim 47, wherein the reduction in the glucose level between the second blood sample and the first blood sample is in the range of 0.15 mM - 2.0 mM.

51. The method of claim 47, wherein the reduction in the glucose level between the second blood sample and the first blood sample is in the range of 0.25 mM – 1.0 mM.

52. The method of any one of claims 41-51, wherein the cytoplasmic p53 stabilizer is an MDM2 inhibitor.

53. The method of claim 52, wherein the MDM2 inhibitor is a nutlin.

54. The method of claim 52, wherein the MDM2 inhibitor is nutlin-3 or idasanutlin.

55. The method of claim 54, wherein the subject is administered 50 mg to 1600 mg of idasanutlin.

56. The method of claim 54 or 55, wherein the subject is administered 100 mg of idasanutlin.

57. The method of claim 54 or 55, wherein the subject is administered 150 mg of idasanutlin.

58. The method of claim 54 or 55, wherein the subject is administered 300 mg of idasanutlin.

59. The method of claim 54 or 55, wherein the subject is administered 400 mg of idasanutlin.

60. The method of claim 54 or 55, wherein the subject is administered 600 mg of idasanutlin.

61. The method of claim 54 or 55, wherein the subject is administered 1600 mg of idasanutlin.

62. The method of claim 52, wherein the MDM2 inhibitor is RO5045337, RO5503781, RO6839921, SAR405838, DS-3032, DS-3032b, or AMG-232.

63. The method of any one of claims 41-51, wherein the cytoplasmic p53 stabilizer is a BCL-2 inhibitor.

64. The method of claim 63, wherein the BCL-2 inhibitor is antisense oligodeoxynucleotide G3139, mRNA antagonist SPC2996, venetoclax (ABT-199), GDC-0199, obatoclax, paclitaxel, navitoclax (ABT-263), ABT-737, NU-0129, S 055746, or APG-1252.

65. The method of any one of claims 41-51, wherein the cytoplasmic p53 stabilizer is a Bcl-xL inhibitor.

66. The method of claim 65, wherein the Bcl-xL inhibitor is WEHI 539, ABT-263, ABT-199, ABT-737, sabutoclax, AT101, TW-37, APG-1252, or gambogic acid.

67. The method of any one of claims 41-66, wherein the glucose metabolism inhibitor and the cytoplasmic p53 stabilizer are administered in the same composition.

68. The method of any one of claims 41-66, wherein the glucose metabolism inhibitor and the cytoplasmic p53 stabilizer are administered in separate compositions.

69. The method of any one of claims 38-68, wherein the cancer is relapsed or refractory.

70. The method of any one of claims 38-68, wherein the cancer is treatment naïve.

71. The method of any one of claims 38-70, wherein the method further comprises administration of an additional therapy.

72. A pharmaceutical composition comprising a glucose metabolism inhibitor and a cytoplasmic p53 stabilizer, wherein the glucose metabolism inhibitor is a compound of any one of claims 1-35.

73. The pharmaceutical composition of claim 72, wherein the cytoplasmic p53 stabilizer is an MDM2 inhibitor.

74. The pharmaceutical composition of claim 73, wherein the MDM2 inhibitor is a nutlin.

75. The pharmaceutical composition of claim 73 or 74, wherein the MDM2 inhibitor is nutlin-3 or idasanutlin.

76. The pharmaceutical composition of claim 73, wherein the MDM2 inhibitor is RO5045337, RO5503781, RO6839921, SAR405838, DS-3032, DS-3032b, or AMG-232.

77. The pharmaceutical composition of claim 73, wherein the cytoplasmic p53 stabilizer is a BCL-2 inhibitor.

78. The pharmaceutical composition of claim 77, wherein the BCL-2 inhibitor is antisense oligodeoxynucleotide G3139, mRNA antagonist SPC2996, venetoclax (ABT-199), GDC-0199, obatoclax, paclitaxel, navitoclax (ABT-263), ABT-737, NU-0129, S 055746, or APG-1252.

79. The pharmaceutical composition of claim 72, wherein the cytoplasmic p53 stabilizer is a Bcl-xL inhibitor.

80. The pharmaceutical composition of claim 79, wherein the Bcl-xL inhibitor is WEHI 539, ABT-263, ABT-199, ABT-737, sabutoclax, AT101, TW-37, APG-1252, or gambogic acid.

