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.

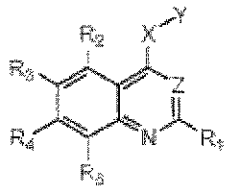
BACKGROUND

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.

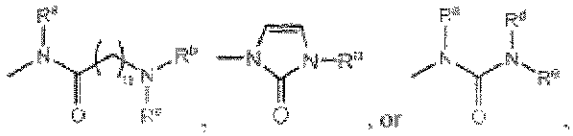
Compounds that inhibit the overexpression and overactivity of EGFR are therefore potential candidates for treating cancer.

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:



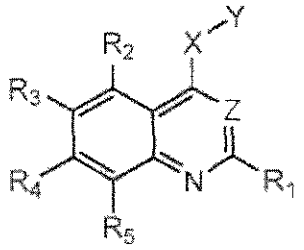
in which each of R_1, R_2, and R_5, independently, is H, halo, nitro, amino, cyano, hydroxy, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkoxy, alkylthio, alkylcarbonyl, carboxy, alkoxycarbonyl, carbonylamino, sulfonylamino, aminocarbonyl, or aminosulfonyl; one of R_3 and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

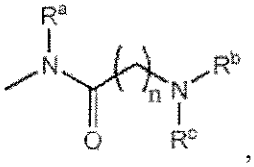
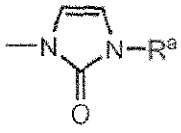
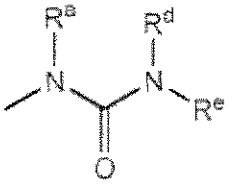
In a first aspect, there is provided a compound of the following formula:



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;

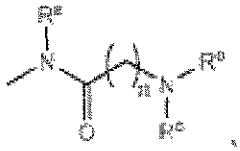
one of R_3 and R_4 is , , or  in which n is 1,2,3,4, or 5; each of R^a, R^b, and R^c, independently, is H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, or R^b and R^c, together with the nitrogen atom to which they are attached, form a 3-12 membered saturated, unsaturated,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

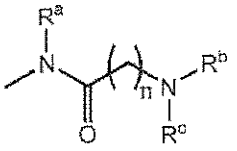
X is O, S, or NR^f, wherein R^f is H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, or aminosulfonyl;

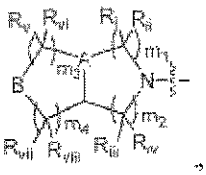
Y is phenyl substituted with alkynyl, or fused with another 3-8 membered ring; and

Z is N or C-CN.

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

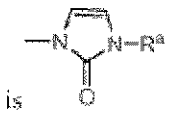
R_3 and R_4 is  in which n is 1 and each of R^a, R^b, and R^c, independently, is H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

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:

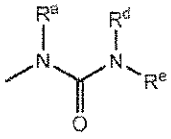


in which each of m_1, m_2, m_3, and m_4, independently, is 0, 1, 2, or 3; A is N or CR; B is NR or CRR', each R and R', independently, being H, alkyl, or halo; and each of R_i, R_{ii}, R_{iii}, R_{iv}, R_v, R_{vi}, R_{vii}, and R_{viii}, independently, is H, alkyl, or halo.

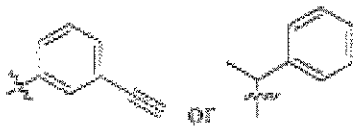
Still another subset of the compounds feature that one of R_3 and R_4

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.

The term "alkynyl" herein refers to a C_{2-10} straight or branched hydrocarbon, containing one or more C≡C triple bonds. Examples of alkynyl groups include, but are not limited to, ethynyl, 2-propynyl, and 2-butynyl.

The term "aryl" refers to a 6-carbon monocyclic, 10-carbon bicyclic, 14-carbon tricyclic aromatic ring system wherein each ring may have 1 to 4 substituents. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, and anthracenyl.

The term "cycloalkyl" refers to a saturated and partially unsaturated cyclic hydrocarbon group having 3 to 12 carbons. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

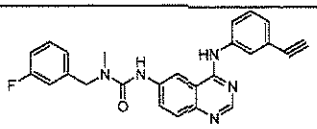
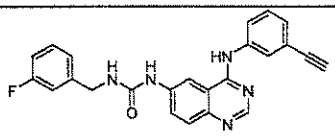
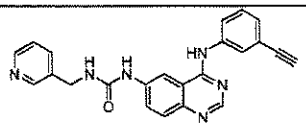
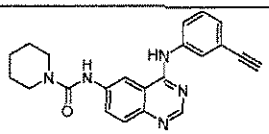
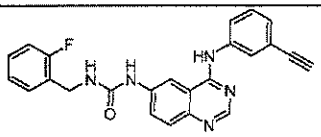
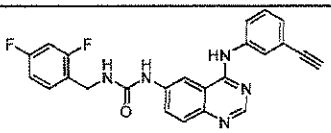
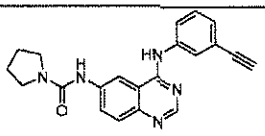
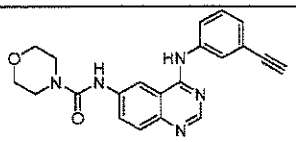
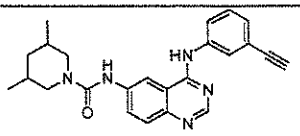
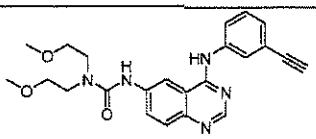
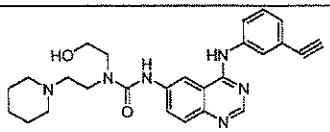
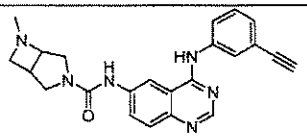
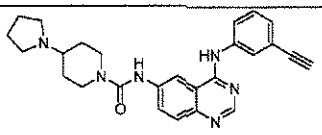
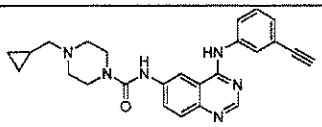
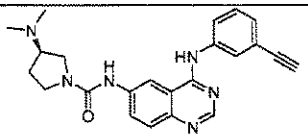
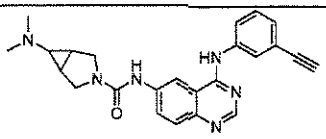
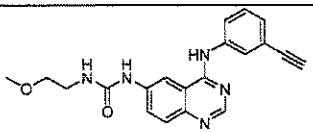
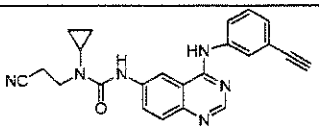
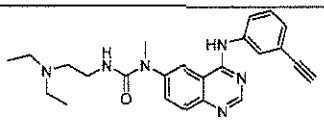
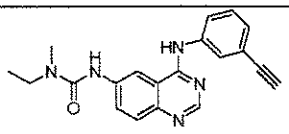
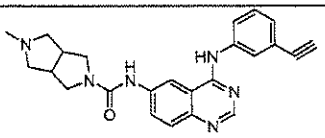
The term "heteroaryl" refers to an aromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having one or more heteroatoms (such as O, N, or S). Examples of heteroaryl groups include pyridyl, furyl, imidazolyl, benzimidazolyl, pyrimidinyl, thienyl, quinolinyl, indolyl, and thiazolyl. The term "heteroaralkyl" refers to an alkyl group substituted with a heteroaryl group.

