# OUINAZOLINE DERIVATIVES

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Application No. 12/164,610, filed June 30, 2008. The content of which is hereby incorporated by reference in its entirety.

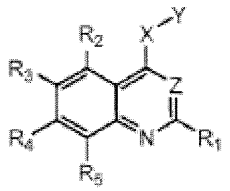
## BACKGROUND

Binding of epidermal growth factor (EGF) to epidermal growth factor receptor (EGFR) activates tyrosine kinase activity and thereby triggers reactions that lead to cellular proliferation. Overexpression and overactivity of EGFR could result in uncontrolled cell division -- a predisposition for cancer. See, e.g., Science, 2004, 304:1497-1500.

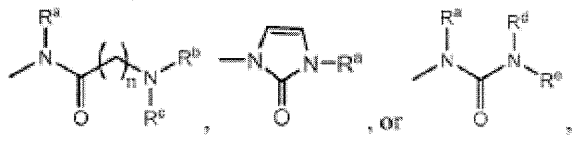
Compounds that inhibit the overexpression and overactivity of EGFR are therefore potential candidates for treating cancer.

## SUMMARY

This ~~invention~~ disclosure is based on the discovery that a number of quinazoline compounds inhibit the activity of EGFR. ~~One aspect of this invention~~The disclosure relates to compound of the following formula:



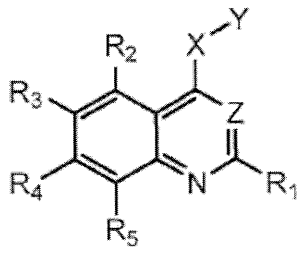
in which each of $R_1$, $R_2$, and $R_5$, independently, is H, halo, nitro, amino, cyano, hydroxy, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkoxy, alkylthio, alkylcarbonyl, carboxy, alkoxycarbonyl, carbonylamino, sulfonylamino, aminocarbonyl, or aminosulfonyl; one Of$R_3$ and $R_4$ is



in which n is 1, 2, 3, 5 or 5; each of $R^a$, $R^b$, and $R^c$, independently, is H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, or $R^b$ and $R^c$, together with the nitrogen atom to which they are attached, form a 3-12 membered saturated, unsaturated, or aromatic

ring containing 1-3 heteroatoms selected from N, O and S; and each of $R^d$ and $R^e$, independently, is H, alkyl, alkenyl, or alkynyl; or $R^d$ and $R^e$, together with the nitrogen to which they are attached, form a 3-12 membered saturated, unsaturated, or aromatic ring containing 1-3 heteroatoms selected from N, O, and S; and the other of $R_3$ and $R_4$ is H, halo, nitro, amino, cyano, hydroxy, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkoxy, alkylthio, alkylcarbonyl, carboxy, alkoxycarbonyl, carbonylamino, sulfonylamino, aminocarbonyl, or aminosulfonyl; X is O, S, or $NR^f$, wherein $R^f$ is H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, or aminosulfonyl; Y is phenyl optionally substituted with halo, nitro, cyano, alkyl, alkenyl, or akynyl, or optionally fused with another 3-8 membered ring, or Y is alkyl substituted with phenyl, which is optionally substituted with halo, nitro, cyano, alkyl, alkenyl, or akynyl, or optionally fused with another 3-8 membered ring; and Z is N or C-CN.

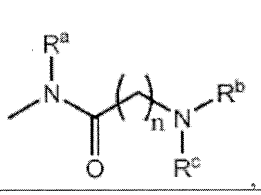
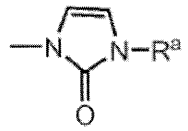
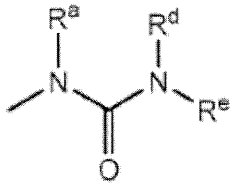
In a first aspect, there is provided a compound of the following formula:



and/or a pharmaceutically acceptable salt thereof,

in which

each of $R_1$, $R_2$, and $R_5$, independently, is H, halo, nitro, amino, cyano, hydroxy, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkoxy, alkylthio, alkylcarbonyl, carboxy, alkoxycarbonyl, carbonylamino, sulfonylamino, aminocarbonyl, or aminosulfonyl;