FIG. 1A

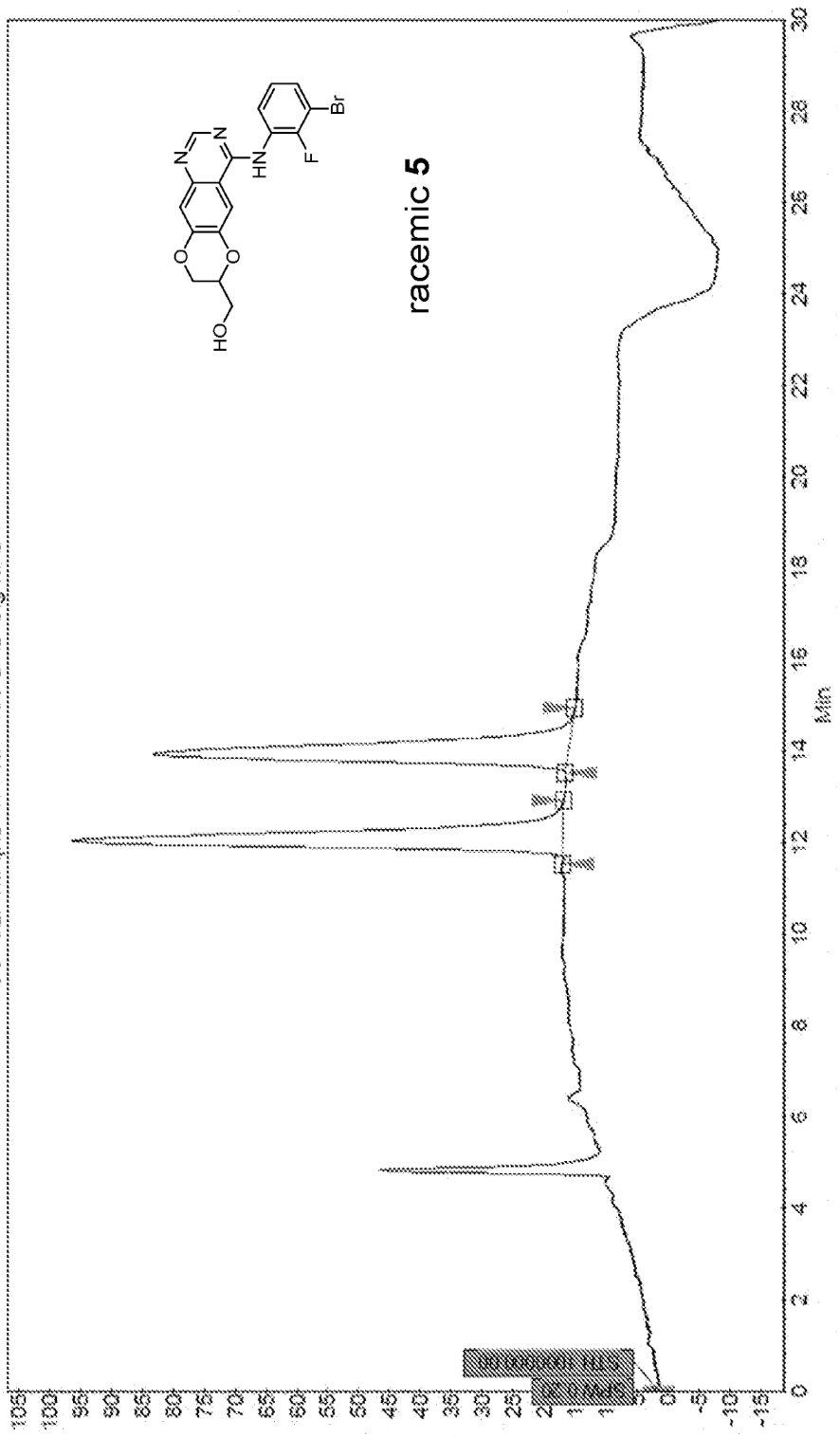


FIG. 1B

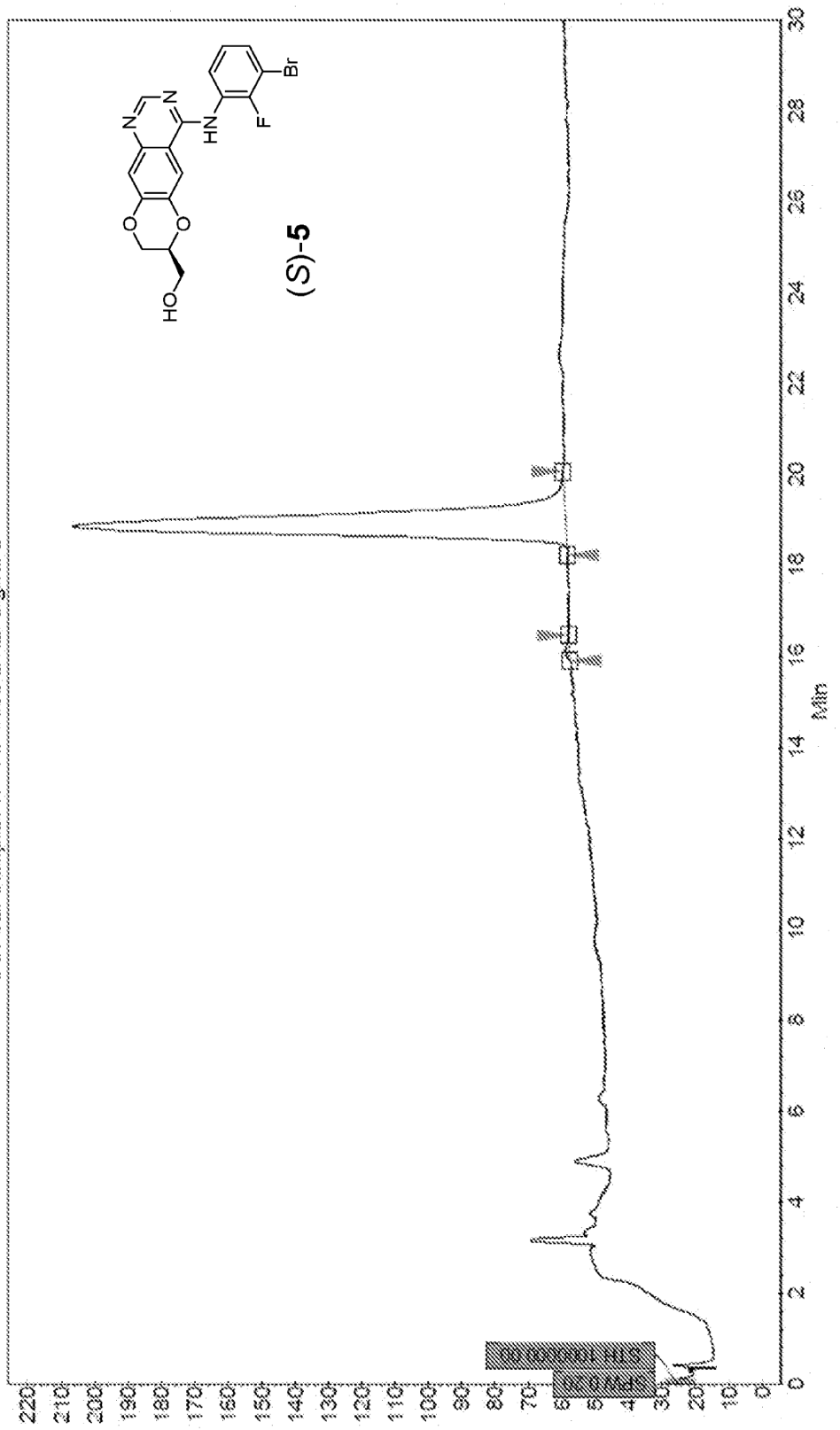


FIG. 1C

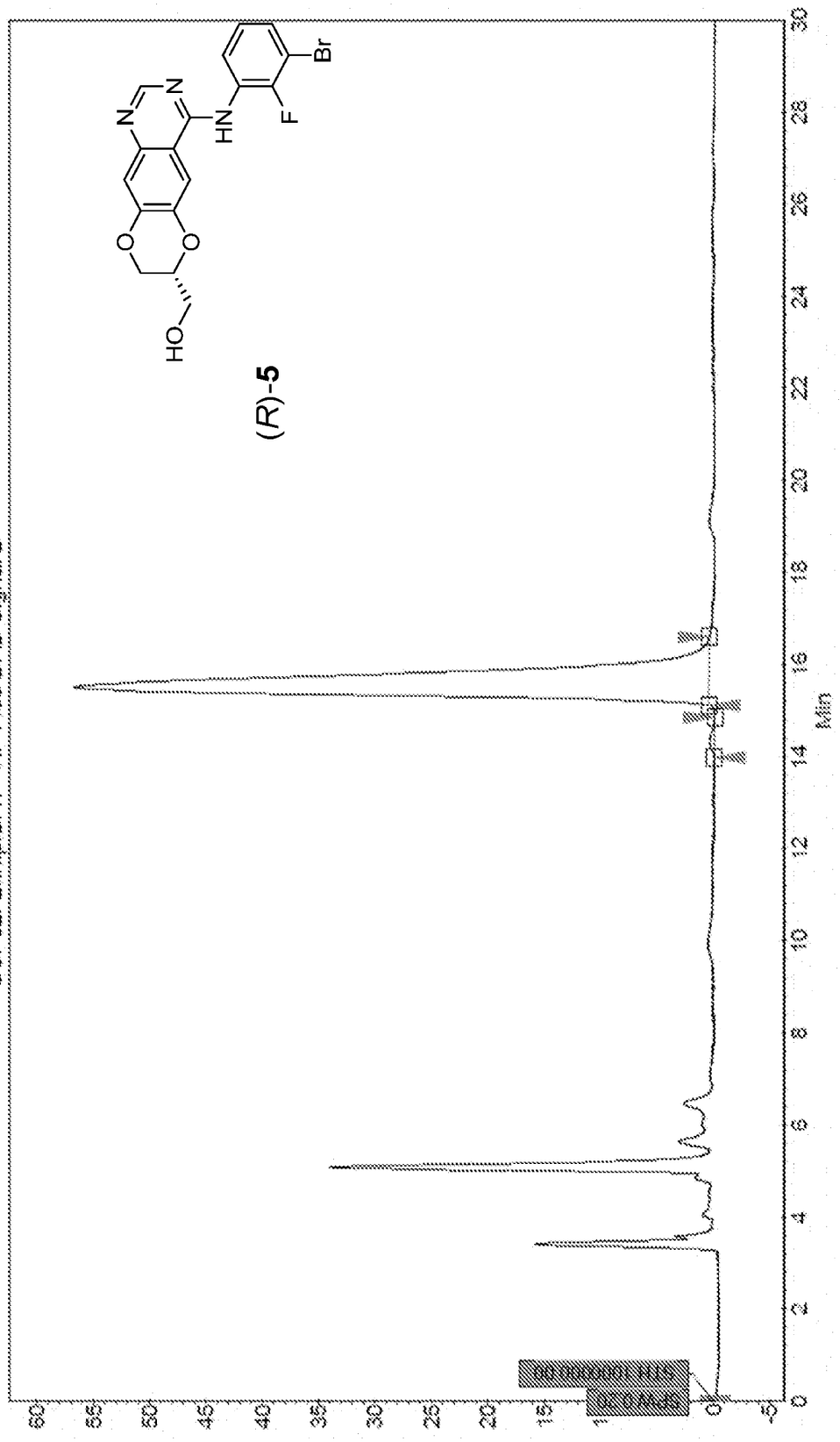

CCP32F2.tmp.DAT - HP1100 DAD Signal B
(R)-5
Br
F
HN
N
N
O
O
HO
Min
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
60
55
50
45
40
35
30
25
20
15
10
5
0
-5

FIG. 1D

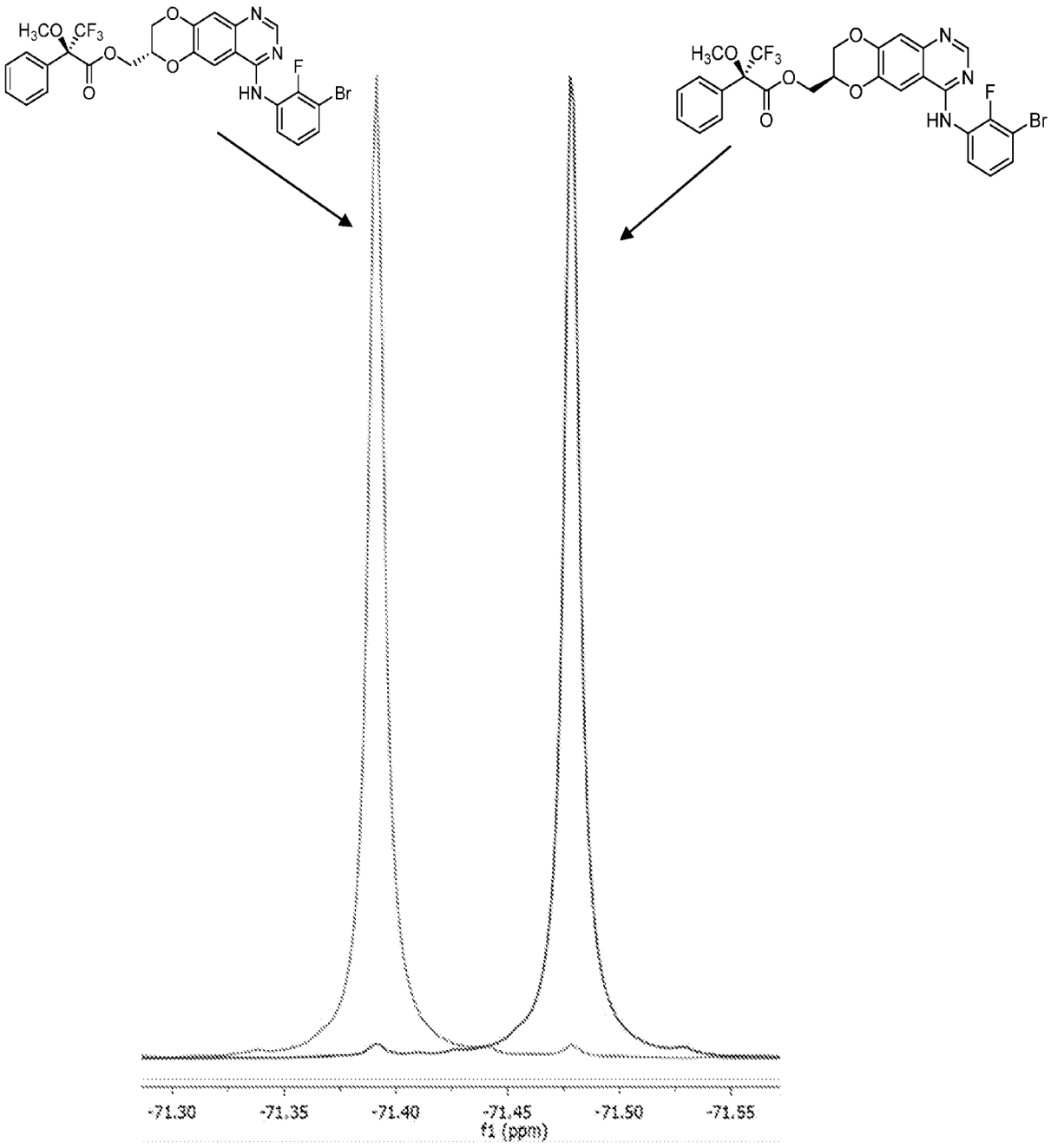
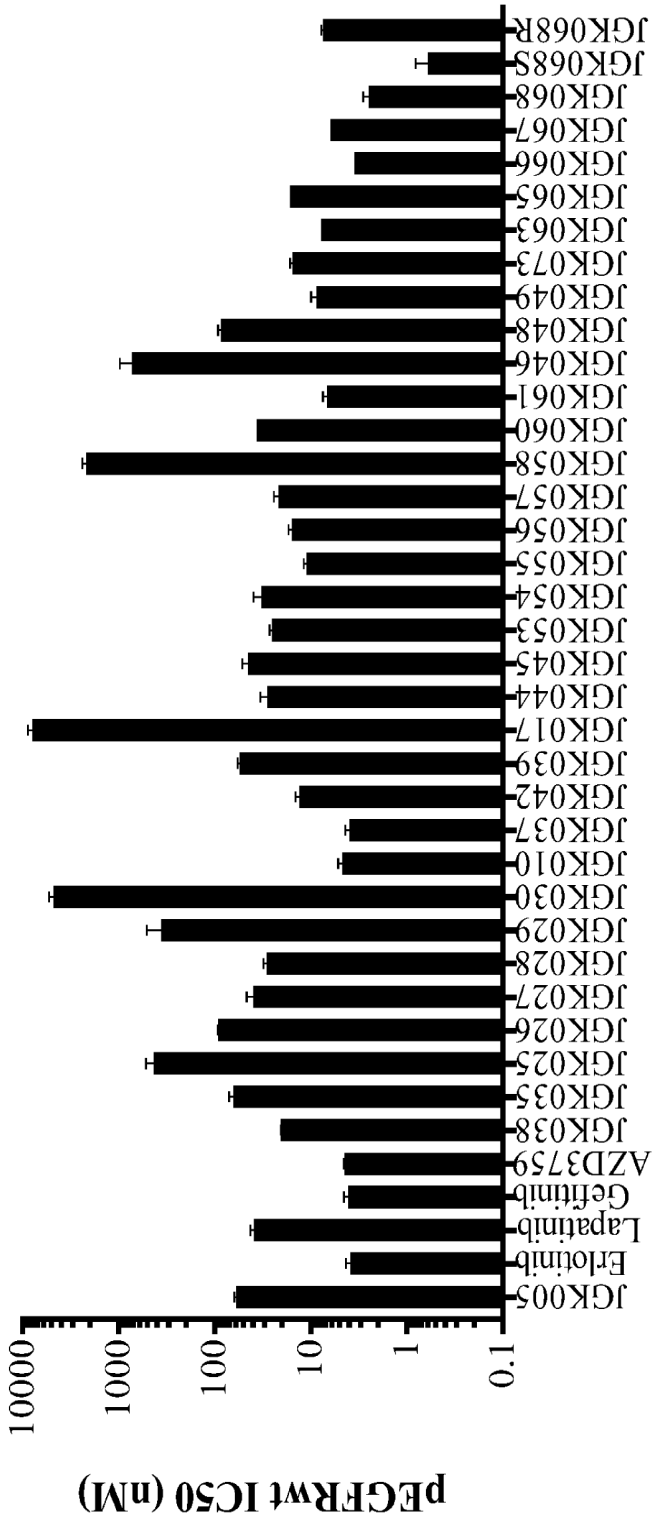