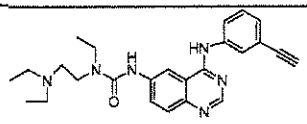
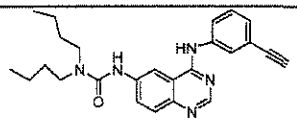
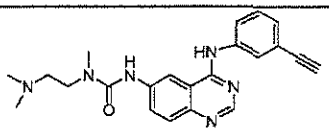
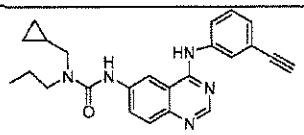
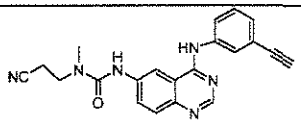
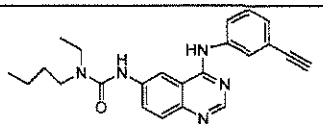
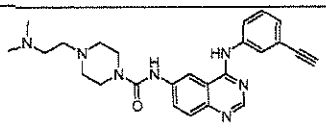
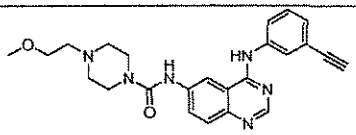
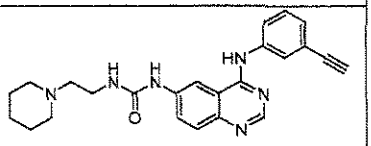
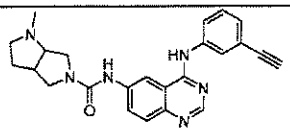
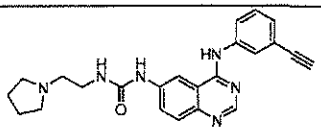
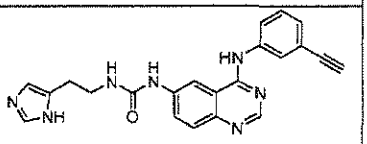
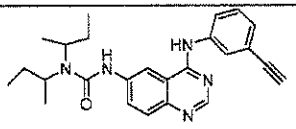
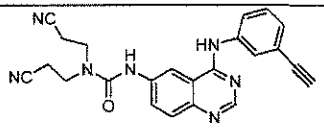
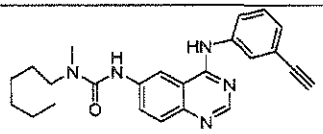
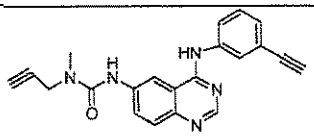
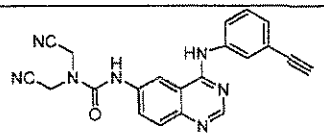
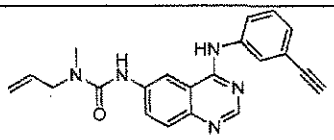
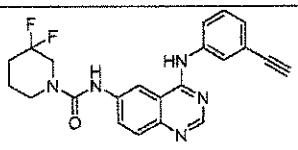
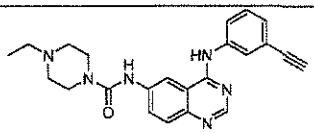
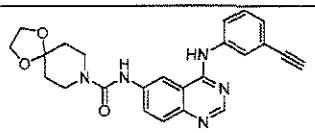
The term "heterocycloalkyl" refers to a nonaromatic 3-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having one or more heteroatoms (such as O, N, or S). Examples of heterocycloalkyl groups include, but are not limited to, piperazinyl, pyrrolidinyl, dioxanyl, morpholinyl, and tetrahydrofuranyl. Heterocycloalkyl can be a saccharide ring, e.g., glucosyl.

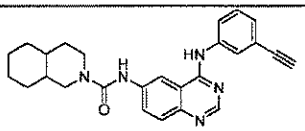
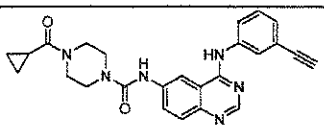
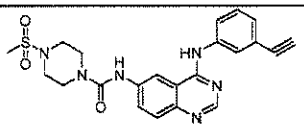
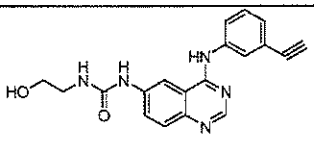
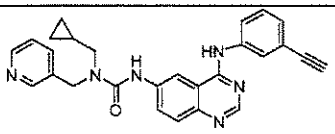
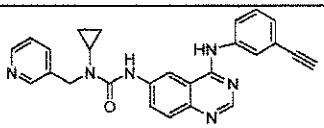
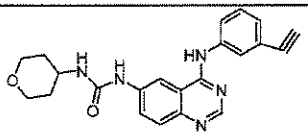
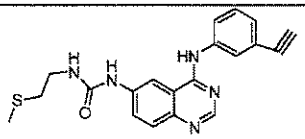
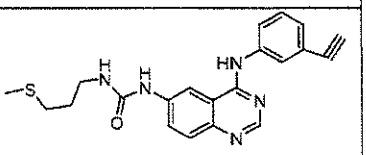
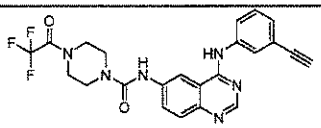
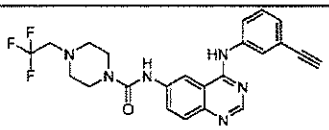
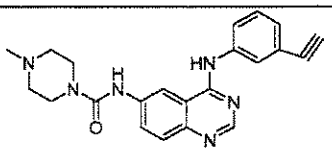
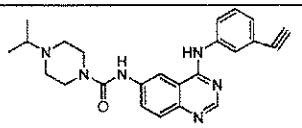
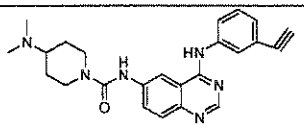
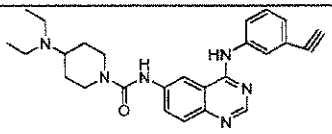
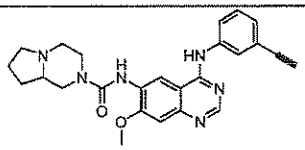
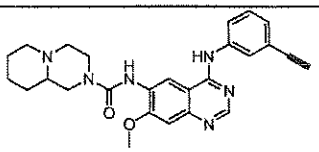
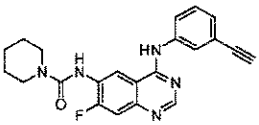
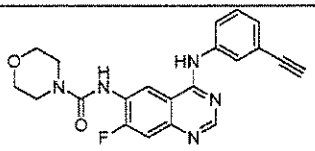
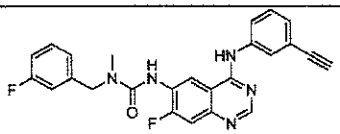
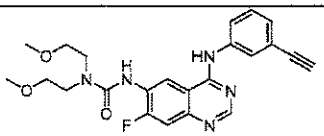
Alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and alkoxy mentioned herein include both substituted and unsubstituted moieties. Examples of substituents include, but are not limited to, halo, hydroxyl, amino, cyano, nitro, mercapto, alkoxycarbonyl, amido, carboxy, alkanesulfonyl, alkylcarbonyl, carbamido, carbamyl, carboxyl, thioureido, thiocyanato, sulfonamido, alkyl, alkenyl, alkynyl, alkyloxy, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, in which alkyl, alkenyl, alkynyl, alkyloxy, aryl, heteroaryl cycloalkyl, and heterocycloalkyl may further substituted.

