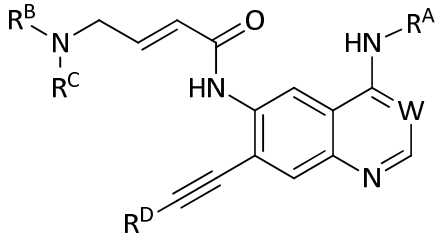
[0007] The incidence of metastasis to the brain is increasing in cancer patients, especially from the lung cancer, breast cancer and melanoma. The brain is considered a 'sanctuary site' as the blood–tumor barrier limits the ability of drugs to enter and kill tumor cells (Steeg, PS; et al., *Nat. Rev. Cancer* (2011) 11:352). Brain metastases from lung cancer account for 40-50% of all brain metastases, and close to half of these lung cancer brain metastases harbor EGFR mutations (Eichler, AF, et al., *Neuro-Oncology* (2010), 12:1193). Similarly, while use of Herceptin has significantly improved the outcome of HER2 positive breast cancer patients, many of these breast cancer patients developed brain metastases while being treated by Herceptin (http://www.cityofhope.org/eHope, 11(2) Feb. 21, 2012; Heitz, F.; et al., *Ann. Oncol.* (2011) 22:1571; Bendell, J. et al., *Cancer* (2003) 97:2972).

[0008] There is a continuing need for new cancer treatment and a significant unmet medical need for compounds capable of treating tumors in the brain.

SUMMARY

[0009] This disclosure provides for alkynyl substituted 4-anilino quinazolines of the formula (I) or any variations detailed herein, and pharmaceutically acceptable salts and prodrugs thereof, that are useful in the treatment of hyperproliferative diseases, such as cancer. Specifically, the present disclosure relates to compounds of the formula (I), or any variations detailed herein, that act as EGFR and ErbB2 inhibitors. Also provided are formulations containing compounds of the formula (I) and methods of using the compounds in treating an individual in need thereof. In addition, described are processes for preparing the inhibitory compounds of the formula (I).

[0010] In one example, provided is a compound of the formula (I):



(I)

,

or a salt, solvate, or physiologically functional derivative thereof, wherein:

W is N or C-CN;

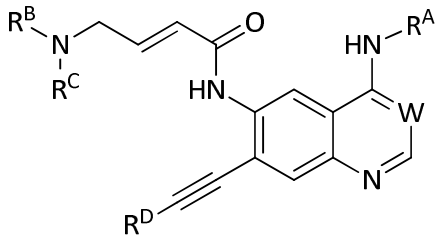
R^A is a substituted aryl or substituted heteroaryl;

each R^B and R^C is independently H, C_1-C_3 alkyl or C_3-C_6 cycloalkyl, where each of the C_1-C_3 alkyl and C_3-C_6 cycloalkyl is optionally substituted with 1 to 3 groups independently selected from the group consisting of oxo, halogen and -OR^1; or R^B and R^C are taken together with the nitrogen atom to which they are attached to form a 4 to 7-membered heterocyclyl, which is optionally substituted with up to 3 groups independently selected from the group consisting of halogen, oxo, -OR^1, -NR^2R^3, C_1-C_3 alkyl and C_3-C_6 cycloalkyl;

R^D is a heterocyclyl containing 1-3 hetero ring atoms selected from "O", "N", "S", S(O)", or "$S(O)_2$", where the heterocyclyl is optionally substituted with 1 to 3 groups independently selected from halogen, oxo, -OCF_3, -OR^1, -CF_3, -NR^2R^3, C_1-C_3 alkyl and C_3-C_6 cycloalkyl; and

each R^1, R^2 and R^3 is independently selected from H and C_1-C_3 alkyl.

[0010a] In one aspect, the present disclosure refers to a compound of the formula (I):



(I) ,

or a salt or solvate thereof,

wherein:

W is N or C-CN;

R^A is 3-chloro-4-fluorophenyl;

each R^B and R^C is C_1-C_3 alkyl; and

R^D is tetrahydrofuran-3-yl, 3-oxabicyclo[3.1.0]hexan-6-yl, or 3-oxabicyclo[3.1.0]hexan-1-yl.