FIG. 2


U87 EGFRwt
pEGFRwt IC50 (nM)
10000
1000
100
10
1
0.1
JGK005
Erlotinib
Lapatinib
Gefitinib
AZD3759
JGK038
JGK035
JGK025
JGK026
JGK027
JGK028
JGK029
JGK030
JGK010
JGK037
JGK042
JGK039
JGK017
JGK044
JGK045
JGK053
JGK054
JGK055
JGK056
JGK057
JGK058
JGK060
JGK061
JGK046
JGK048
JGK049
JGK073
JGK063
JGK065
JGK066
JGK067
JGK068
JGK068S
JGK068R

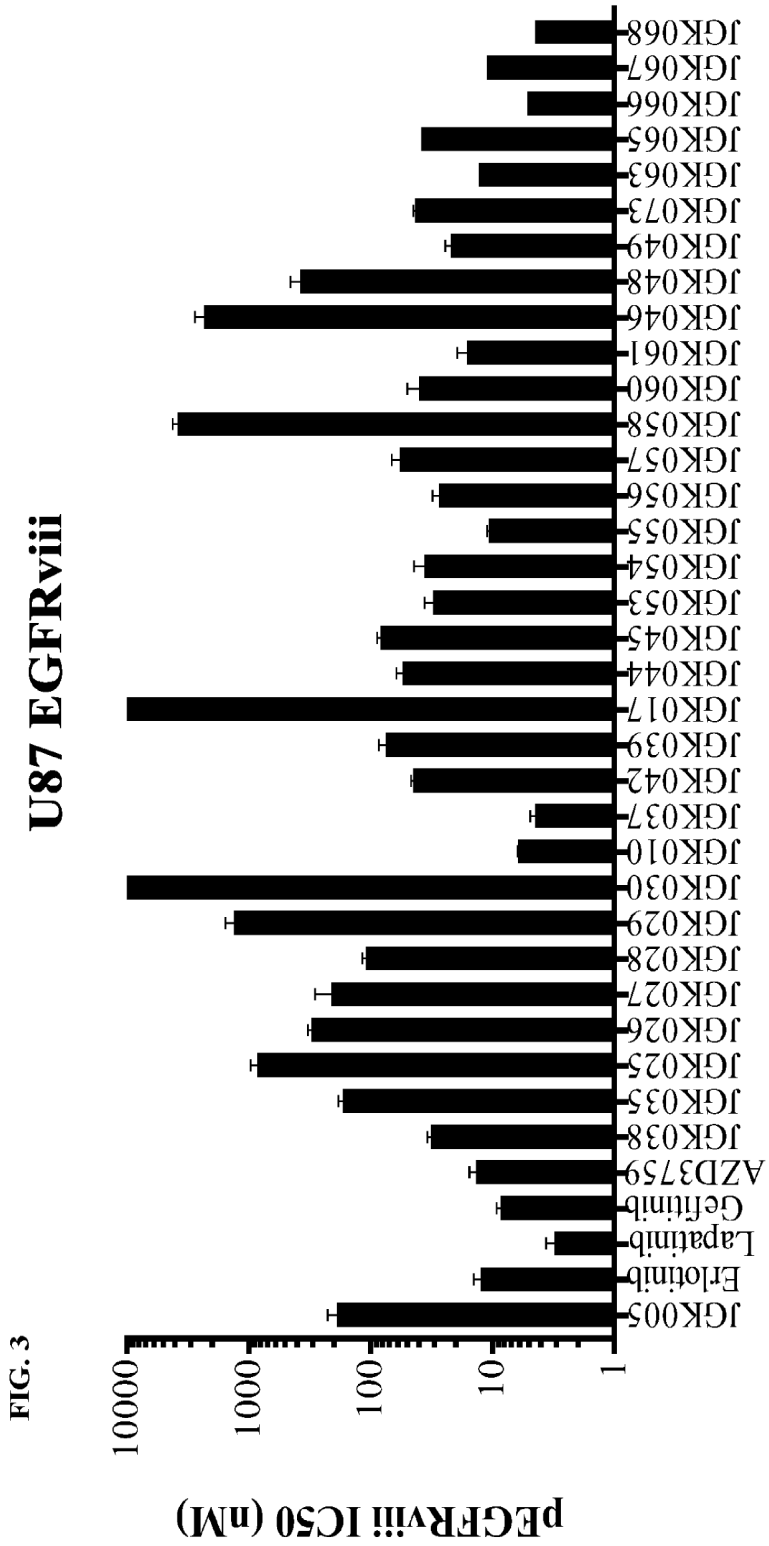

U87 EGFRviii
pEGFRviii IC50 (nM)
10000
1000
100
10
1
JGK005
Erlotinib
Lapatinib
Gefitinib
AZD3759
JGK038
JGK035
JGK025
JGK026
JGK027
JGK028
JGK029
JGK030
JGK010
JGK037
JGK042
JGK039
JGK017
JGK044
JGK045
JGK053
JGK054
JGK055
JGK056
JGK057
JGK058
JGK060
JGK061
JGK046
JGK048
JGK049
JGK073
JGK063
JGK065
JGK066
JGK067
JGK068

FIG. 3

FIG. 4

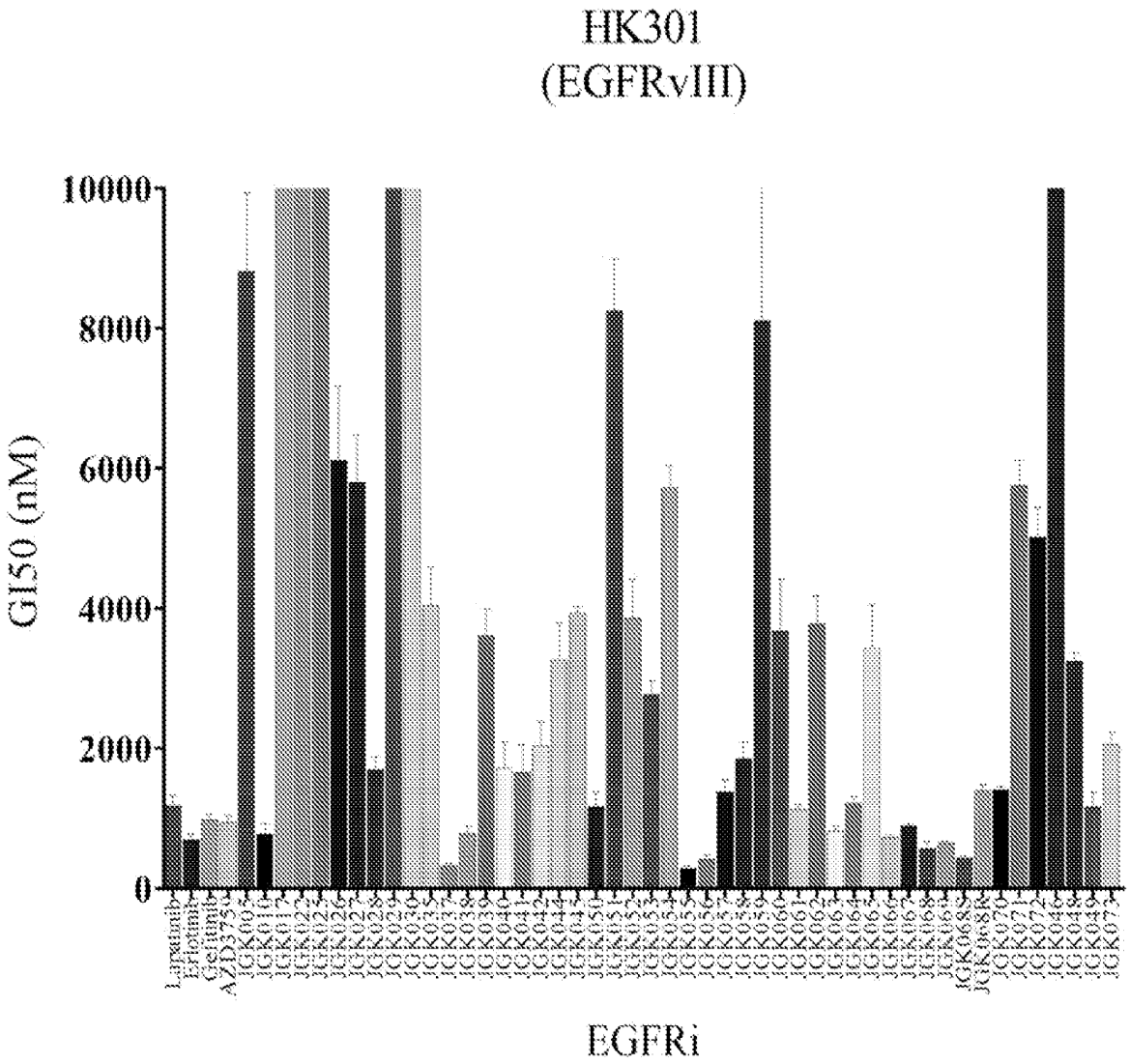

HK301
(EGFRvIII)
GI50 (nM)
10000
8000
6000
4000
2000
0
Lapatinib
Erlotinib
Gefitinib
AZD3759
EGFRi