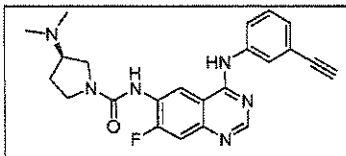
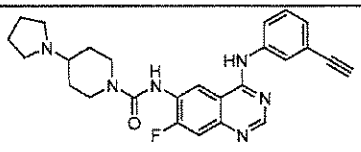
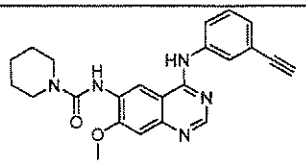
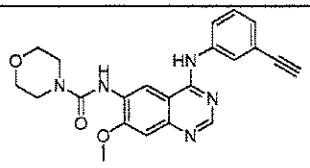
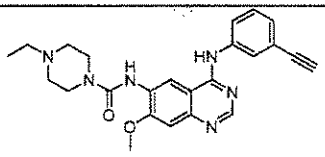
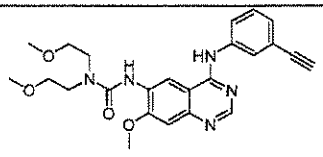
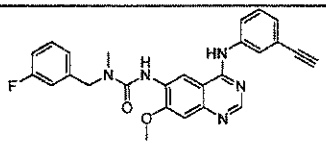
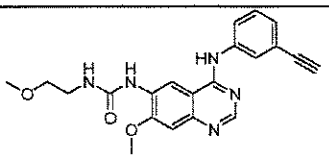
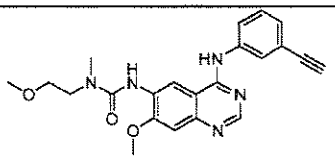
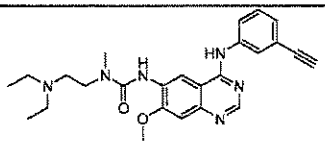
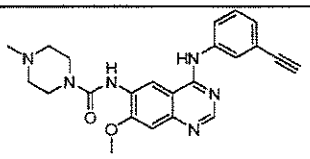
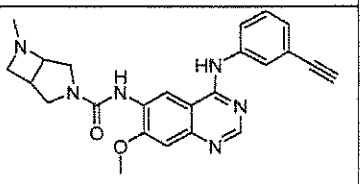
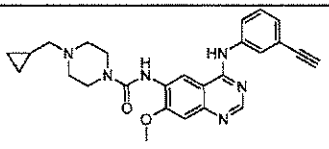
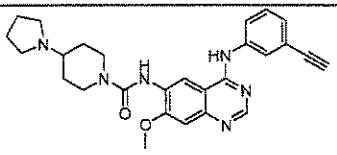
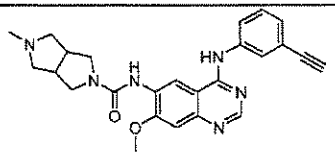
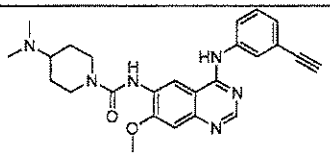
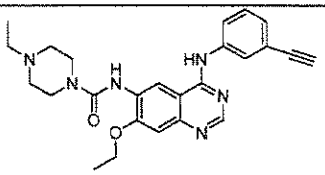
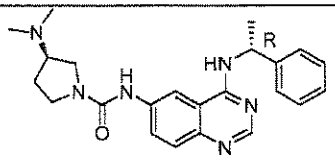
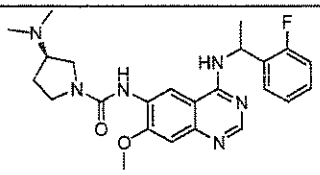
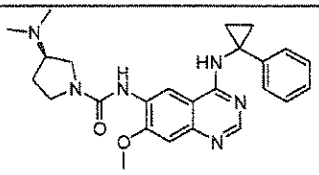
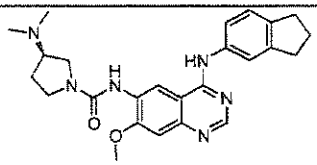
The quinazoline compounds described above include their pharmaceutically acceptable salts, solvate, and prodrug, if applicable.