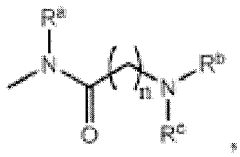
one of $R_3$ and $R_4$ is , , or  in which n is 1,2,3,4, or 5; each of $R^a$, $R^b$, and $R^c$, independently, is H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, or $R^b$ and $R^c$, together with the nitrogen atom to which they are attached, form a 3-12 membered saturated, unsaturated, or aromatic ring containing 1-3 heteroatoms selected from N, O and S; and each of $R^d$ and $R^e$, independently, is H, alkyl, alkenyl, or alkynyl; or $R^d$ and $R^e$, together with the nitrogen to which they are attached, form a 3-12 membered saturated, unsaturated, or aromatic ring containing 1-3 heteroatoms selected from N, O, and S; and the other of $R_3$ and $R_4$ is H, halo, nitro, amino, cyano, hydroxy, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkoxy, alkylthio, alkylcarbonyl, carboxy, alkoxycarbonyl, carbonylamino, sulfonylamino, aminocarbonyl, or aminosulfonyl;

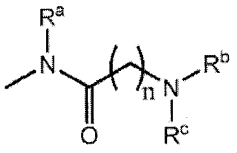
X is O, S, or $NR^f$, wherein $R^f$ is H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, or aminosulfonyl;

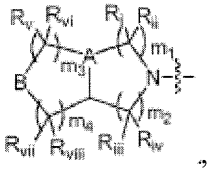
Y is phenyl substituted with alkynyl, or fused with another 3-8 membered ring; and

Z is N or C-CN.

Referring to the above formula, a subset of the compounds feature that one of

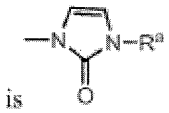
$R_3$ and $R_4$ is  in which n is 1 and each of $R^a$, $R^b$, and $R^c$, independently, is H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

Another subset of the compounds feature that one of R3 and $R_4$ , in which n is 1 or 2; $R^a$ is H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and $R^b$ and $R^c$, together with the nitrogen atom to which they are attached, form a 3-12 membered saturated, unsaturated, or aromatic ring containing 1-3 heteroatoms selected from N, O and S. In some of the compounds, $R^b$ and $R^c$, together with the nitrogen atom to which they are attached, form a bicyclic ring of the following formula:

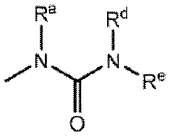


in which each of $m_1$, $m_2$, $m_3$, and $m_4$, independently, is 0, 1, 2, or 3; A is N or CR; B is NR or CRR', each R and R', independently, being H, alkyl, or halo; and each of $R_i$, $R_{ii}$, $R_{iii}$, $R_{iv}$, $R_v$, $R_{vi}$, $R_{vii}$, and $R_{viii}$, independently, is H, alkyl, or halo.

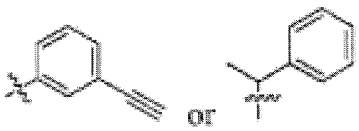
Still another subset of the compounds feature that one of $R_3$ and $R_4$

is , in which $R^a$ is H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

Still another subset of the compounds feature that one of $R_3$ and $R_4$ is

, in which $R^a$ is H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and each of $R^d$ and $R^e$, independently, is H, alkyl, alkenyl, or alkynyl; or $R^a$ is H, alkyl, alkenyl, or alkynyl; and $R^d$ and $R^e$, together with the nitrogen to which they are attached, form a 3-12 membered saturated, unsaturated, or aromatic ring containing 1-3 heteroatoms selected from N, O, and S.

Further another subset of the compounds feature that X is O, NH, or N-$CH_3$; Z is N; or Y is



In another aspect, there is provided a pharmaceutical composition, comprising a compound as defined above and/or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier thereof.