FIG. 5

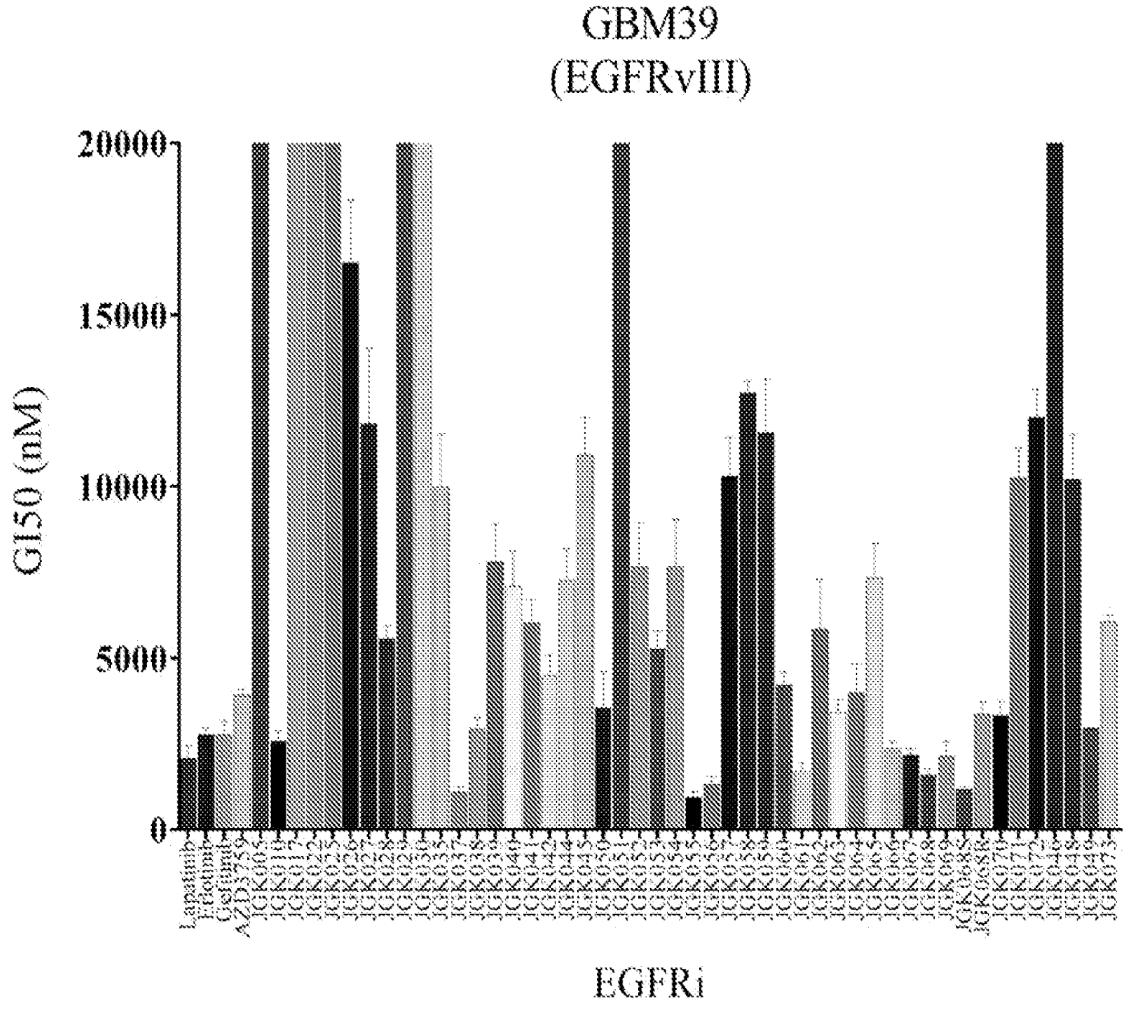

GBM39
(EGFRvIII)
G150 (nM)
20000
15000
10000
5000
0
Lapatinib
Erlotinib
Gefitinib
AZD3759
JGK0015
JGK0117
JGK0122
JGK0125
JGK0126
JGK0127
JGK0128
JGK0129
JGK0130
JGK0135
JGK0137
JGK0138
JGK0139
JGK0140
JGK0142
JGK0144
JGK0145
JGK0150
JGK0151
JGK0152
JGK0154
JGK0155
JGK0156
JGK0157
JGK0158
JGK0159
JGK0160
JGK0161
JGK0162
JGK0163
JGK0164
JGK0165
JGK0166
JGK0167
JGK0168
JGK0169
JGK0682
JGK0685
JGK0703
JGK0171
JGK0172
JGK0446
JGK0448
JGK0449
JGK0673
EGFRi

FIG. 6

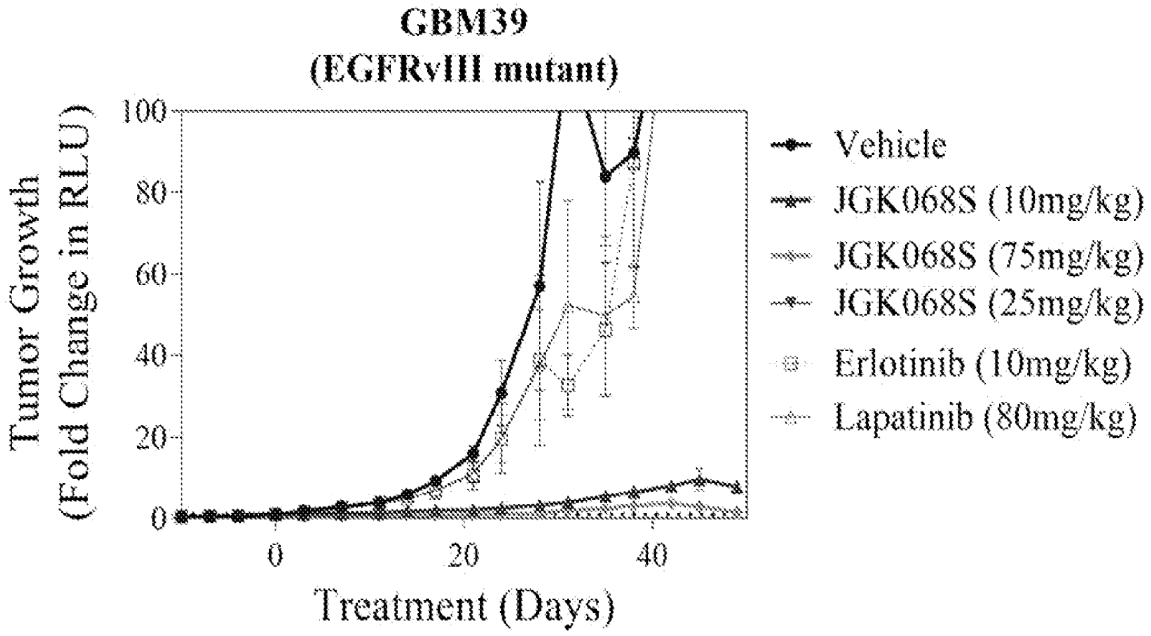

GBM39
(EGFRvIII mutant)
Tumor Growth
(Fold Change in RLU)
100
80
60
40
20
0
0
20
40
Treatment (Days)
Vehicle
JGK068S (10mg/kg)
JGK068S (75mg/kg)
JGK068S (25mg/kg)
Erlotinib (10mg/kg)
Lapatinib (80mg/kg)

FIG. 7A

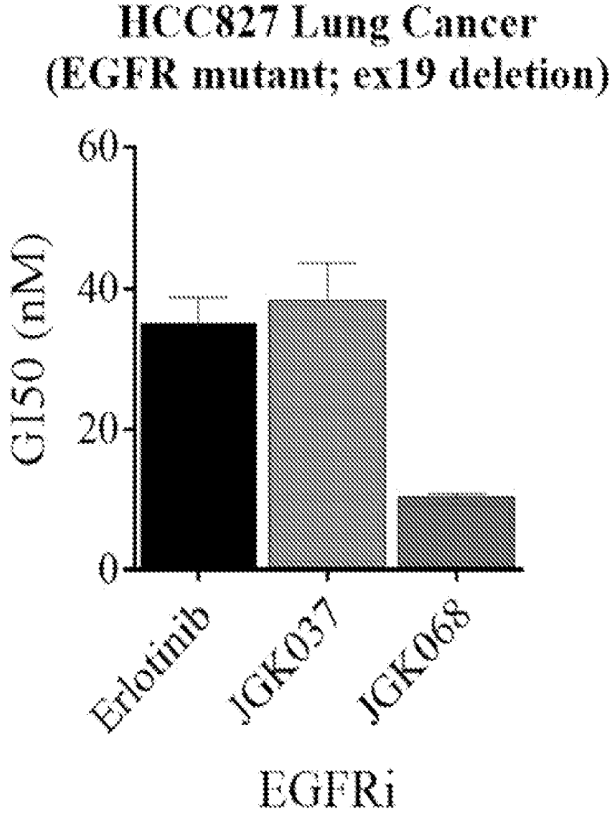

HCC827 Lung Cancer
(EGFR mutant; ex19 deletion)
GI50 (nM)
60
40
20
0
Erlotinib
JGK037
JGK068
EGFRi

FIG. 7B

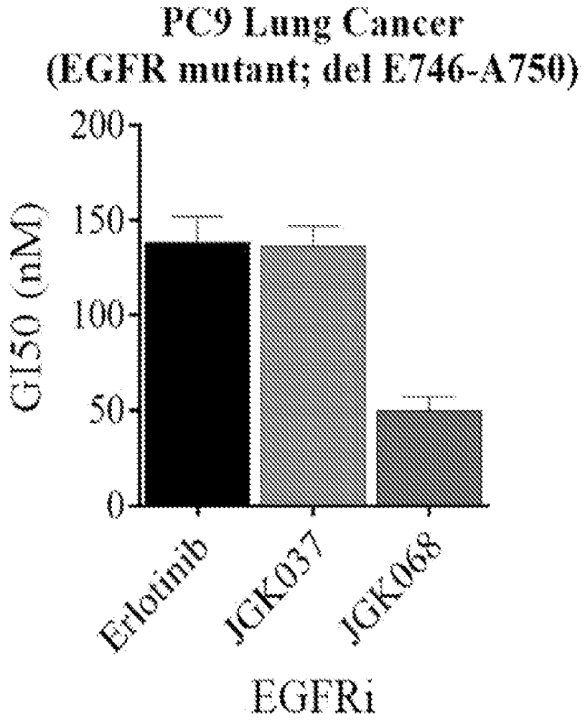

PC9 Lung Cancer
(EGFR mutant; del E746-A750)
GI50 (nM)
200
150
100
50
0
Erlotinib
JGK037
JGK068
EGFRi

FIG. 7C

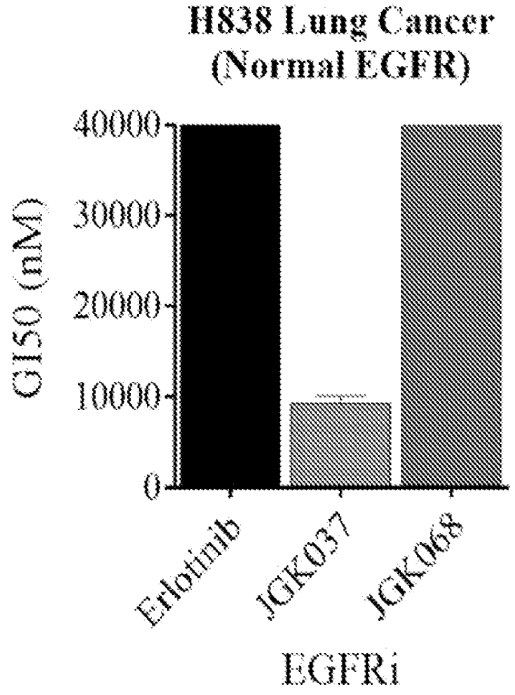

H838 Lung Cancer
(Normal EGFR)
GI50 (nM)
40000
30000
20000
10000
0
Erlotinib
JGK037
JGK068
EGFRi