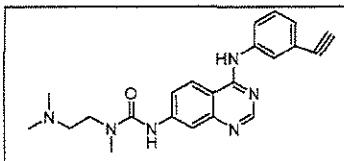
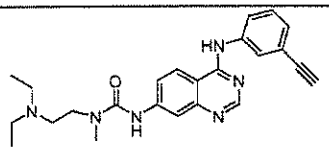
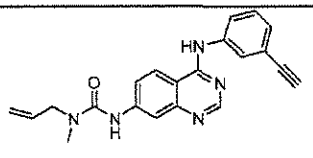
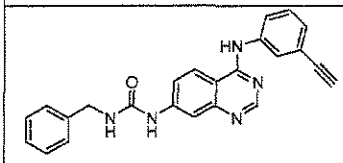
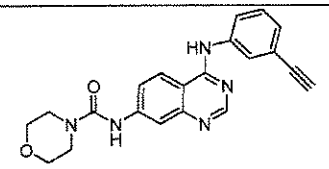
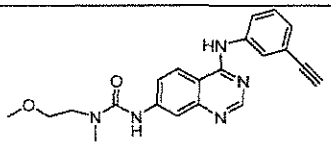
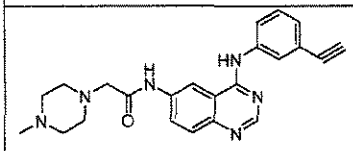
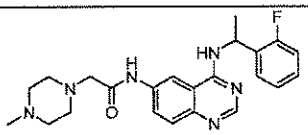
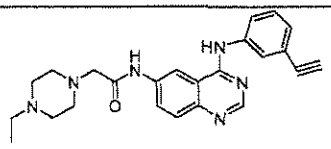
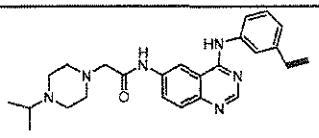
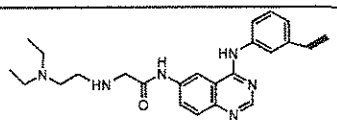
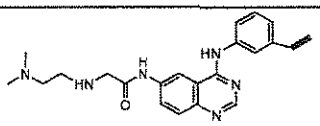
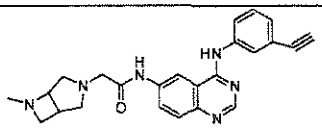
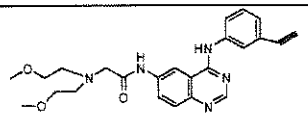
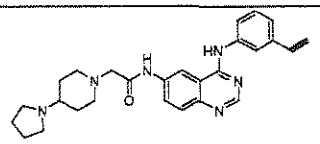
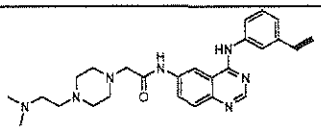
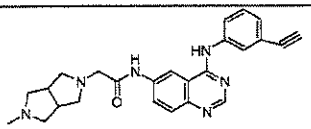
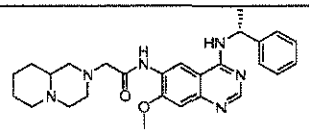
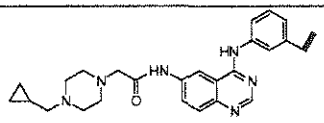
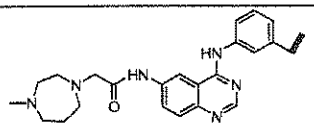
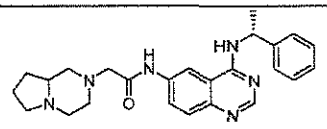
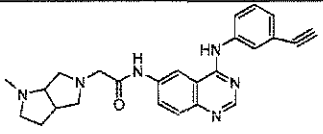
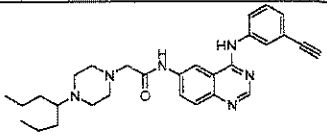
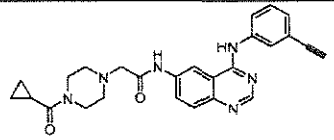
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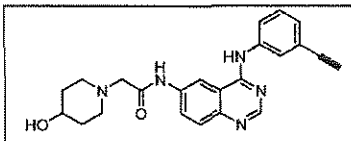
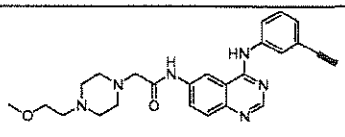
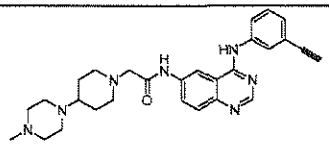
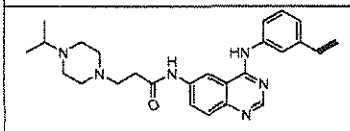
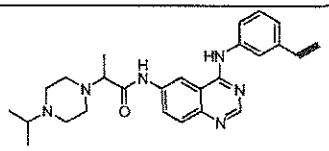
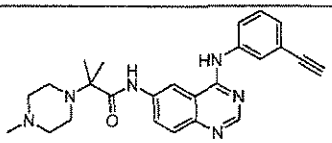
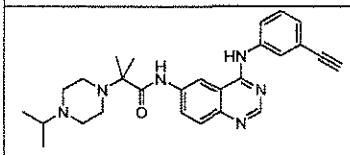
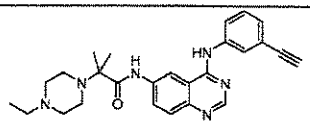
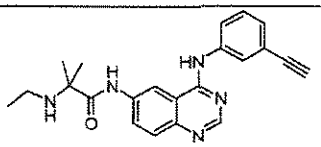
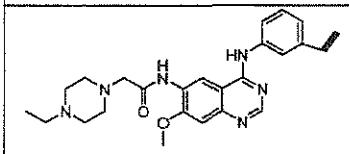
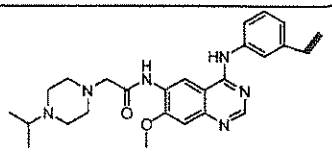
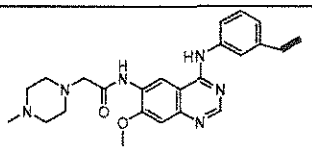
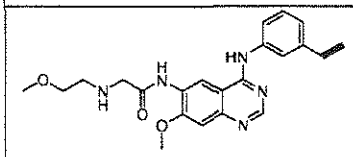
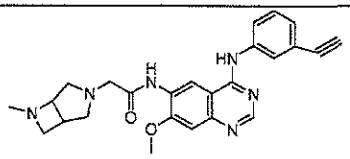
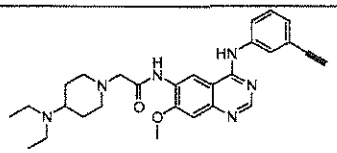
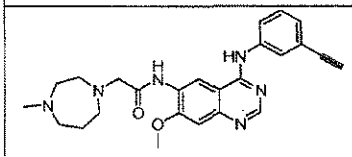
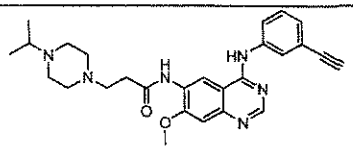
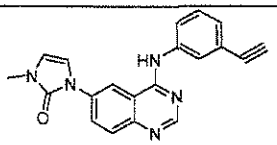
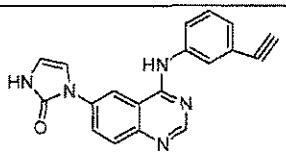
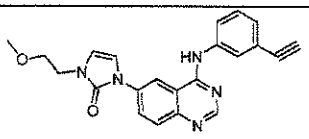
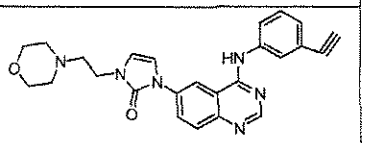
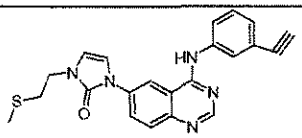
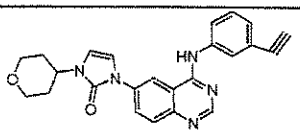
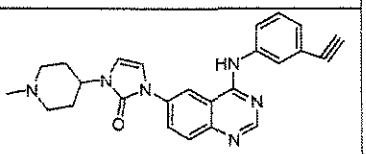
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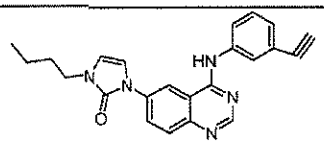
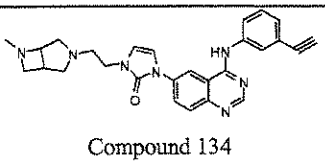
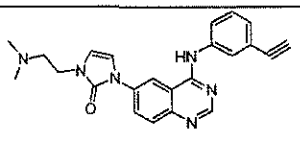
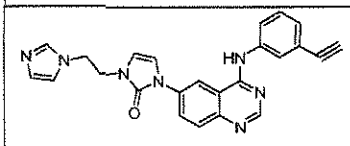
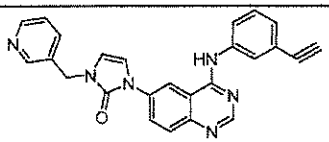
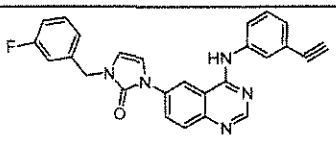
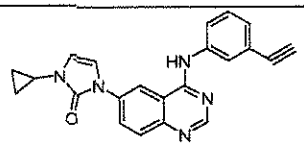
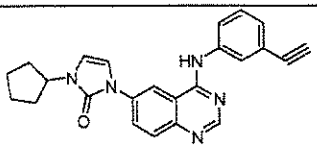
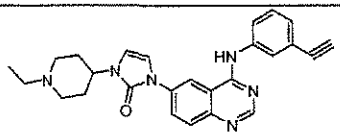
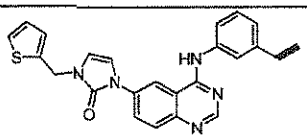
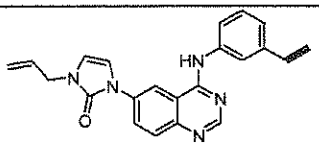
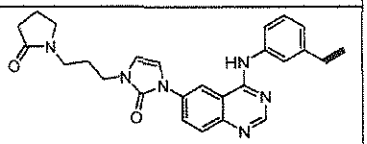
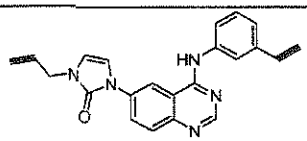
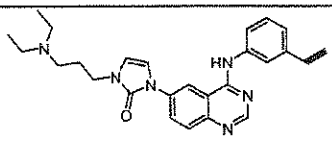
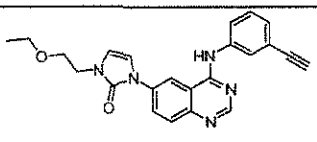
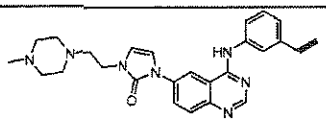
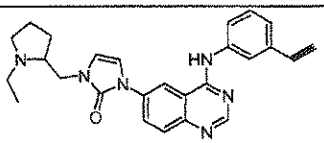
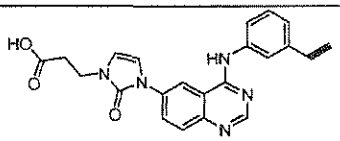
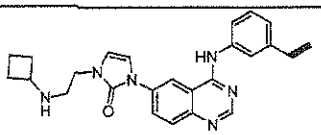
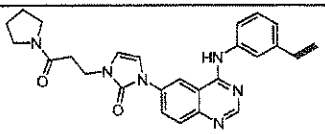
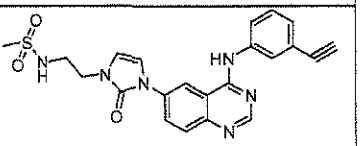
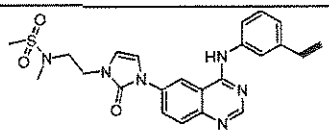
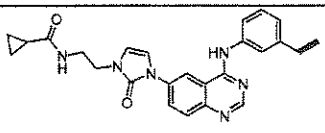
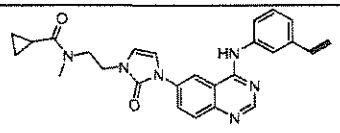
 Compound 22	 Compound 23	 Compound 24
 Compound 25	 Compound 26	 Compound 27
 Compound 28	 Compound 29	 Compound 30
 Compound 31	 Compound 32	 Compound 33
 Compound 34	 Compound 35	 Compound 36
 Compound 37	 Compound 38	 Compound 39
 Compound 40	 Compound 41	 Compound 42

