QUINAZOLINE 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.

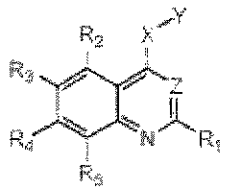
BACKGROUND

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.

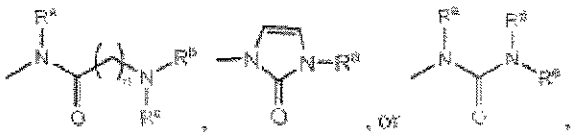
Compounds that inhibit the overexpression and overactivity of EGFR are therefore potential candidates for treating cancer.

SUMMARY

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



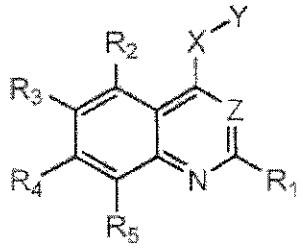
in which each of R_1, R_2, and R_5, independently, is H, halo, nitro, amino, cyano, hydroxy, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkoxy, alkylthio, alkylcarbonyl, carboxy, alkoxycarbonyl, carbonylamino, sulfonylamino, aminocarbonyl, or aminosulfonyl; one of R_3 and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

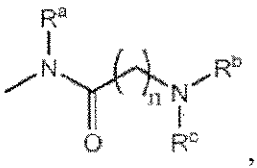
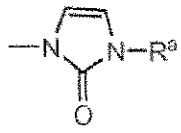
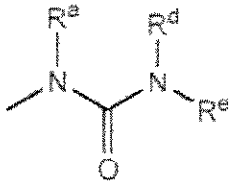
In a first aspect, there is provided a compound of the following formula:



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;

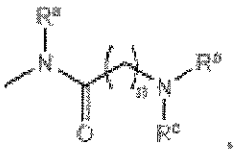
one of R_3 and R_4 is , , or  in which n is 1,2,3,4, or 5; each of R^a, R^b, and R^c, independently, is H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, or R^b and R^c, together with the nitrogen atom to which they are attached, form a 3-12 membered saturated, unsaturated, 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;

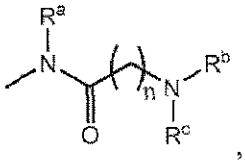
X is O, S, or NR^f, wherein R^f is H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, or aminosulfonyl;

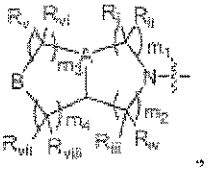
Y is phenyl substituted with alkynyl, or fused with another 3-8 membered ring; and

Z is N or C-CN.

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

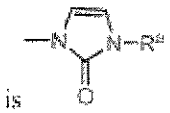
R_3 and R_4 is  , in which n is 1 and each of R^a, R^b, and R^c, independently, is H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

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:

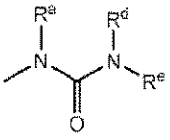


in which each of m_1, m_2, m_3, and m_4, independently, is 0, 1, 2, or 3; A is N or CR; B is NR or CRR', each R and R', independently, being H, alkyl, or halo; and each of R_i, R_{ii}, R_{iii}, R_{iv}, R_v, R_{vi}, R_{vii}, and R_{viii}, independently, is H, alkyl, or halo.

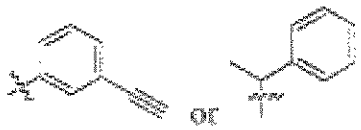
Still another subset of the compounds feature that one of R_3 and R_4

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.