FIG. 8

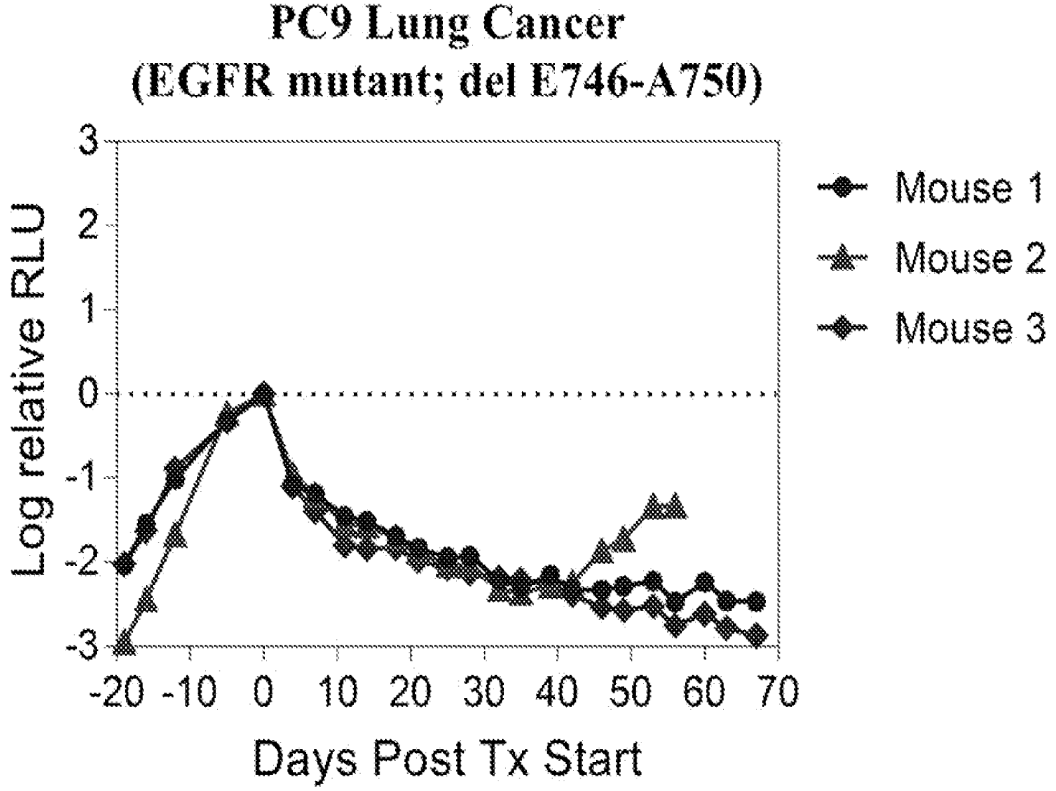
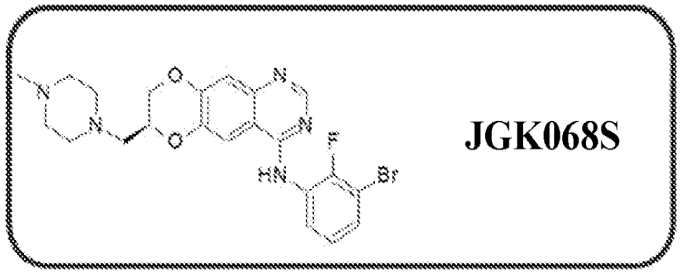
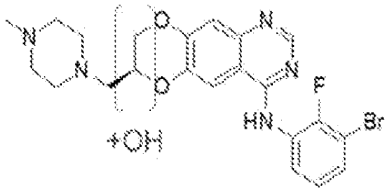
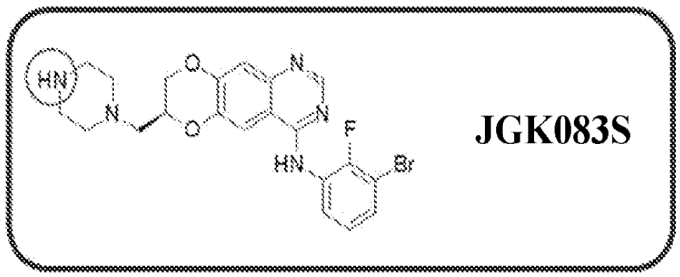
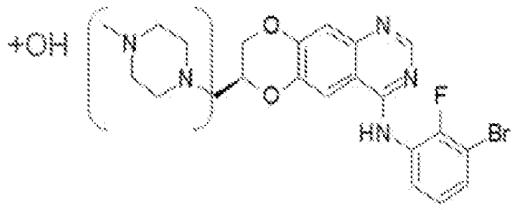

PC9 Lung Cancer
(EGFR mutant; del E746-A750)
Log relative RLU
3
2
1
0
-1
-2
-3
-20 -10 0 10 20 30 40 50 60 70
Days Post Tx Start
Mouse 1
Mouse 2
Mouse 3

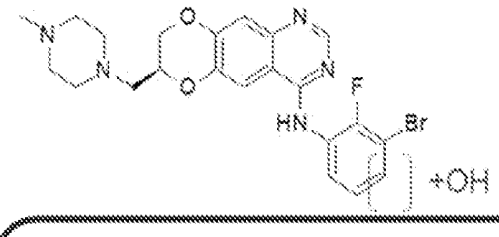
FIG. 9

1. 

2. 

3. 

4. 

5. 

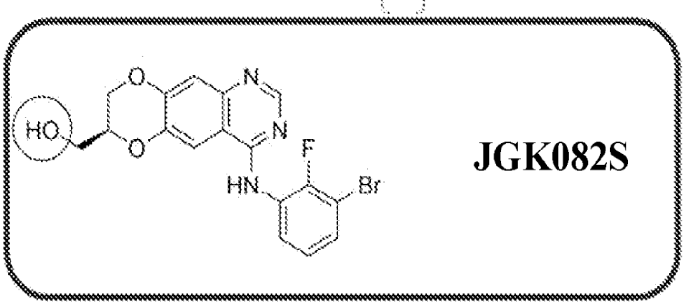
6. 