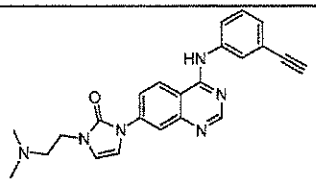
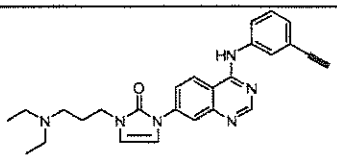
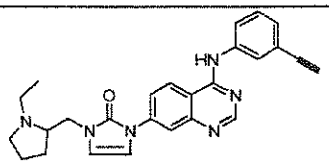
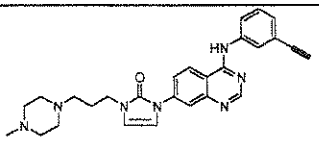
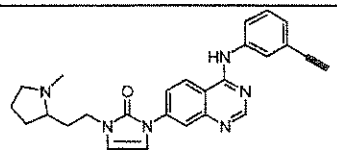
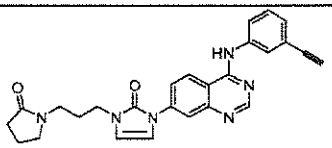
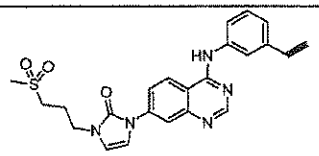
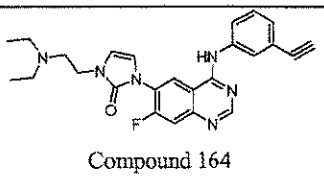
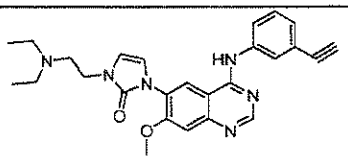
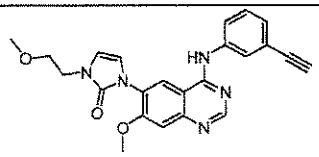
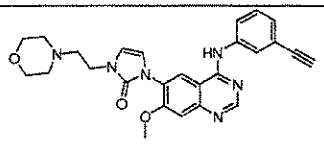
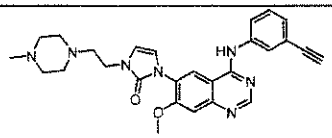
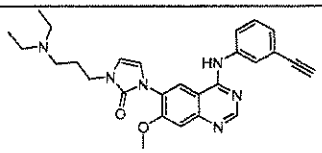
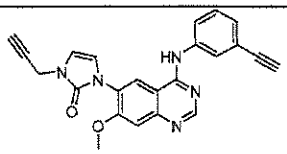
 Compound 43	 Compound 44	 Compound 45
 Compound 46	 Compound 47	 Compound 48
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 Compound 55	 Compound 56	 Compound 57
 Compound 58	 Compound 59	 Compound 60
 Compound 61	 Compound 62	 Compound 63

 Compound 64	 Compound 65	 Compound 66
 Compound 67	 Compound 68	 Compound 69
 Compound 70	 Compound 71	 Compound 72
 Compound 73	 Compound 74	 Compound 75
 Compound 76	 Compound 77	 Compound 78
 Compound 79	 Compound 80	 Compound 81
 Compound 82	 Compound 83	 Compound 84

 Compound 85	 Compound 86	 Compound 87
 Compound 88	 Compound 89	 Compound 90
 Compound 91	 Compound 92	 Compound 93
 Compound 94	 Compound 95	 Compound 96
 Compound 97	 Compound 98	 Compound 99
 Compound 100	 Compound 101	 Compound 102
 Compound 103	 Compound 104	 Compound 105
 Compound 106	 Compound 107	 Compound 108

 Compound 109	 Compound 110	 Compound 111
 Compound 112	 Compound 113	 Compound 114
 Compound 115	 Compound 116	 Compound 117
 Compound 118	 Compound 119	 Compound 120
 Compound 121	 Compound 122	 Compound 123
 Compound 124	 Compound 125	 Compound 126
 Compound 127	 Compound 128	 Compound 129
 Compound 130	 Compound 131	 Compound 132

 Compound 133	 Compound 134	 Compound 135
 Compound 136	 Compound 137	 Compound 138
 Compound 139	 Compound 140	 Compound 141
 Compound 142	 Compound 143	 Compound 144
 Compound 145	 Compound 146	 Compound 147
 Compound 148	 Compound 149	 Compound 150
 Compound 151	 Compound 152	 Compound 153
 Compound 154	 Compound 155	 Compound 156

 Compound 157	 Compound 158	 Compound 159
 Compound 160	 Compound 161	 Compound 162
 Compound 163	 Compound 164	 Compound 165
 Compound 166	 Compound 167	 Compound 168
 Compound 169	 Compound 170	

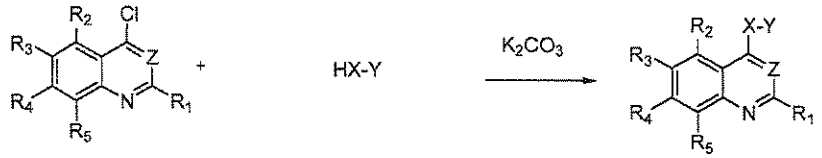
Another aspect of this invention relates to a method of treating cancer. The method includes administering to a subject having cancer an effective amount of one or more of the quinazoline compounds of this invention. Examples of the cancer to be treated include, but are not limited to, lung cancer, head and neck cancer, colorectal cancer, pancreatic cancer, colon cancer, breast cancer, ovarian cancer, prostate cancer, stomach cancer, kidney cancer, liver cancer, brain cancer, bone cancer, and leukemia.

Also within the scope of this invention are (1) a composition containing one or more of the quinazoline compounds described above and a pharmaceutically acceptable carrier for use in treating cancer, and (2) use of one or more of the quinazoline compounds for the manufacture of a medicament for treating cancer.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects and advantages of the invention will be apparent from the description and from the claims.

DETAILED DESCRIPTION

The quinazoline compounds of this invention can be synthesized from commercially available starting materials by methods well known in the art. For example, as shown in the scheme below, one can couple a suitable 4-chloro-quinazoline derivative with a benzene compound to obtain a compound of this invention.



Z is N or C-CN X is O, S, NH, or NCH_3

The compound thus obtained can be further modified at their peripheral positions to provide other compounds of this invention.

Synthetic chemistry transformations useful in synthesizing desirable quinazoline compounds are described, for example, in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

Before use, the compounds can be purified by column chromatography, high performance liquid chromatography, crystallization, or other suitable methods.

The quinazoline compounds of this invention, when contacting with EGFR, inhibit this receptor's activity. An effective amount of one or more of these compounds can be therefore used to treat cancers that are associated with over-expression and over-activity of EGFR.

The term "an effective amount" refers to the amount of a quinazoline compound that is required to confer the intended effect in the subject. Effective amounts may vary, as recognized by those skilled in the art, depending on route of

administration, excipient usage, and the possibility of co-usage with other agents. The term "treating" refers to administering one or more of the above-described quinazoline compounds to a subject that has cancer, or has a symptom of cancer, or has a predisposition toward cancer, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, or affect cancer, the symptoms of cancer, or the predisposition toward cancer.

