inhibitors. (Blakely, 2012; Kobayashi, 2005). This secondary mutation reduces the affinity of the drug with the target, thereby producing drug resistance, and resulting in tumor recurrence or disease progression.

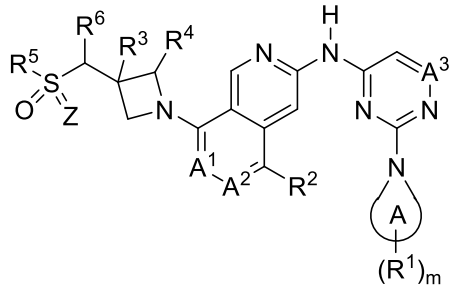
In view of the prevelance of this mutation in drug resistance produced in therapy targeting EGFR of lung cancer, a number of companies have attempted to develop new small molecule EGFR inhibitors for treating these patients with drug-resistant lung cancer by inhibiting the resistant mutant EGFR-T790M. For example, osimertinib (Tagrisso®), a third generation EGFR TKI, has been developed to treat NSCLC patients if the cancer cells are positive for the primary EGFR mutations del19 or L858R with or without the T790M mutation in the gene coding for EGFR.

Although the third generation EGFR TKI, osimertinib, has shown efficacy on NSCLC patients, unfortunately, resistance mediated by an exon 20 C797 mutation in EGFR usually develops within approximately 10 months (*European Journal of Medicinal Chemistry* 2017 Vol. 142: 32–47) and accounts for the majority of osimertinib resistance cases (*Cancer Letters* 2016 Vol. 385: 51–54). The EGFR del19/L858R T790M C797S cis mutant kinase variant typically emerges in second line (2L) patients following treatment with osimertinib and is often referred to as "triple mutant" EGFR and it can no longer be inhibited by first, second, or third generation EGFR inhibitors.

No approved EGFR TKI can inhibit the triple mutant variant. Therefore, there is a need to develop new EGFR inhibitors, which can inhibit with high selectivity EGFR mutants with the triple mutant, del19/L858R T790M C797S, while at the same time have no or low activity to wild-type EGFR. In addition to treating a mutant form of EGFR for which there is no current therapy, such selective EGFR inhibitors are likely to be more suitable as therapeutic agents, particularly for the treatment of cancer, due to reduction of toxicologies (diarrhea, skin rash) associated with wild-type EGFR inhibition.

SUMMARY

In one aspect of the present disclosure, there is provided a compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

Z is O or NH;

each A^1, A^2, and A^3 is independently N or CR; wherein each R is independently H, halogen, or CH_3;

Ring A is 4-12 membered heterocyclyl;

each R^1 is independently halogen, CN, OH, NR_aR_b, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl or -O-C_3-C_6 cycloalkyl, wherein the alkyl, alkoxy or cycloalkyl represented by R^1 or in the group represented by R^1 is optionally substituted with 1 to 3 groups selected from deuterium, halogen, OH, NR_aR_b, C_1-C_2 alkyl, and C_1-C_2 alkoxy; and/or

m is 0, 1, 2, 3, 4, 5, or 6;

R^2 is H, halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, or C_3-C_6 cycloalkyl, wherein the alkyl, alkoxy or cycloalkyl represented by R^2 is optionally substituted with 1 to 3 groups selected from halogen and OH;

R^3 is H or methyl;

R^4 is H or methyl;

R^5 is H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl or 4-6 membered monocyclic heterocyclyl, wherein the alkyl, cycloalkyl or heterocyclyl represented by R^5 is optionally substituted with 1 to 3 three groups selected from halogen, CN, OH, NR_aR_b, C_1-C_2 alkyl, and C_1-C_2 alkoxy;

R^6 is H or C_1-C_4 alkyl optionally substituted with 1 to 3 three groups selected from halogen, CN, OH, NR_aR_b, and C_1-C_2 alkoxy; and

each R_a and R_b is independently H or C_1-C_4 alkyl.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound disclosed herein, or a pharmaceutically acceptable salt thereof.

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a cancer in a subject.

In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for inhibiting epidermal growth factor receptor (EGFR).