FIG. 10A

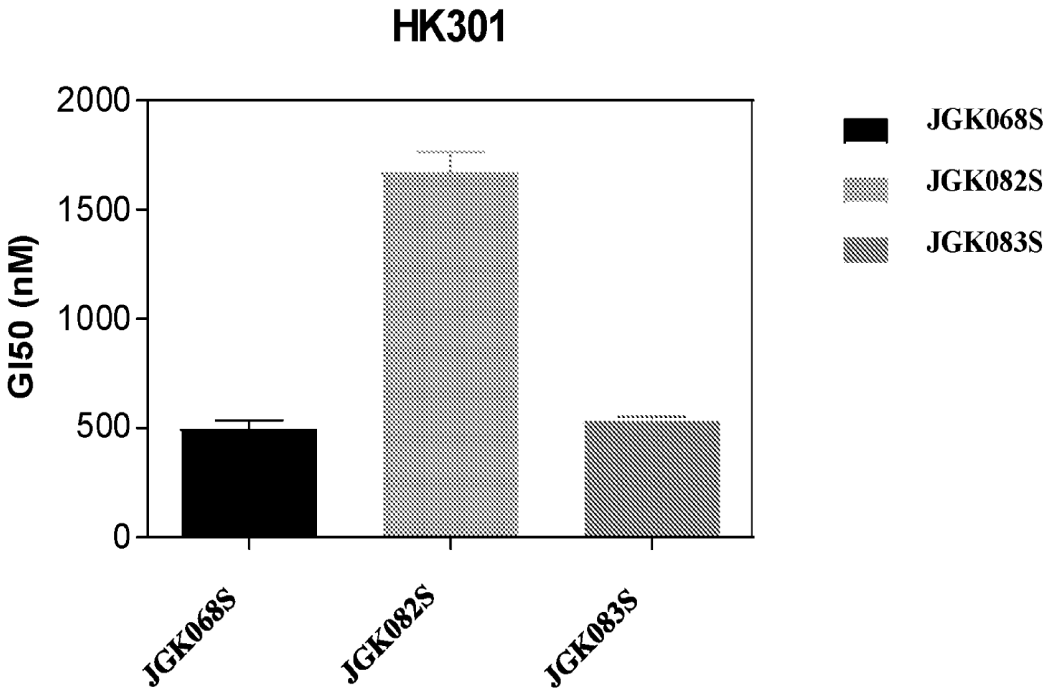


FIG. 10B

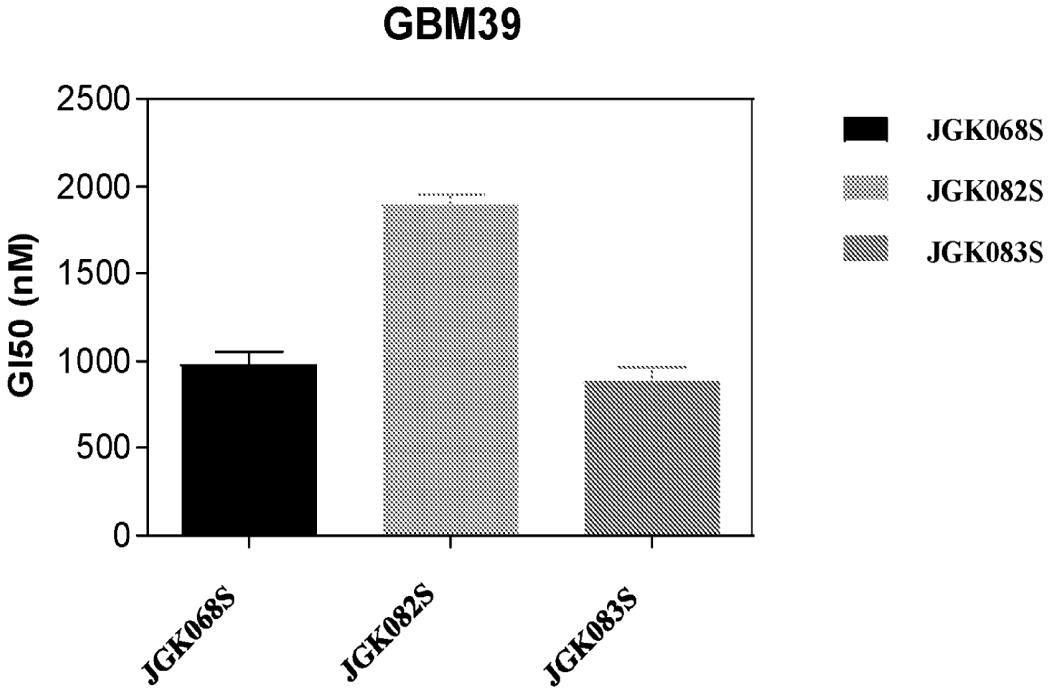


FIG. 10C

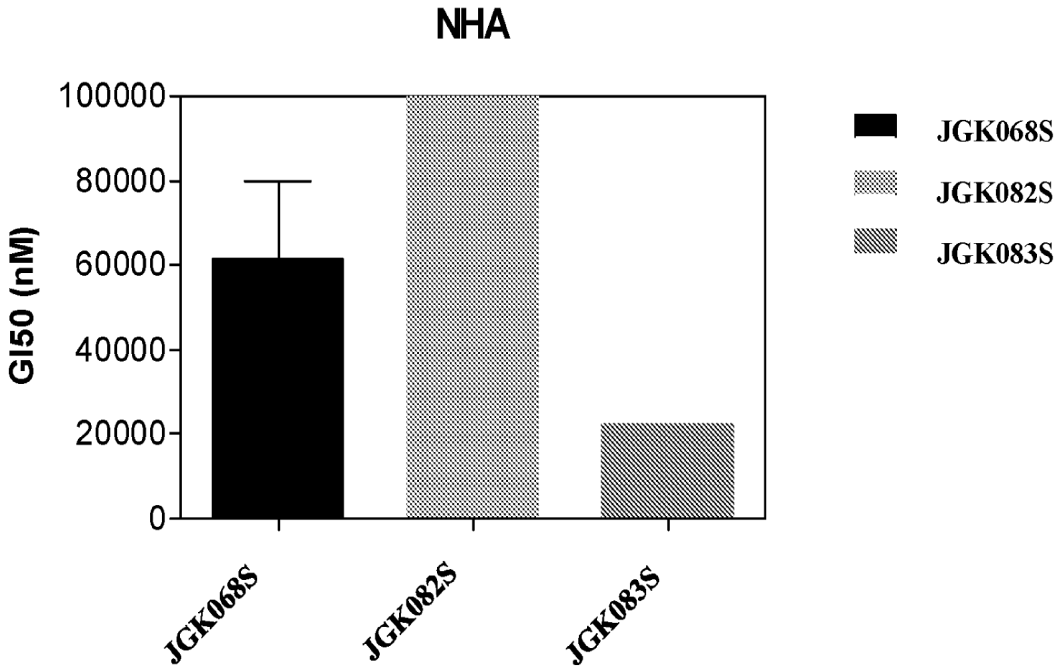


FIG. 11A

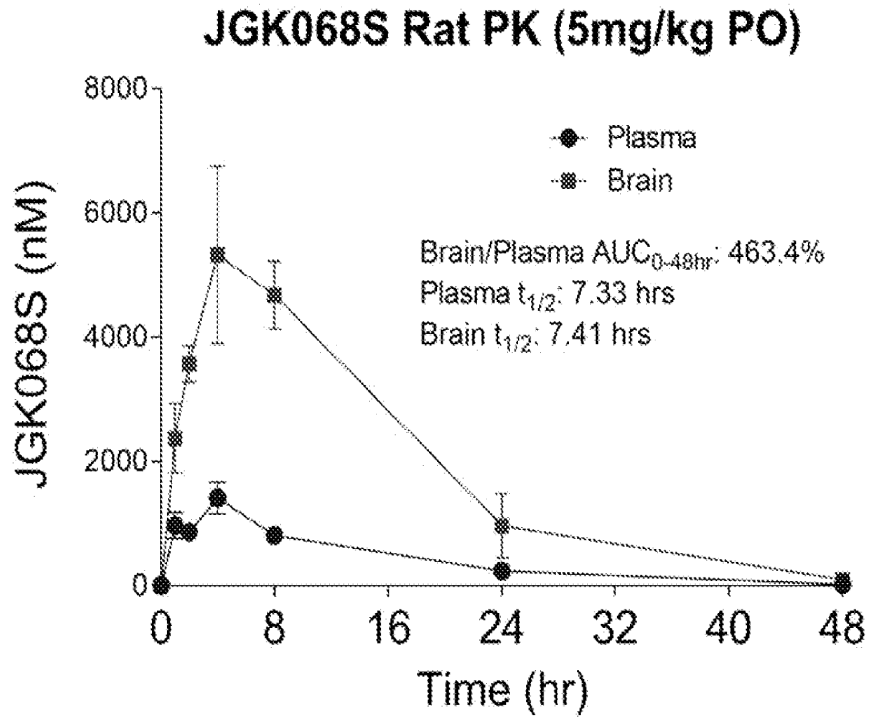


FIG. 11B

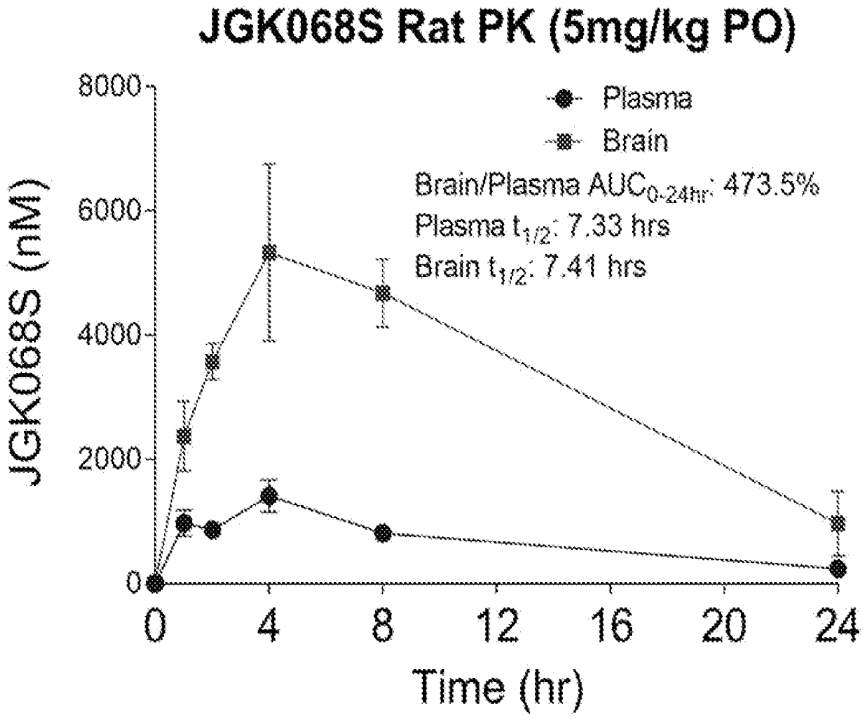

JGK068S Rat PK (5mg/kg PO)
Plasma
Brain
Brain/Plasma AUC0-24hr: 473.5%
Plasma t1/2: 7.33 hrs
Brain t1/2: 7.41 hrs
JGK068S (nM)
8000
6000
4000
2000
0
0
4
8
12
16
20
24
Time (hr)