To practice this method, a composition having one or more of the quinazoline compounds of this invention can be administered orally, parenterally, by inhalation spray, or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

An oral composition can be any orally acceptable dosage form including, but not limited to, tablets, capsules, emulsions and aqueous suspensions, dispersions and solutions. Commonly used carriers for tablets include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added to tablets. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions or emulsions are administered orally, the active ingredient can be suspended or dissolved in an oily phase combined with emulsifying or suspending agents. If desired, certain sweetening, flavoring, or coloring agents can be added.

A sterile injectable composition (e.g., aqueous or oleaginous suspension) can be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium (e.g., synthetic mono- or di-glycerides). Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions can also contain a

long-chain alcohol diluent or dispersant, or carboxymethyl cellulose or similar dispersing agents.

An inhalation composition can be prepared according to techniques well known in the art of pharmaceutical formulation and can be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

A topical composition can be formulated in form of oil, cream, lotion, ointment and the like. Suitable carriers for the composition include vegetable or mineral oils, white petrolatum (white soft paraffin), branched chain fats or oils, animal fats and high molecular weight alcohols (greater than C12). The preferred carriers are those in which the active ingredient is soluble. Emulsifiers, stabilizers, humectants and antioxidants may also be included as well as agents imparting color or fragrance, if desired. Additionally, transdermal penetration enhancers may be employed in these topical formulations. Examples of such enhancers can be found in U.S. Patents 3,989,816 and 4,444,762. Creams are preferably formulated from a mixture of mineral oil, self-emulsifying beeswax and water in which mixture the active ingredient, dissolved in a small amount of an oil, such as almond oil, is admixed. An example of such a cream is one which includes about 40 parts water, about 20 parts beeswax, about 40 parts mineral oil and about 1 part almond oil. Ointments may be formulated by mixing a solution of the active ingredient in a vegetable oil, such as almond oil, with warm soft paraffin and allowing the mixture to cool. An example of such an ointment is one which includes about 30% by weight almond and about 70% by weight white soft paraffin.

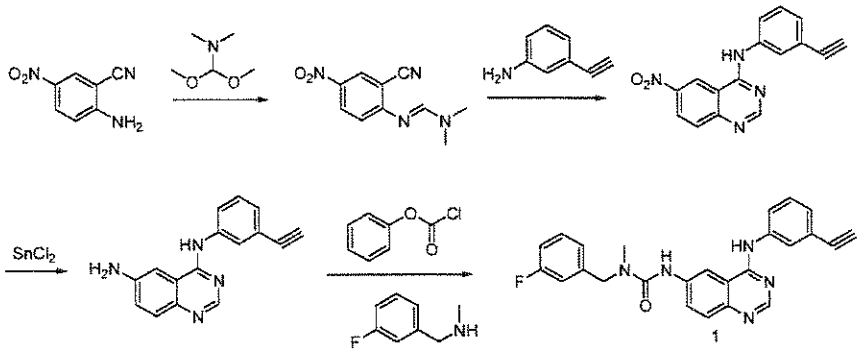
A carrier in a pharmaceutical composition must be "acceptable" in the sense that it is compatible with active ingredients of the formulation (and preferably, capable of stabilizing it) and not deleterious to the subject to be treated. For example, solubilizing agents, such as cyclodextrins (which form specific, more soluble complexes with one or more of active quinazoline compounds of the extract), can be utilized as pharmaceutical excipients for delivery of the active ingredients. Examples of other carriers include colloidal silicon dioxide, magnesium stearate, cellulose, sodium lauryl sulfate, and D&C Yellow # 10.

Suitable *in vitro* assays can be used to preliminarily evaluate the efficacy of the above-described quinazoline compounds in inhibiting the activity of EGFR. The compounds can further be examined for its efficacy in treating cancers by *in vivo* assays. For example, the compounds can be administered to an animal (e.g., a mouse model) having cancer and its therapeutic effects are then accessed. Based on the results, an appropriate dosage range and administration route can also be determined.

Without further elaboration, it is believed that the above description has adequately enabled the present invention. The following specific examples are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

Example 1: Synthesis of 1-(3-fluorobenzyl)-3- (4-(3-ethynylphenylamino) quinazolin-6-yl)-1-methylurea (Compound 1)

The synthetic route to Compound 1 is shown below:



To a solution of 5-nitroanthranilonitrile (1.00g, 6.13 mmol) in dioxane (25 mL) was added dimethylformamide dimethylacetal (0.88g, 7.36 mmol). After stirred at 100°C for 2 h, the reaction mixture was cooled to room temperature and refrigerated. The precipitate was filtered out, washed with cold ether several times, and dried in vacuo to give 1.30g (97%) of product (E)-N'-(2- cyano- 4-nitrophenyl)-N,N-dimethylformamidine as a yellow solid.

A mixture of (E)-N'-(2-cyano-4-nitrophenyl)-N,N-dimethylformamidine (1.00 g, 4.58 mmol) and 3-aminophenylacetylene (0.64 g, 5.49 mmol) in HOAc (15 mL) was stirred at 100°C for 3 h. The resulting mixture was cooled to room temperature.

The precipitate was filtered out, washed with ether, and dried in vacuo to give 1.23g (93%) of N-(3-ethynylphenyl)-6-nitroquinazolin-4-amine as a yellow solid.

A mixture of N-(3-ethynylphenyl)-6-nitroquinazolin-4-amine (1.00 g, 3.45 mmol) and $SnCl_2 \cdot 2H_2O$ (3.10 g, 13.8 mmol) in ethyl acetate (35 mL) was refluxed for 2 h and then cooled to room temperature. After its pH was adjusted to 9-10 with 5% aqueous $NaHCO_3$, the mixture was subject to extraction with EtOAc. The combined organic layers were washed with saturated brine and H_2O and dried. The solvent was removed under reduced pressure to provide 0.79 g (89%) of N4-(3-ethynylphenyl)quinazoline-4,6-diamine as a yellow solid.

To a solution of N4-(3-ethynylphenyl)quinazoline-4,6-diamine (100 mg, 0.38 mmol) in DMF (2 mL) containing pyridine (37 μL, 0.46 mmol) was added phenyl chloroformate (49 μL, 0.38 mmol) in dropwise at room temperature. After 10 min, (3-fluorobenzyl)methylamine (52.9 mg, 0.38 mmol) was added and the reaction mixture was heated to 80°C for 1 h. After cooled to r.t, the reaction mixture was diluted with ethyl acetate and washed with water. The combined organic layers were concentrated and purified with a silica column to give Compound 1 as a yellow solid in 86% yield.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.83 (s, 1H), 8.89 (s, 1H), 8.55 (d, J =8Hz, 2H), 8.04 (s, 1H), 7.79 (dd, J = 2.4Hz, 2.0Hz, 1H), 7.79 (dd, J = 2.0Hz, 2.4Hz, 1H), 7.74 (d, J = 2.0Hz 1H), 7.41~7.37 (m, 3H), 7.13~7.10 (m, 3H), 4.64 (s, 2H),4.20 (s, 1H), 3.03 (s, 3H); MS (m/e): 426 (M+1).

Examples 2- 59: Synthesis of Compounds 2-59

Compounds 2-59 were prepared in a manner similar to that described in Example 1.

Compound 2:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.83 (s, 1H), 8.88 (s, 1H), 8.79 (s, 1H) 8.43 (d, J = 8Hz, 2H), 8.10 (s, 1H), 7.94 (t, J = 2.4Hz, 1H), 7.82 (t, J = 2.0Hz, 1H), 7.80 (d, J = 2.0Hz, 1H), 7.42~7.36(m, 3H), 7.09~7.06 (m, 3H), 4.48 (s, 2H), 3.53 (s, 1H); MS (*m/e*): 412 (M+1).