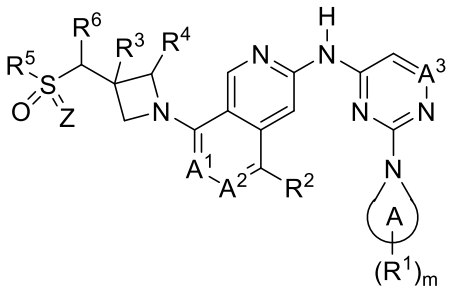
In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, for use in therapy.

The applicant has discovered novel compounds which are effective inhibitors of certain mutant forms of EGFR (*see* Synthetic Examples 1-43). In particular, it has been demonstrated that the compounds of the present disclosure effectively inhibit certain mutant forms of EGFR. Compounds of the present disclosure (also referred to herein as the "disclosed compounds") or pharmaceutically acceptable salts thereof effectively inhibit EGFR with one or more alterations, including L858R

and/or exon 19 deletion mutation, T790M mutation, and/or C797S mutation. Compounds of the present disclosure or pharmaceutically acceptable salts thereof effectively inhibit EGFR with L858R and/or exon 19 deletion mutation, T790M mutation, and C797S mutation (hereinafter "EGFR with LRTMCS mutations" or "triple mutant EGFR") (*see* Biological Example 1) and can be used treat various cancers, for example, lung cancer (*see* Biological Example 2). Importantly, the disclosed compounds are selective EGFR inhibitors, *i.e.*, the disclosed compounds have no or low activity against wild-type EGFR and the kinome. Advantages associated with such selectivity may include facilitating

efficacious dosing and reducing EGFR-mediated on-target toxicities. Some of the disclosed compounds exhibit good penetration of the brain and blood brain barrier (*e.g.*, a PGP efflux ratio of less than 5). As such, the compounds of the present disclosure or pharmaceutically acceptable salts thereof are expected to be effective for the treatment of metastatic cancer, including brain metastesis, including leptomeningeal disease and other systemic metastesis. Some of the disclosed compounds also have the advantage of having high microsomal stability. Compounds of the present disclosure also may have favorable toxicity profiles related to other non-kinase targets.

In one ~~aspect~~example, the present disclosure provides a compound represented by the following structural Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, the definition of each variable is provided below.

In another ~~aspect~~example, the present disclosure provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and one or more of the compounds disclosed herein, or a pharmaceutically acceptable salt thereof (a "pharmaceutical composition of the present disclosure").

The present disclosure provides a method of treating a subject with cancer, comprising administering to the subject an effective amount of a compound of the present disclosure (*e.g.*, a compound of Formula (I)) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the present disclosure. In one ~~embodiment~~example, the cancer is non-small cell lung cancer. In another ~~embodiment~~example, the subject cancer has metastasized to the brain. In another ~~embodiment~~example, the subject has brain metastasis from non-small cell lung cancer.

In one ~~embodiment~~example, the cancer to be treated has epidermal growth factor receptor (EGFR) L858R mutation and/or exon 19 deletion mutation and T790M mutation. In another ~~embodiment~~example, the cancer to be treated may further has epidermal growth factor receptor (EGFR) L858R mutation and/or exon 19 deletion mutation and the T790M mutation and the C797S mutation. In another ~~embodiment~~example, the cancer to be treated in either of the foregoing ~~embodiment~~examples is lung cancer, *e.g.*, non-small cell lung cancer. In a specific ~~embodiment~~example, the cancer is non-small cell lung cancer with brain metastasis.

The treatment method disclosed herein further comprises administering to the subject an effective amount of afatinib, osimertinib, erlotinib, or gefitinib.

The present disclosure also provides a method of inhibiting epidermal growth factor receptor (EGFR) in a subject in need thereof, comprising administering to the subject an effective amount of a

compound of the present disclosure (*e.g.*, a compound of Formula (I)) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the present disclosure.

The present disclosure also provides the use of an effective amount of a compound of the present disclosure (*e.g.*, a compound of Formula (I)), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure, for the preparation of a medicament for the treatment of cancers.

In another ~~aspect~~example, provided herein a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure for use in treating cancers.