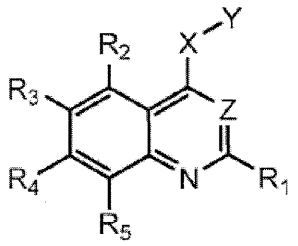
In another aspect, there is provided a compound as defined above and/or a pharmaceutically acceptable salt thereof for use in treating cancer.

The term "alkyl" herein refers to a straight or branched hydrocarbon, containing 1-10 carbon atoms. Examples of alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, *i* -propyl, n-butyl, *i* -butyl, and *t*-butyl. The term "alkoxy" refers to an -O-alkyl.

The term "alkenyl" herein refers to a $C_{2-10}$ straight or branched hydrocarbon, containing one or more C=C double bonds. Examples of alkenyl groups include, but are not limited to, vinyl, 2-propenyl, and 2-butenyl.

WHAT IS CLAIMED IS:

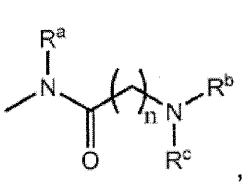
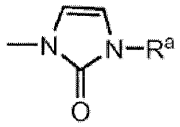
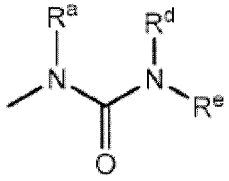
1. A compound of the following formula:



and/or a pharmaceutically acceptable salt thereof,

in which

each of $R_1$, $R_2$, and $R_5$, independently, is H, halo, nitro, amino, cyano, hydroxy, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkoxy, alkylthio, alkylcarbonyl, carboxy, alkoxycarbonyl, carbonylamino, sulfonylamino, aminocarbonyl, or aminosulfonyl;

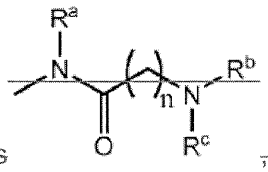
one of $R_3$ and $R_4$ is , , or  in which n is 1,2,3,4, or 5; each of $R^a$, $R^b$, and $R^c$, independently, is H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, or $R^b$ and $R^c$, together with the nitrogen atom to which they are attached, form a 3-12 membered saturated, unsaturated, or aromatic ring containing 1-3 heteroatoms selected from N, O and S; and each of $R^d$ and $R^e$, independently, is H, alkyl, alkenyl, or alkynyl; or $R^d$ and $R^e$, together with the nitrogen to which they are attached, form a 3-12 membered saturated, unsaturated, or aromatic ring containing 1-3 heteroatoms selected from N, O, and S; and the other of $R_3$ and $R_4$ is H, halo, nitro, amino, cyano, hydroxy, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkoxy, alkylthio, alkylcarbonyl, carboxy, alkoxycarbonyl, carbonylamino, sulfonylamino, aminocarbonyl, or aminosulfonyl;

X is O, S, or $NR^f$, wherein $R^f$ is H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, or aminosulfonyl;

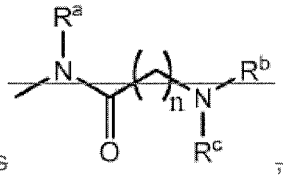
Y is phenyl ~~optionally~~ substituted with ~~halo, nitro, cyano, alkyl, alkenyl, or~~ alkynyl, or ~~optionally fused with another 3-8 membered ring, or Y is alkyl substituted~~

with phenyl which is optionally substituted with halo, nitro, cyano, alkyl, alkenyl, or akynyl, or optionally fused with another 3-8 membered ring; and

Z is N or C-CN.