[0011] In some examples, the compound is of the formula (I), or salt, solvate, or physiologically functional derivative thereof, wherein W is N, R^A is 3-chloro-4-fluorophenyl, each R^B and R^C is methyl, and R^D is a tetrahydrofuanyl, 3-oxabicyclo[3.1.0]hexan-6-yl or 3-oxabicyclo[3.1.0]hexan-1-yl. In a particular variation, R^D is 3-oxabicyclo[3.1.0]hexan-6-yl.

[0011a] In one aspect, the present disclosure refers to a compound detailed herein, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.

[0011b] In one aspect, the present disclosure refers to use of a compound detailed herein, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a hyperproliferative disorder.

[0011c] In one aspect, the present disclosure refers to use of a compound detailed herein, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a brain tumor.

[0011d] In one aspect, the present disclosure refers to use of a compound detailed herein, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for preventing or delaying the development of brain metastasis of a cancer.

[0012] In another example, provided are methods for treating a hyperproliferative disorder in an individual in need thereof comprising administering to the individual an effective amount of a compound of the formula (I), or salt, solvate, or physiologically functional derivative thereof. In some examples, the hyperproliferative disorder is a tumor in the brain such as a primary brain tumor (*e.g.*, glioma and GBM) or a metastatic brain tumor *(e.g.*, brain metastasis of breast cancer or lung cancer).

[0013] The disclosure also provides pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs, and pharmaceutically active metabolites of the compound of the formula (I) or any variations described herein. Methods of making the compounds of the formula (I) are also described.

[0014] In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound detailed herein or a pharmaceutically acceptable salt or solvate thereof; and a pharmaceutically acceptable carrier. Also provided are pharmaceutical compositions comprising a compound detailed herein such as a compound of the formula (I), or a pharmaceutically acceptable prodrug, pharmaceutically active metabolite, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient. Compounds as detailed herein or a pharmaceutically acceptable salt thereof are also provided for the manufacture of a medicament for the treatment of cancer. Kits comprising a compound detailed herein are provided, which optionally includes instructions for use in the methods detailed herein (*e.g.*, in treating a hyperproliferative disorder including brain tumors).

[0015] It is to be understood that one, some, or all of the features of the various examples described herein may be combined to form other examples of the present disclosure. These and other examples of the disclosure will become apparent to one of skill in the art.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] Figure 1 shows the anticancer effect of Compound KU113 to the NCI-N87 xenograft in the Balb/c nude mice. The structure of Compound KU113, also referred to as "NT113", is described in Example 4.

[0017] Figure 2 shows the anticancer effect of Compound KU113 on the H1975 xenograft in the nude mice in comparison with erlotinib and afatinib.

[0018] Figure 3 shows the rat pharmacokinetics data for Compound KU113 with brain concentration.

[0019] Figure 4 shows the rat pharmacokinetics data for afatinib (KU041). The brain concentration was below detection limit.

DETAILED DESCRIPTION OF THE INVENTION

[0020] This invention provides compounds that are inhibitrors of EGFR and HER2 kinases, and are capable of crossing the blood-brain-barrier. Compounds and compositions provided herein having durable exposure in brain can help patients suffering from brain cancers, who currently have limited options of effective therapies.

Definitions

[0021] Except as expressly defined otherwise, the following definition of terms is employed throughout this specification.

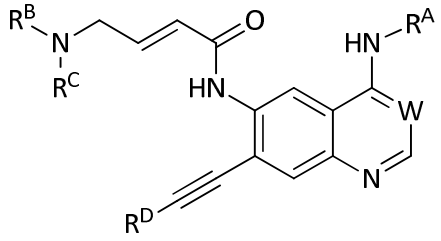
[0022] The term “alkyl” as used herein refers to a saturated linear or branched-chain hydrocarbon of one to twelve carbon atoms, wherein the alkyl radical may be independently substituted with one or more substituents described below. Examples of alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, tert-pentyl, hexyl, isohexyl, and the like. More preferred alkyl radicals have 1 to 8 carbon atoms ("C_1-C_8 alkyl"). More preferred alkyl radicals have 1 to 4 carbon atomes ("C_1-C_4 alkyl").