DETAILED DESCRIPTION

Definitions

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

The term "alkyl" used alone or as part of a larger moiety, such as "alkoxy" or "haloalkyl" and the like, means saturated aliphatic straight-chain or branched monovalent hydrocarbon radical. Unless otherwise specified, an alkyl group typically has 1-4 carbon atoms, *i.e.* (C_1-C_4)alkyl. As used herein, a "(C_1-C_4)alkyl" group means a radical having from 1 to 4 carbon atoms in a linear or branched arrangement. Examples include methyl, ethyl, *n*-propyl, *iso*-propyl, and the like.

The term "alkenyl" means an alkyl group in which one or more carbon/carbon single bond is replaced by a double bond.

The term "alkoxy" means an alkyl radical attached through an oxygen linking atom, represented by –O-alkyl. For example, "(C_1-C_4)alkoxy" includes methoxy, ethoxy, propoxy, and butoxy.

The term "aminoalkyl" means an alkyl group substituted $–NH_2$.

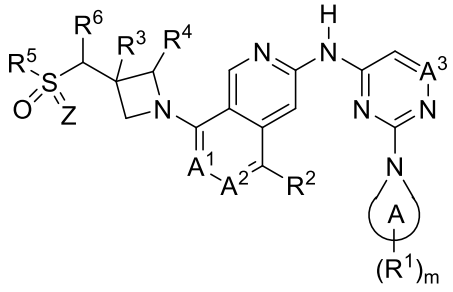
The terms "haloalkyl" and "haloalkoxy" means alkyl or alkoxy, as the case may be, substituted with one or more halogen atoms.

The term "cycloalkyl" refers to a monocyclic saturated hydrocarbon ring system. Unless otherwise specified, cycloalkyl has from 3-6 carbon atoms. For example, a C_3-C_6 cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Unless otherwise described, a "cycloalkyl" has from three to six carbon atoms.

The term "heterocyclyl" or "heterocyclic" refers to a radical of a 4- to 12-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, quaternary nitrogen, oxidized nitrogen (*e.g.*, NO), oxygen, and sulfur, including sulfoxide and sulfone ("4-12 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 4-10 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("4-10 membered heterocyclyl"). In heterocyclyl groups that contain one or more nitrogen

CLAIMS

1. A compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

Z is O or NH;

each A^1, A^2, and A^3 is independently N or CR; wherein each R is independently H, halogen, or CH_3;

Ring A is 4-12 membered heterocyclyl;

each R^1 is independently halogen, CN, OH, NR_aR_b, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl or -O-C_3-C_6 cycloalkyl, wherein the alkyl, alkoxy or cycloalkyl represented by R^1 or in the group represented by R^1 is optionally substituted with 1 to 3 groups selected from deuterium, halogen, OH, NR_aR_b, C_1-C_2 alkyl, and C_1-C_2 alkoxy; and/or

m is 0, 1, 2, 3, 4, 5, or 6;

R^2 is H, halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, or C_3-C_6 cycloalkyl, wherein the alkyl, alkoxy or cycloalkyl represented by R^2 is optionally substituted with 1 to 3 groups selected from halogen and OH;

R^3 is H or methyl;

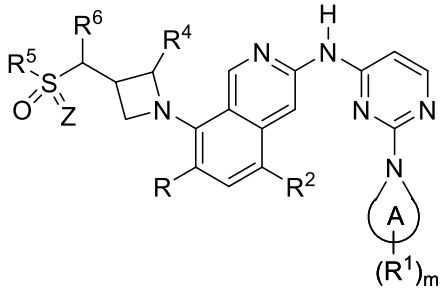
R^4 is H or methyl;

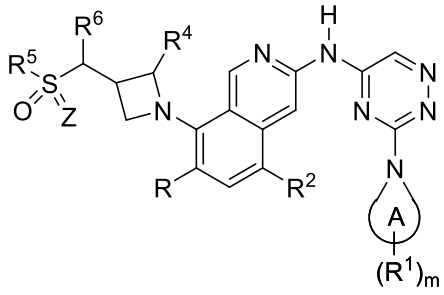
R^5 is H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl or 4-6 membered monocyclic heterocyclyl, wherein the alkyl, cycloalkyl or heterocyclyl represented by R^5 is optionally substituted with 1 to 3 three groups selected from halogen, CN, OH, NR_aR_b, C_1-C_2 alkyl, and C_1-C_2 alkoxy;