FIG. 12A

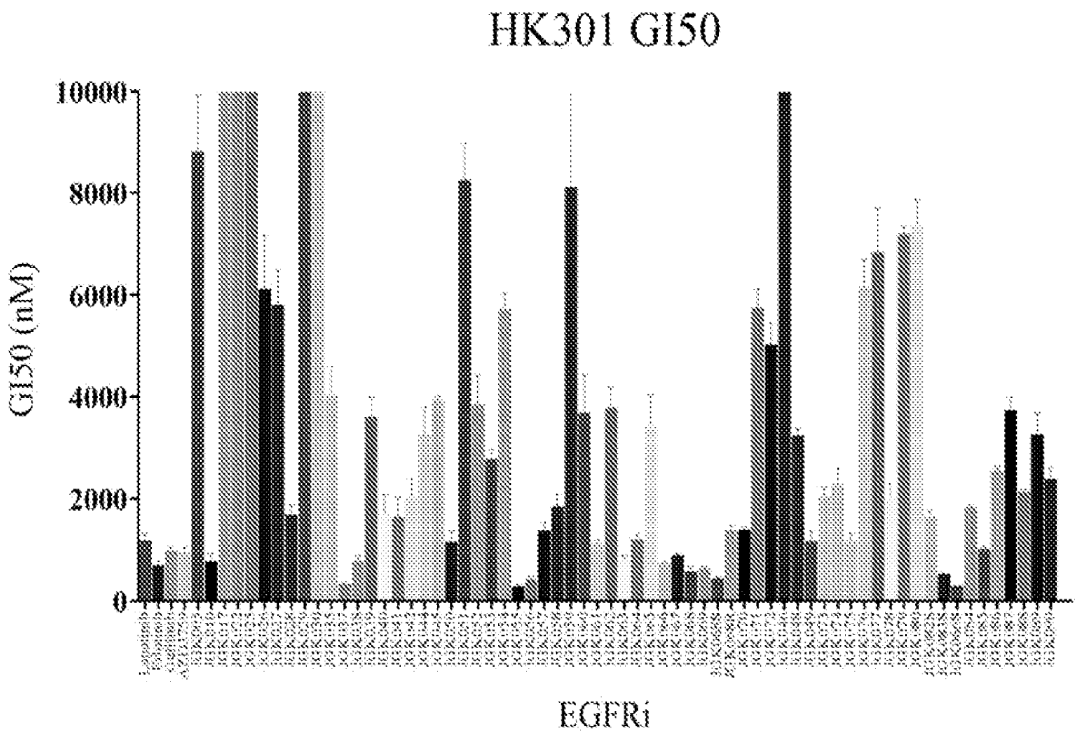


FIG. 12B

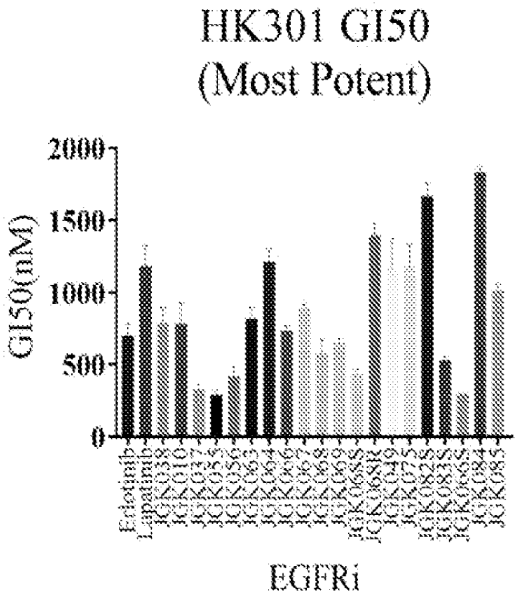


FIG. 13A

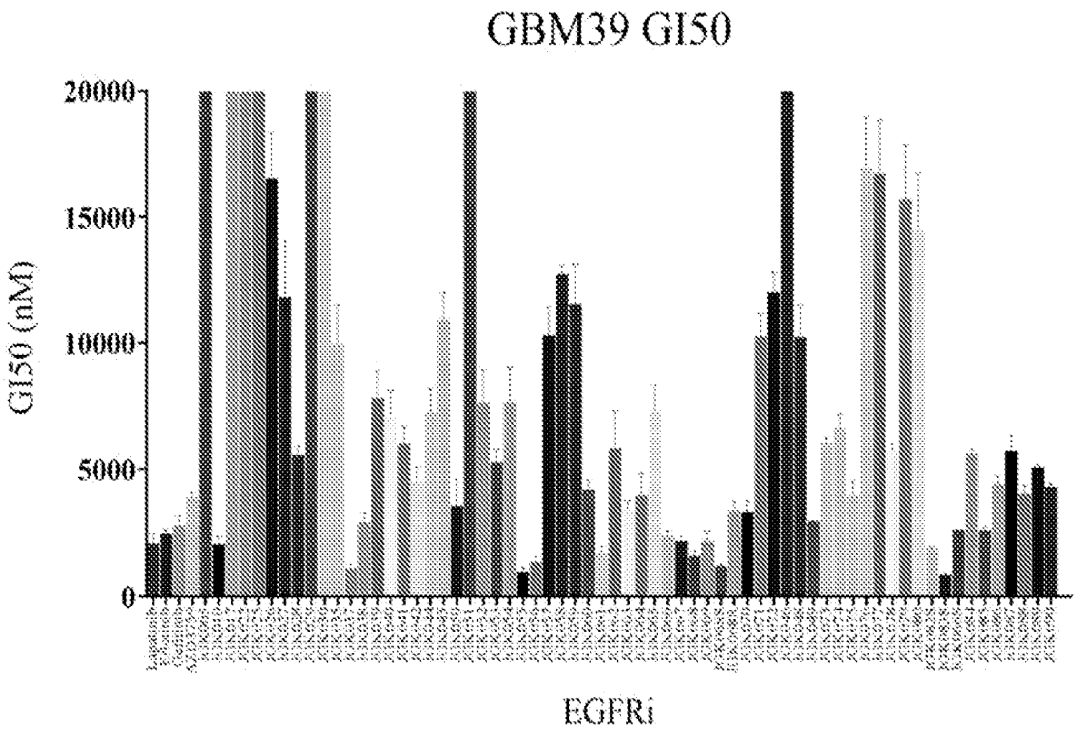


FIG. 13B

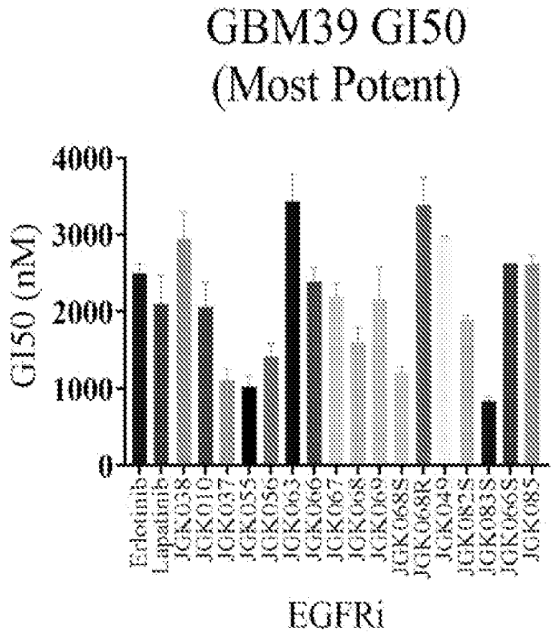


FIG. 14A

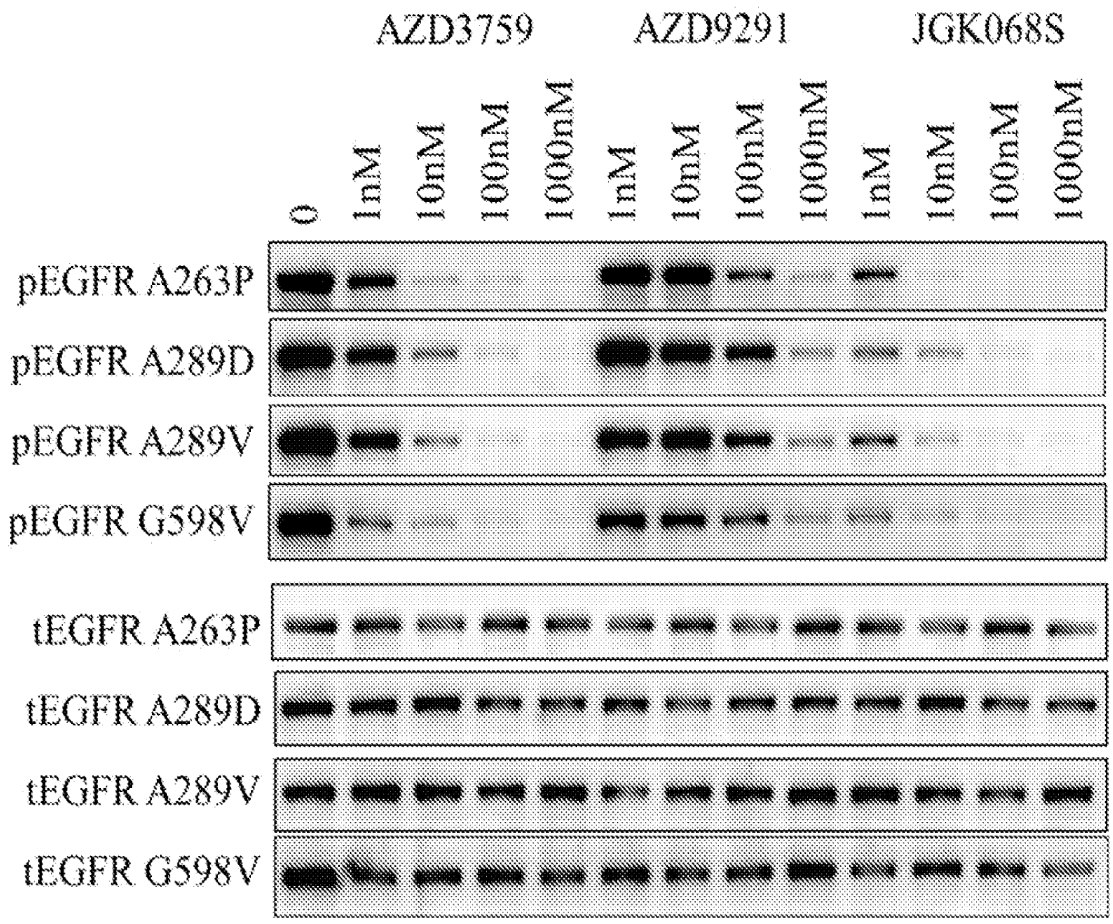

AZD3759
AZD9291
JGK068S
0
1nM
10nM
100nM
1000nM
1nM
10nM
100nM
1000nM
1nM
10nM
100nM
1000nM
pEGFR A263P
pEGFR A289D
pEGFR A289V
pEGFR G598V
tEGFR A263P
tEGFR A289D
tEGFR A289V
tEGFR G598V