Compound 3:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.42 (s, 1H), 8.93 (s, 1H), 8.63 (s, 1H), 8.53 (s, 1H), 8.44 (d, *J* = 3.2Hz, 2H), 8.21 (s, 1H), 7.35 (t, *J* = 2.4Hz,1H), 7.32~6.88(m, 5H), 6.80 (d, *J* = 2.0Hz 1H), 6.68(d, *J* = 2.4Hz, 1H), 6.65(s, 1H), 4.44 (s, 2H), 4.04 (s, 1H); MS (*m/e*): 395 (M+1).

Compound 4:

^{1}H NMR (DMSO -d_6, 400 MHz):9.68 (s, 1H), 9.14 (s, 1H), 8.51 (s, 1H), 8.51 (d, *J* = 2.0Hz, 1H), 8.11 (s, 1H), 7.89 (t, *J* = 2.0Hz,2H), 7.72 (d, *J* = 8Hz, 1H), 7.40(t, *J* = 3.6Hz, 1H), 7.21 (d, *J* = 4Hz, 1H), 4.24(s, 1H), 3.46(s, 4H), 1.53 (s, 6H): MS (*m/e*):372 (M+1).

Compound 5:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.83 (s, 1H), 8.88 (s, 1H), 8.79 (s,1H) 8.43 (d, *J* = 8Hz, 2H), 8.10 (s, 1H), 7.94 (t, *J* = 2.4Hz,1H), 7.82 (t, *J* = 2.0Hz, 1H), 7.80 (d, *J* = 2.0Hz,1H), 7.42~7.36(m, 3H), 7.09~7.06 (m, 3H), 4.48 (s, 2H), 3.53 (s, 1H); MS (*m/e*): 412 (M+1).

Compound 6:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.83 (s, 1H), 8.87 (d, 1H), 8.79 (s, 1H) 8.43 (d, J = 8Hz, 2H), 8.10 (s, 1H), 7.94 (t, J = 2.4Hz, 1H), 7.80 (d, *J* = 2.0Hz, 1H), 7.42~7.36(m, 3H), 7.09~7.06 (m, 3H), 4.48 (s, 2H), 3.53 (s, 1H); MS (*m/e*): 430 (M+1).

Compound 7:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.77 (s, 1H), 8.57 (d, *J* = 10.8Hz, 1H), 8.50 (s, 1H), 8.04 (s, 1H), 7.96 (d, *J* = 2Hz, 1H), 7.89 (d, *J* = 8Hz, 1H), 7.69 (d, *J* = 20Hz, 1H), 7.35 (t, *J* = 8.0Hz, 1H), 4.20(s, 1H), 2.49 (s, 4H), 1.86 (s, 4H); MS (*m/e*): 358 (M+1).

Compound 8:

^{1}H NMR (DMSO-d_6, 400 MHz):δ 9.77 (s, 1H), 9.02(s, 1H), 8.53 (s, 1H), 8.51(d, *J* = 2Hz, 1H), 8.05 (s, 1H), 7.88 (t, *J* = 8Hz, 2H), 7.72 (d, *J* = 8Hz, 1H), 7.38 (d, *J* = 8Hz, 1H), 7.20 (d, *J* = 7.2Hz, 1H), 4.18(s, 1H), 3.65 (t, *J* = 4.4Hz, 4H), 3.51 (t, *J* = 4.8Hz, 4H); MS (*m/e*): 374 (M+1).

Compound 9:

^{1}H NMR (DMSO-d_6, 400 MHz):δ 9.77 (s, 1H), 8.99(s, 1H), 8.52 (s, 2H), 8.05 (s, 1H), 7.93 (m, 2H), 7.69 (d, *J* = 8.8Hz,1H), 7.38 (t, *J* = 8Hz, 1H), 7.19 (d, *J* = 8Hz, 1H), 4.23(s, 1H), 2.23-0.91 (m, 8H), 0.91(m, *J* = 2.8Hz, 6H); MS (*m/e*): 400 (M+1).

Compound 10:

^{1}H NMR (DMSO-d_6, 400 MHz):δ 9.83 (s, 1H), 8.75(s, 1H), 8.52 (s, 1H), 8.44 (s, 1H), 7.90 (m, 2H), 7.71 (d, *J* = 8.4Hz, 2H), 7.39 (t, *J* = 8Hz, 1H), 7.20 (d, *J* = 8Hz, 1H), 4.20(s, 1H), 3.59 (s, 4H), 3.53 (s, 4H), 3.53 (s, 6H); MS (*m/e*): 420 (M+1).

Compound 11:

^{1}H NMR (CD_3OD, 400 MHz): δ 8.5 (s 1H), 8.06 (s 1H), 8.05 (s, 1H), 7.68-7.80 (d, *J* = 9.2 Hz, 3H), 7.39-7.42 (t, *J* = 8.0 Hz 1H), 7.29-7.31 (d, *J* = 3.2 Hz ,1H), 7.20-7.20 (d, *J* = 0.4 Hz, 1H), 4.08-4.12 (t, *J* = 8.0 Hz, 2H), 3.67-3.73 (m, 4H), 3.21-3.25 (m, 6H),1.65-1.85 (m, 6H); MS (*m/e*): 459.3 (M+1).

Compound 13:

^{1}H NMR (DMSO-d_6, 400 MHz):δ 9.81(s, 1H), 8.63 (s, 1H), 8.54 (s, 1H), 8.49 (s, 1H), 8.51(s, 1H), 8.05(s, 1H), 7.92 (m, 2H), 7.70 (d, *J* = 12Hz, 1H), 7.37 (t, *J* = 2.4Hz, 1H), 7.19 (d, *J* = 4Hz, 1H), 4.17(s, 1H), 3.71(m, 2H), 3.76(m, 2H), 3.16(m, 1H), 2.70(m, 1H), 2.18-2.07 (m, 8H), 1.73 (m, 1H), 1.31 (m, 1H); MS (*m/e*): 441 (M+1).

Compound 14:

^{1}H NMR (DMSO-d_6, 400 MHz):δ 9.76(s, 1H), 8.97 (s, 1H), 8.51 (d, *J* = 8.8, 2H), 8.05 (s, 1H), 7.89(t, *J* = 8.8Hz,2H), 7.71(d, *J* = 8.8Hz, 1H), 7.38 (t, *J* = 8.0Hz, 1H), 7.20 (d, *J* = 8Hz,1H), 4.19(s, 1H), 3.54 (s, 4H), 2.26(t, *J* = 2Hz, 2H), 0.87(d, *J* = 4Hz, 1H), 0.49(d, *J* = 8Hz, 2H), 0.11(s, 2H); MS (*m/e*): 427 (M+1).

Compound 15:

^{1}H NMR (DMSO-d_6, 400 MHz):δ 9.95(s, 1H), 8.87 (s, 1H), 8.51 (s, 1H), 8.47 (s, 1H), 8.03 (s, 1H), 7.85(m, 2H), 7.69(d, *J* = 8.8Hz, 1H), 7.37 (t, *J* = 8.0Hz, 1H), 7.19(d, *J* = 8Hz, 1H), 4.41(s, 1H), 4.08(s, 1H), 4.05(s, 1H), 2.94(t, *J* = 10.8Hz, 2H), 2.17(t, *J* = 4Hz, 1H), 1.86(t, *J* = 6Hz, 2H), 1.66(s, 4H), 1.33(m, 2H); MS (*m/e*): 401(M+1).

Compound 17:

^{1}H NMR (DMSO-d_6, 400 MHz):δ 9.96(s, 1H), 9.44 (s, 1H), 8.50 (s, 1H), 8.45 (s, 1H), 8.00 (s, 1H),7.88(t, *J* = 2.8Hz, 1H), 7.70(d, *J* = 8.8Hz, 1H), 7.36 (t, *J* = 8.0Hz, 1H), 7.19(d, *J* = 7.6Hz,1H), 6.85(d, *J* = 6Hz,1H), 4.19(s, 1H), 3.33 (m, 4H),3.22(s, 3H); MS (*m/e*):362(M+1).