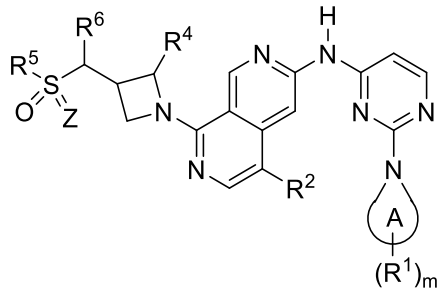
R^6 is H or C_1-C_4 alkyl optionally substituted with 1 to 3 three groups selected from halogen, CN, OH, NR_aR_b, and C_1-C_2 alkoxy; and

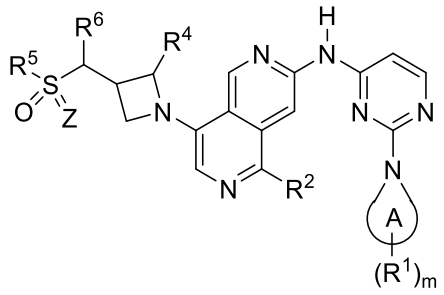
each R_a and R_b is independently H or C_1-C_4 alkyl.

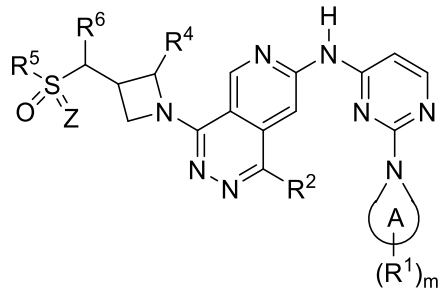
2. The compound of claim 1, wherein the compound is represented by structural formula (II-A), (II-B), (II-C), (II-D), or (II-E):


(II-A),


(II-B),

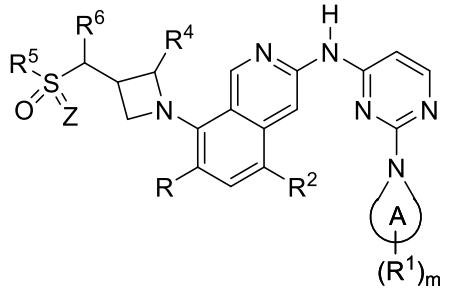

(II-C),


(II-D),


(II-E),

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein the compound is represented by structural formula (II-A):



(II-A),

or a pharmaceutically acceptable salt thereof.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein Z is O.

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R^2 is H, fluorine, C_1-C_4 alkyl, C_1-C_4 alkoxy, or C_3-C_6 cycloalkyl, wherein the alkyl, alkoxy, or cycloalkyl represented by R^2 is optionally substituted with 1 to 3 groups selected from halogen and OH.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein R^6 is H, methyl, ethyl, C_1-C_2 haloalkyl, or C_1-C_2 aminoalkyl.

7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^5 is H; C_1-C_4 alkyl optionally substituted with 1 to 3 three groups selected from halogen, CN, and NR_aR_b; C_3-C_6 cycloalkyl; or 4-6 membered monocyclic heterocyclyl optionally substituted with C_1-C_4 alkyl; and wherein R_a and R_b are each independently selected from H, methyl and ethyl.

8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein Ring A is 4-7 membered monocyclic heterocyclyl optionally substituted with 1-6 R^1.

9. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein Ring A is 7-12 membered bicyclic heterocyclyl optionally substituted with 1-6 R^1.

10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein m is 1, 2, 3, 4, or 5; and

each R^1 is independently halogen, CN, OH, NR_aR_b, C_1-C_4 alkyl, C_1-C_4 alkoxy, -O-C_3-C_6 cycloalkyl, wherein the alkyl, alkoxy, or cycloalkyl represented by R^1 or in the group

represented by R^1 is optionally substituted with 1 to 3 groups selected from deuterium, halogen, OH, NR_aR_b, C_1-C_2 alkyl, and C_1-C_2 alkoxy.