FIG. 14B

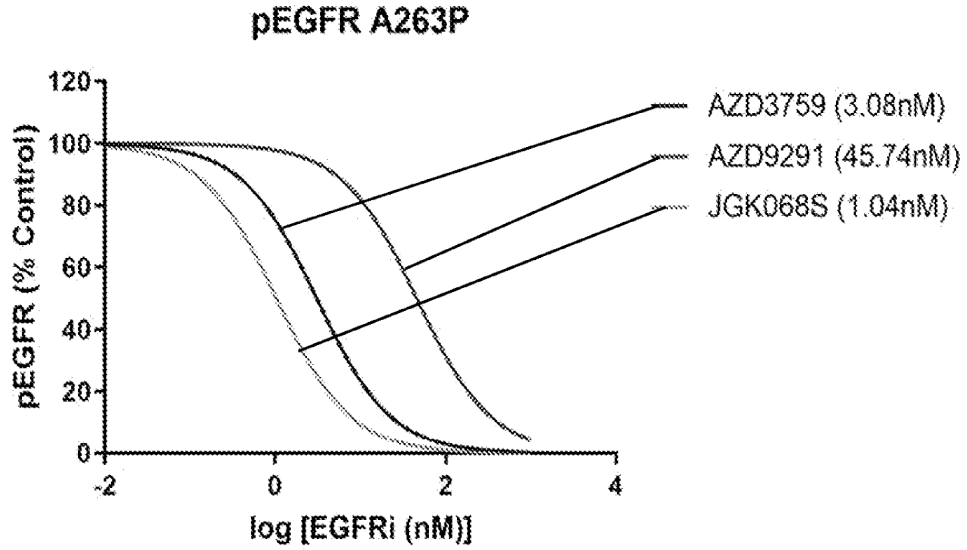


FIG. 14C

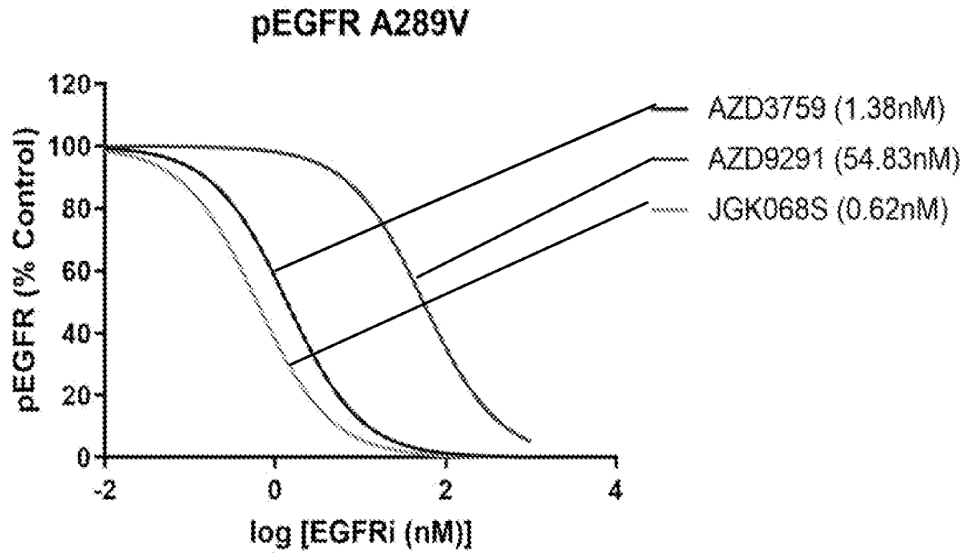


FIG. 14D

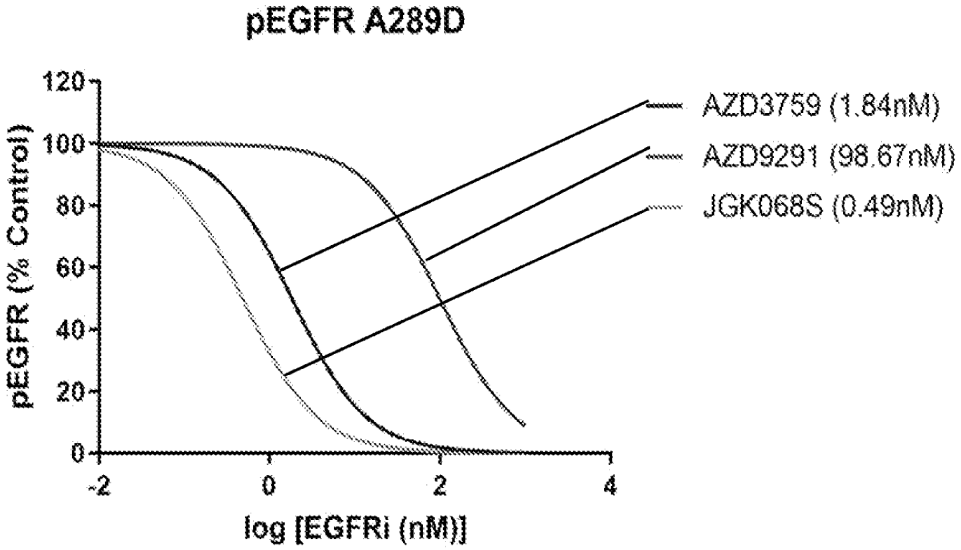


FIG. 14E

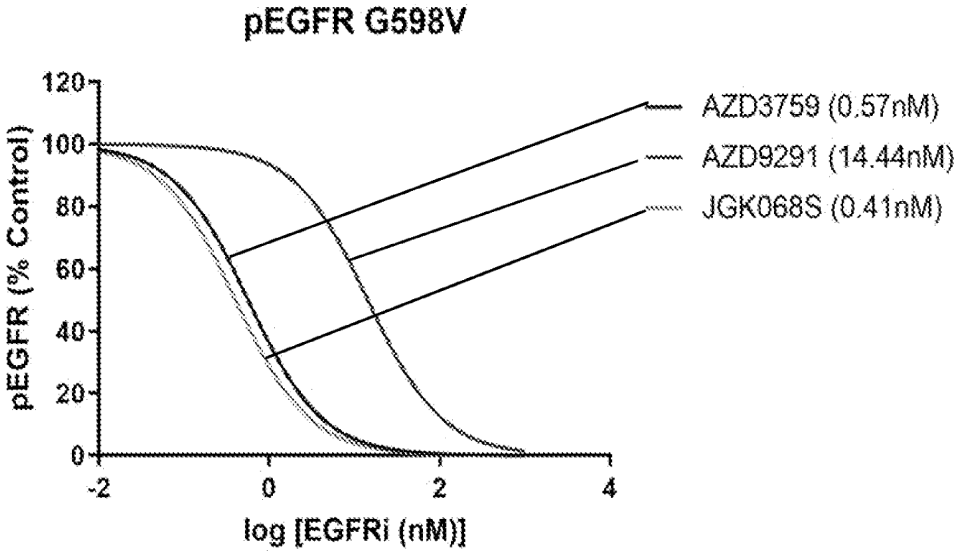


FIG. 15A

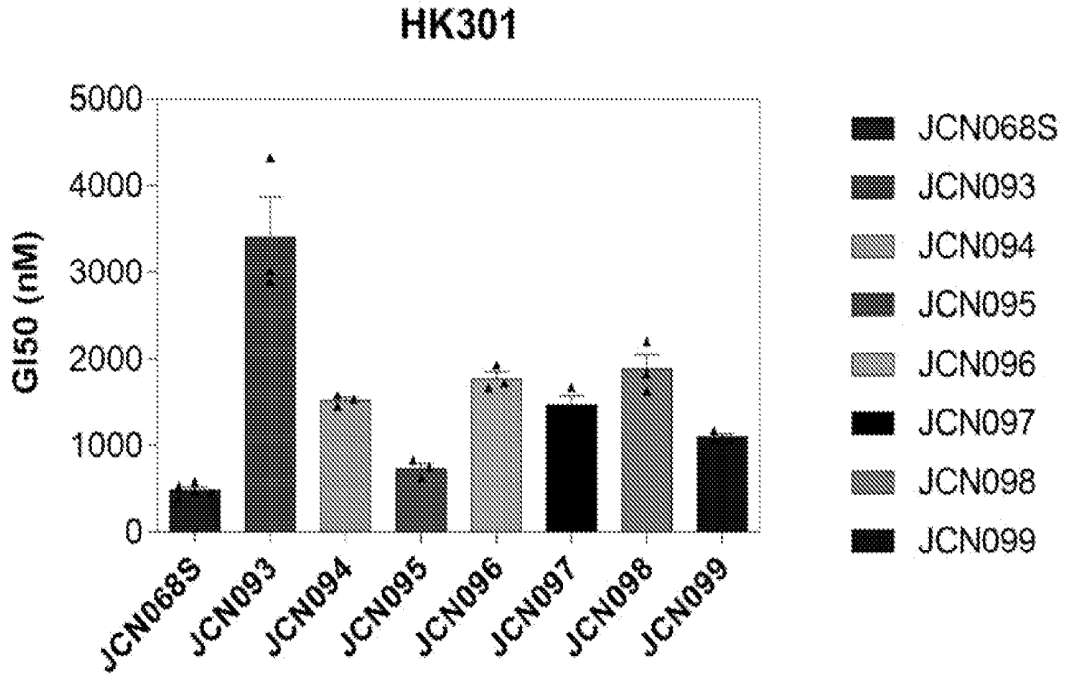
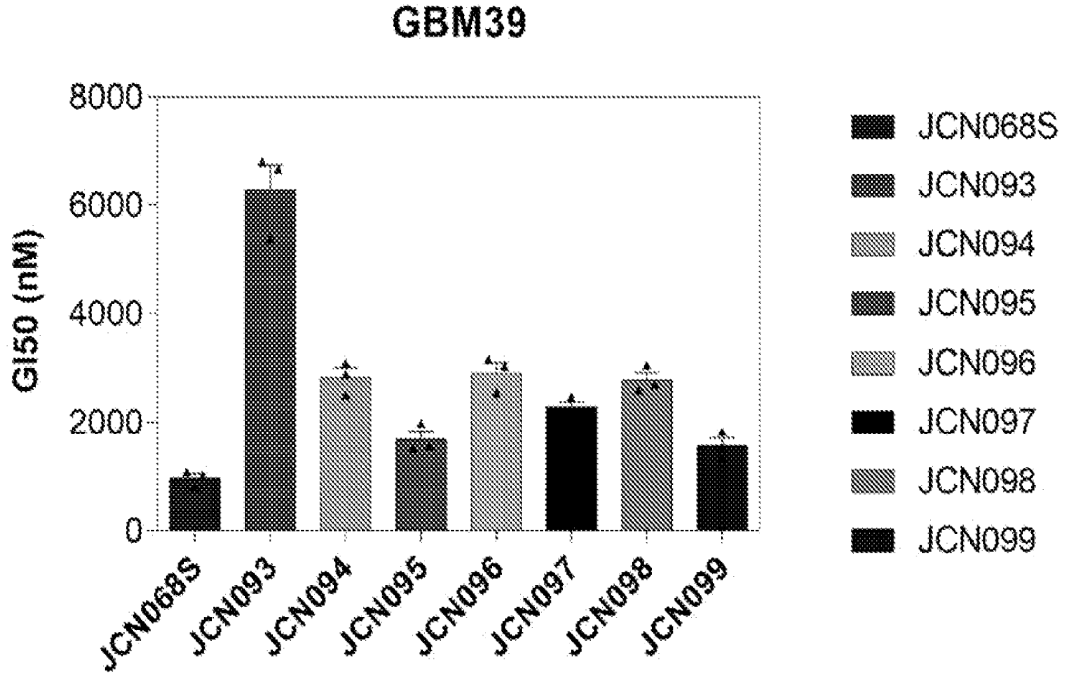


FIG. 15B



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/051023

A. CLASSIFICATION OF SUBJECT MATTER
IPC (20210101) C07D 491/056, A61K 31/519, A61P 35/00
CPC (20130101) C07D 491/056, A61K 31/519, A61P 35/00
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 (20210101) C07D 491/056, A61K 31/519, A61P 35/00
CPC (20130101) C07D 491/056, A61K 31/519, A61P 35/00

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 practicable, search terms used)
Databases consulted: CAPLUS, BIOSIS, EMBASE, MEDLINE, MARPAT, REGISTRY, PubMed, Google Scholar, DWPI
Search terms used: EGFR, epidermal growth factor, glucose metabolism, *cancer, *carcinoma, *neoplasm*, *prolifer*, glioblastoma, Erlotinib, Lapatinib, Gefitinib, Afatinib.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/0045537 A1 (Yong-Sup Lee [KR]) 06 Mar 2003 (2003/03/06) Examples 22, 23, 28, 30, 31, 36 and 37; table 3; claim 17.	1-12,18,21-24,26-40, 45,69-71
Y		1-12,18-24,26-80
X	LEE, Jae Yeol, et al. 7-Substituted-[1,4]dioxano[2,3-g]quinazolines as Inhibitors of Epidermal Growth Factor Receptor Kinase. Archiv der Pharmazie: An International Journal Pharmaceutical and Medicinal Chemistry, 2002, 335.10: 487-494. First published: 23 December 2002. DOI: <10.1002/ardp.200290003>. Retrieved from Google Scholar. 23 Dec 2002 (2002/12/23) Table 1, compounds 4a, 4d and 4g; table 2.	1-12,18,21-24,26-40, 45,69-71
Y		1-12,18-24,26-80

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
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"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	Date of mailing of the international search report
20 Dec 2021	21 Dec 2021
Name and mailing address of the ISA: Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel Email address: pctoffice@justice.gov.il	Authorized officer SOMECH Erez Telephone No. 972-73-3927252

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/051023

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Sakka, Ola K. et al. Discovery of novel EGFR inhibitors: in silico study and 3D-pharmacophore model generation. Journal of Computational Methods in Molecular Design, 2013, 3.2: 10-25. Retrieved from URL: <https://www.scholarsresearchlibrary.com/articles/discovery-of-novel-egfr-inhibitors-in-silico-study-and-3dpharmacophore-model-generation.pdf>. 31 Dec 2013 (2013/12/31) Page 10; compounds 9-12 (page 12, table 1 in page 13); figure 4.	1-9,12,18,21-24, 28-34,36-40,45,69-71
Y		1-12,18-24,26-80
X	HA, Jae-Du, et al. Design and synthesis of novel epidermal growth factor receptor kinase inhibitors. Bulletin of the Korean Chemical Society, 2005, 26.6: 959-965. Published: 20 June 2005. DOI: <10.5012/bkcs.2005.26.6.959>. Retrieved from URL: <https://www.koreascience.or.kr/article/JAKO200502727174326.pdf>. 20 Jun 2005 (2005/06/20) Page 595; compounds 3a-3c, 3e-3g, 3i-3l and 3n-3q (page 961, table 2).	1-9,12,18,21-24, 28-34,36-40,45,69-71
Y		1-12,18-24,26-80
Y	TSANG, Jonathan E., et al. Development of a potent brain-penetrant EGFR tyrosine kinase inhibitor against malignant brain tumors. ACS Medicinal Chemistry Letters, 2020, 11.10: 1799-1809. Published online: 01 May 2020. DOI: <10.1021/acsmedchemlett.9b00599>. 01 May 2020 (2020/05/01) Abstract; tables 2-5.	18-24,26,27,35,39, 40,45
Y	MAI, Wilson X., et al. Cytoplasmic p53 couples oncogene-driven glucose metabolism to apoptosis and is a therapeutic target in glioblastoma. Nature medicine, 2017, 23.11: 1342-1351. Published: 09 October 2017. DOI: <10.1038/nm.4418>. Retrieved from URL: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5683421/>. 09 Oct 2017 (2017/10/09) Abstract.	39-80
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2021/051023

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
US 2003/0045537 A1	06 Mar 2003	US 2003045537 A1	06 Mar 2003
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		JP 2003026682 A	29 Jan 2003
		JP 4000268 B2	31 Oct 2007
		KR 20030001992 A	08 Jan 2003
		KR 100397792 B1	13 Sep 2003
WO 2020/190765 A2	24 Sep 2020	WO 2020190765 A2	24 Sep 2020
		WO 2020190765 A3	26 Nov 2020
		AU 2020241703 A1	14 Oct 2021
		CA 3133688 A1	24 Sep 2020
		IL 286350 D0	31 Oct 2021
		SG 11202109662Y A	28 Oct 2021