[0023] The term “alkenyl” refers to linear or branched-chain hydrocarbon radical of two to twelve carbon atoms, containing at least one double bond, such as ethenyl, propenyl,

CLAIMS

What is claimed is:

1. A compound of the formula (I):



(I)

,

or a salt or solvate thereof,

wherein:

W is N or C-CN;

R^A is 3-chloro-4-fluorophenyl;

each R^B and R^C is C_1-C_3 alkyl; and

R^D is tetrahydrofuran-3-yl, 3-oxabicyclo[3.1.0]hexan-6-yl, or 3-oxabicyclo[3.1.0]hexan-1-yl.

2. A compound according to claim 1, or a salt or solvate thereof, wherein W is N.

3. A compound according to claim 1 or 2, or a salt or solvate thereof, wherein each R^B and R^C is methyl.

4. A compound according to any one of claims 1 to 3, or a salt or solvate thereof, wherein R^D is 3-oxabicyclo[3.1.0]hexan-6-yl.

5. A compound according to claim 1, or a salt or solvate thereof, wherein the compound is selected from:

(*E*)-N-(4-(3-chloro-4-fluorophenylamino)-7-(2-(tetrahydrofuran-3-yl)ethynyl)quinazolin-6-yl)-4-(dimethylamino)but-2-enamide,

(*E*)-N-(4-(3-chloro-4-fluorophenylamino)-7-(2-((S)-tetrahydrofuran-2-yl)ethynyl)quinazolin-6-yl)-4-(dimethylamino)but-2-enamide,

(*E*)-N-(4-(3-chloro-4-fluorophenylamino)-7-(2-((*R*)-tetrahydrofuran-2-yl)ethynyl)quinazolin-6-yl)-4-(dimethylamino)but-2-enamide,

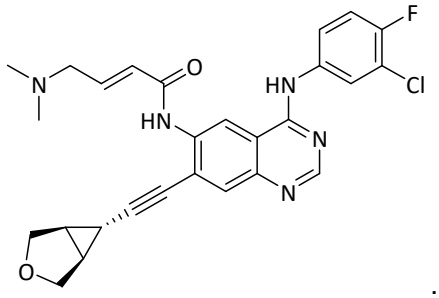
(*E*)-N-(4-(3-chloro-4-fluorophenylamino)-7-(2-((*1R,5S,6s*)-3-oxa-bicyclo[3.1.0]hexan-6-yl)ethynyl)quinazolin-6-yl)-4-(dimethylamino)but-2-enamide,

(*E*)-N-(4-(3-chloro-4-fluorophenylamino)-7-(2-(3-oxa-bicyclo[3.1.0]hexan-1-yl)ethynyl)quinazolin-6-yl)-4-(dimethylamino)but-2-enamide,

(*E*)-N-(4-(3-chloro-4-fluorophenylamino)-7-(2-((*1R,5S*)-3-oxa-bicyclo[3.1.0]hexan-1-yl)ethynyl)quinazolin-6-yl)-4-(dimethylamino)but-2-enamide, and

(*E*)-N-(4-(3-chloro-4-fluorophenylamino)-7-(2-((*1S,5R*)-3-oxa-bicyclo[3.1.0]hexan-1-yl)ethynyl)quinazolin-6-yl)-4-(dimethylamino)but-2-enamide.

6. A compound according to claim 1, or a salt or solvate thereof, wherein the compound is of the formula:



.

7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt or solvate thereof; and a pharmaceutically acceptable carrier.

8. A compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.

9. Use of a compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a hyperproliferative disorder.

10. The use according to claim 9, wherein the hyperproliferative disorder is head and neck cancer, lung cancer, breast cancer, colon cancer, ovarian cancer, bladder cancer, gastric cancer, kidney cancer, skin cancer, pancreatic cancer, a leukemia, a lymphoma, esophageal cancer, uterine cancer or prostate cancer.

11. Use of a compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a brain tumor.

12. The use according to claim 11, wherein the brain tumour is a primary brain tumour, and is glioma.

13. The use according to claim 11, wherein the brain tumour is a primary brain tumour, and is glioblastoma multiforme.

14. Use of a compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for preventing or delaying the development of brain metastasis of a cancer.