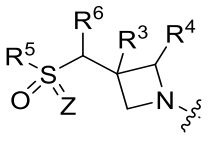
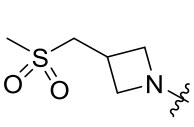
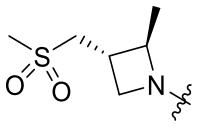
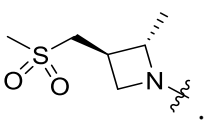
11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R^2 is H, F, methyl, ethyl, isopropyl, $CH(CH_3)CH_2F$, $CH(CH_3)CH_2OH$, CF_3, OCH_3, OCH_2CH_3, or cyclopropyl.

12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein R^6 is H, CH_3, or CH_2NH_2.

13. The compound of any one of claims 1-7 and 10-12, or a pharmaceutically acceptable salt thereof, wherein Ring A is optionally substituted with 1-6 R^1, and Ring A is pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, azepanyl, 2-azabicyclo[2.2.1]heptanyl, 3-azabicyclo[3.2.1]octanyl, 6-oxa-2-azabicyclo[3.2.1]octanyl, 6-oxa-3-azabicyclo[3.2.1]octanyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, hexahydro-1H-furo[3,4-b]pyrrolyl, hexahydro-1H-furo[3,4-c]pyrrolyl, 1-oxa-7-azaspiro[3.5]nonan-7-yl, 1,4-dioxa-8-azaspiro[4.5]decan-8-yl or 1,4-dioxa-9-azaspiro[5.5]undecan-9-yl.

14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein at least one R^1 is OH, C_1-C_4 alkoxy, or -O-C_3-C_6 cycloalkyl, wherein the alkoxy or cycloalkyl represented by R^1 or in the group represented by R^1 is optionally substituted with 1 to 3 groups selected from deuterium, halogen, OH, NR_aR_b, C_1-C_2 alkyl, and C_1-C_2 alkoxy.

15. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein each R^1 is independently F, CN, OH, NH_2, CH_3, CH_2CH_3, CHF_2, $CH(OH)CH_3$, CH_2OH, CH_2NH_2, $CH_2CH_2NH_2$, OCH_3, OCD_3, OCH_2CH_2OH, $OCH_2CH(OH)CH_3$, $OCH_2C(OH)(CH_3)_2$, $OCH_2CH_2OCH_3$, $OCH_2CH_2NH_2$, $OCH_2CH_2NHCH_3$, $OCH_2CH_2N(CH_3)_2$, -O-cyclopropyl, $NHCH_3$, $N(CH_3)_2$.

16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein  is , , or .

17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R^2 is H or isopropyl.

18. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein Ring A is piperidinyl optionally substituted with 1-6 R^1.

19. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof.

20. Use of ~~A method of treating a cancer, comprising administering a subject in need thereof an effective amount of~~ a compound of any of claims 1-18, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 19, in the manufacture of a medicament for treating a cancer in a subject.

21. The ~~method~~use of claim 20, wherein the cancer is non-small cell lung cancer.

22. The ~~method~~use of claim 20 or 21, wherein the cancer in the subject in need thereof has metastasized.

23. The ~~method~~use of any one of claims 20-22, wherein the cancer is characterized by: i) epidermal growth factor receptor EGFR L858R mutation and/or exon 19 deletion; and ii) T790M mutation.

24. The ~~method~~use of claim 23, wherein the cancer is further characterized by epidermal growth factor receptor (EGFR) C797S mutation.

25. The ~~method~~use of any one of claims 20-24, ~~further comprises administering the subject in need thereof~~wherein an effective amount of afatinib, osimertinib, erlotinib, or gefitinib is to be administered to the subject in need thereof.

26. Use of ~~A method of inhibiting epidermal growth factor receptor (EGFR), comprising administering to a subject in need thereof an effective amount of~~ a compound of any of claims 1-18, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 19, in the manufacture of a medicament for inhibiting epidermal growth factor receptor (EGFR).

27. The compound of any of claims 1-18, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 19, for use in therapy.