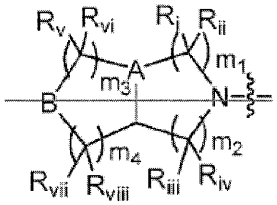


2. The compound of claim 1, wherein one of $R_3$ and $R_4$ is , in which n is 1 and each of of $R^a$, $R^b$, and $R^c$, independently, is H, alkyl, alkenyl, alkynyl,cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

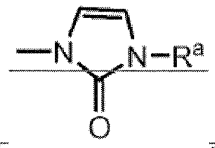


3. The compound of claim 1, wherein one of $R_3$ and $R_4$ is , in which n is 1 or 2; $R^a$ is H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and $R^b$ and $R^c$, together with the nitrogen atom to which they are attached, form a 3-12 membered saturated, unsaturated, or aromatic ring containing 1-3 heteroatoms selected from N, O and S.

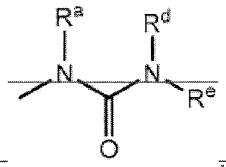
4. The compound of claim 3, wherein $R^b$ and $R^c$, together with the nitrogen atom to which they are attached, form a bicyclic ring of the following formula:

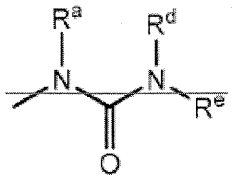


wherein each of $m_1$, $m_2$, $m_3$, and $m_4$, independently, is 0,1, 2, or 3; A is N or CR; B is NR or CRR', each R and R', independently, being H, alkyl, or halo; and each of $R_i$, $R_{ii}$, $R_{iii}$, $R_{iv}$, $R_v$, $R_{vi}$, $R_{vii}$, and $R_{viii}$, independently, is H, alkyl, or halo.

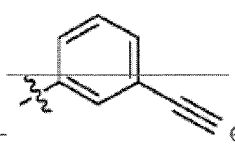
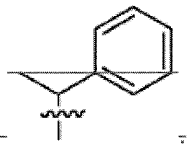


5. The compound of claim 1, wherein one of $R_3$ and $R_4$ is , in which $R^a$ is H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

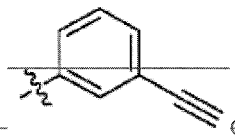
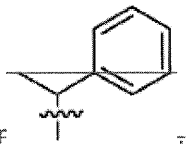
6. The compound of claim 1, wherein one of $R_3$ and $R_4$ is , in which $R^a$ is H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and each of $R^d$ and $R^e$, independently, is H, alkyl, alkenyl, or alkynyl.

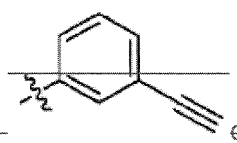
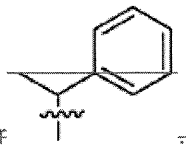
7. The compound of claim 1, wherein one of $R_3$ and $R_4$ is , in which $R^a$ is H, alkyl, alkenyl, or alkynyl; and $R^d$ and $R^e$, together with the nitrogen to which they are attached, form a 3-12 membered saturated, unsaturated, or aromatic ring containing 1-3 heteroatoms selected from N, O, and S.

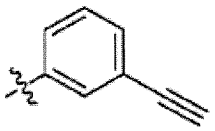
82. The compound of claim 1 and/or a pharmaceutically acceptable salt thereof, wherein Z is N.

9. The compound of claim 8, wherein Y is  or .

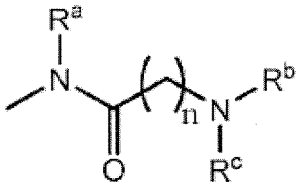
103. The compound of claim 1 and/or a pharmaceutically acceptable salt thereof, wherein X is O, NH, or N-$CH_3$.

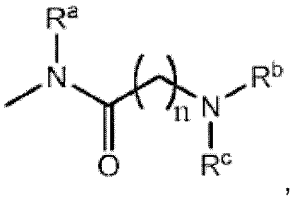
11. The compound of claim 10, wherein Y is  or .

12. The compound of claim 1, wherein Y is  or .

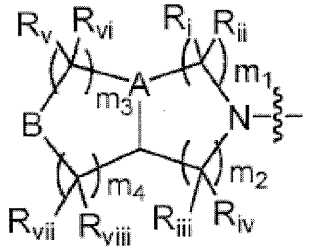
134. The compound of claim 12 and/or a pharmaceutically acceptable salt thereof, wherein Y is .

~~145~~. The compound of claim ~~124~~ and/or a pharmaceutically acceptable salt thereof, wherein X is O, NH, or N-$CH_3$ and Z is N.

~~156~~. The compound of claim 14 or 5 and/or a pharmaceutically acceptable salt thereof, wherein one of $R_3$ and $R_4$ is , in which n is 1 and each of $R^a$, $R^b$, and $R^c$, independently, is H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

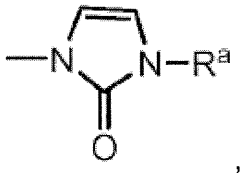
~~167~~. The compound of claim 14 or 5 and/or a pharmaceutically acceptable salt thereof, wherein one of $R_3$ and $R_4$ is ,in which n is 1 or 2; $R^a$ is H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and $R^b$ and $R^c$, together with the nitrogen atom to which they are attached, form a 3-12 membered saturated, unsaturated, or aromatic ring containing 1-3 heteroatoms selected from N, O and S.

~~178~~. The compound of claim ~~167~~ and/or a pharmaceutically acceptable salt thereof, wherein $R^b$ and $R^e$, together with the nitrogen atom to which they are attached, form a bicyclic ring of the following formula:



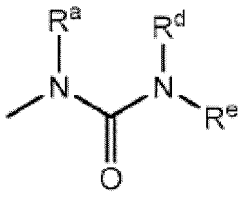
wherein each of $m_1$, $m_2$, $m_3$, and $m_4$, independently, is 0,1,2, or 3; A is N or CR; B is NR or CRR', each R and R', independently, being H, alkyl, or halo; and each of $R_i$, $R_{ii}$, $R_{iii}$, $R_{iv}$, $R_v$, $R_{vi}$, $R_{vii}$, and $R_{viii}$, independently, is H, alkyl, or halo.

9~~18~~. The compound of claim ~~1~~41 or 5 and/or a pharmaceutically acceptable salt thereof,



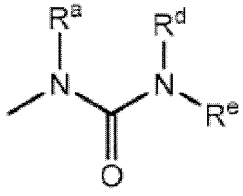
wherein one of $R_3$ and $R_4$ is , in which $R^a$ is H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

10~~19~~. The compound of claim ~~1~~41 or 5 and/or a pharmaceutically acceptable salt thereof,



wherein one of $R_3$ and $R_4$ is , in which $R^a$ is H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and each of $R^d$ and $R^e$, independently, is H, alkyl, alkenyl, or alkynyl.

11~~20~~. The compound of claim ~~1~~41 or 5 and/or a pharmaceutically acceptable salt thereof,



wherein one of $R_3$ and $R_4$ is , in which $R^a$ is H, alkyl, alkenyl, or alkynyl; and $R^d$ and $R^e$, together with the nitrogen to which they are attached, form a 3-12 membered saturated, unsaturated, or aromatic ring containing 1-3 heteroatoms selected from N, O, and S.

~~21~~12. The compound of claim 1 and/or a pharmaceutically acceptable salt thereof, wherein the compound is any of Compounds ~~1-170~~1-80, 84-91, 93-101, 103, 104 and 106-170.

~~22~~13. A pharmaceutical composition, comprising a compound of claim 1 and/or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier thereof.

~~23~~14. A compound of claim 1 and/or a pharmaceutically acceptable salt thereof for use in ~~method of~~ treating cancer~~, comprising administering to a subject in need thereof an effective amount of a compound of claim 1~~.

~~24~~15. The compound for use of~~method~~ claim ~~14~~23 and/or a pharmaceutically acceptable salt thereof, wherein the cancer is lung cancer, head and neck cancer, colorectal cancer, or pancreatic cancer.