Compound 18:

^{1}H NMR (CD_3OD, 400 MHz): δ 8.51 (s, 1H), 8.47~8.46 (d, *J* = 2.4Hz, 1H), 7.97 (s, 1H), 7.93~7.91 (dd, *J* = 2.4Hz, 8.8Hz, 1H), 7.83~7.81 (dd, *J* = 1.6Hz, 8.4Hz, 1H), 7.77~7.74 (d, *J* = 8.8Hz, 1H), 7.40~7.36 (t, *J* = 8.0Hz, 1H), 7.28~7.26 (dd, *J* = 1.2Hz, 8Hz, 1H), 3.78~7.74 (t, *J* = 6.4Hz, 2H), 3.52 (s, 1H), 2.93~2.90 (m, 1H), 2.86~2.82 (t, *J* = 6.0Hz, 2H), 1.13~1.10 (m, 2H), 0.97~0.95 (m, 2H); MS (*m/e*): 397.4 (M+1)

Compound 19:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.77 (s, 1H), 8.90 (s,1H), 8.55~8.55 (d, *J* = 2Hz, 1H), 8,44 (s, 1H), 8.18~8,17 (d, *J* = 1.2Hz, 1H), 8.07 (s, 1H), 7.94~7.91 (dd, *J* = 2Hz, 9.2Hz, 1H), 7.70~7.65 (m, 2H), 7.56~7.54 (d, *J* = 8.8Hz, 1H), 7.43~7.40 (m, 1H), 7.17~7.09 (m, 3H), 4.64 (s, 2H), 3.03 (s, 3H); MS (*m/e*): 417.5 (M+1)

Compound 20:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.78 (s, 1H), 8.71 (s, 1H), 8.54~8.53 (d, *J* = 1.6Hz, 1H), 8.52 (s, 1H), 8.06 (s, 1H), 7.96~7.90 (m, 2H). 7.71~7.69 (d, *J* = 9.2Hz,

1H), 7.40~7.36 (t, J = 8Hz, 1H), 7.20~7.19 (d, J = 7.2Hz, 1H), 4.20 (s, 1H), 3.43~3.41 (m, 2H), 2.99 (s, 3H), 1.13~1.09 (t, J = 7.2Hz, 3H); MS (*m/e*): 346.4 (M+1)

Compound 22:

^{1}H NMR (CD_3OD, 400 MHz): δ 8.49 (s, 1H), 8.40~8.39 (d, J = 2.4Hz, 1H), 7.99 (s, 1H), 7.94 (s, 1H), 7.80~7.77 (d, J = 8.8Hz, 1H), 7.74~7.72 (d, J = 8.8Hz, 1H), 7.62~7.57 (m, 1H), 7.39~7.35 (t, J = 7.6Hz, 1H), 7.28~7.26 (d, J = 7.6Hz, 1H), 3.55 (s, 1H), 3.56~3.49 (m, 4H), 2.85~2.78 (m, 6H), 1.28~1.25 (t, J = 6.8Hz, 3H), 1.19~1.15 (t, J = 6.8Hz, 6H); MS (*m/e*): 431.5 (M+1)

Compound 23:

^{1}H NMR (CD_3OD, 400 MHz): δ 8.51 (s, 1H), 8.39~8.39 (d, J = 2.4Hz, 1H), 7.98 (s, 1H), 7.83 (s, 1H), 7.81~7.78 (dd, J = 2Hz, 9.6Hz, 1H), 7.75~7.73 (d, J = 9.4Hz, 1H), 7.41~7.37 (t, J = 8Hz, 1H), 7.30~7.27 (m, 1H), 3.53 (s, 1H), 3.46~3.43 (t, J = 7.2Hz, 4H), 1.68~1.65 (m, 4H), 1.45~1.40 (m, 4H), 1.03~0.99 (t, J = 7.2Hz, 6H); MS (*m/e*): 416.5 (M+1)

Compound 24:

^{1}H NMR (CD_3OD, 400 MHz): δ 8.50 (s, 1H), 8.40~8.39 (d, J = 2.0Hz, 1H), 7.97 (s, 1H), 7.83~7.81 (d, J = 8.4Hz, 1H), 7.75~7.68 (m, 2H), 7.41~7.37 (t, J = 8.4Hz, 1H), 7.29~7.27 (m, 1H), 3.61~3.58 (t, J = 6.0Hz, 2H), 3.53 (s, 1H), 3.12 (s, 1H), 2.72~2.69 (t, J = 6.0Hz, 2H), 2.45 (s, 6H); MS (*m/e*): 389.5 (M+1).

Compound 25:

^{1}H NMR (CD_3OD, 400 MHz): δ 8.51 (s, 1H), 8.40~8.39 (d, J = 2Hz, 1H), 7.98 (s, 1H), 7.83~7.80 (dd, J = 2.4Hz, 9.2Hz, 1H), 7.75~7.73 (d, J = 9.2Hz, 1H), 7.41~7.27 (t, J = 8Hz, 1H), 7.29~7.27 (d, J = 7.6Hz, 1H), 3.53 (s, 1H), 3.53~3.48 (t, J = 7.6Hz, 2H), 3.39~3.36 (t, J = 6.8Hz, 2H), 1.77~1.71 (m, 2H), 1.15~1.14 (m, 1H), 1.02~0.98 (t, J = 7.2Hz, 3H), 0.62~0.58 (m, 2H), 0.37~0.34 (m, 2H); MS (*m/e*): 400.5 (M+1)

Compound 26:

^{1}H NMR (CD_3OD, 400 MHz): δ 8.75 (s, 1H), 8.73~8.72 (d, J = 2Hz, 1H), 8.08~8.05 (dd, J = 2.4Hz, 9.2Hz, 1H), 7.92~7.92 (d, J = 1.2Hz,1H), 7.83 (s, 1H), 7.81

(s, 1H), 7.78~7.75 (m, 1H), 7.50~7.47 (m, 2H), 3.80~3.77 (t, J = 6.4Hz, 2H), 3.63 (s, 1H), 3.24 (s, 3H), 2.86~2.83 (t, J = 6.4Hz, 2H); MS (*m/e*): 371.4 (M+1)

Compound 27:

^{1}H NMR (CD_3OD, 400 MHz): δ 8.50 (s, 1H), 8.40~8.39 (d, J = 2.4Hz, 1H), 7.79 (s, 1H), 7.82~7.79 (dd, J = 2.0Hz, 8.8Hz, 2H), 7.73~7.71 (d, J = 8.8Hz, 1H), 7.40~7.36 (t, J = 8.0Hz, 1H), 7.28~7.26 (d, J = 8.4Hz, 1H), 3.53 (s, 1H), 3.51~3.4 (q, J = 7.2Hz, 2H), 3.46~3.42 (t, J = 7.6Hz, 2H), 1.68~1.64 (m, 2H), 1.45~1.40 (m, 2H), 1.28~1.25 (t, J = 7.2Hz, 3H), 1.02~0.99 (t, J = 7.6Hz, 3H); MS (*m/e*): 388.5 (M+1)

Compound 28:

^{1}H NMR (DMSO-d_6, 400 MHz):δ 9.76(s, 1H), 8.91 (s, 1H), 8.53 (s, 1H), 8.49 (s, 1H), 8.04 (s, 1H), 7.90 (d, J = 8Hz,1H), 7.75 (d, J = 8.8Hz, 1H), 7.39 (t, J = 8.0Hz, 1H), 7.20 (d, J = 7.6Hz, 1H), 4.19 (s, 1H), 3.50 (s, 8H), 2.43 (s, 4H), 2.16 (s, 6H); MS (*m/e*):444(M+1).

Compound 29:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.78 (s, 1H), 9.11 (s, 1H), 8.52 (s, 2H), 8.04 (s, 1H), 7.91 (d, J = 8Hz, 2H), 7.69 (t, J = 8.0Hz, 1H), 7.37 (d, J = 7.6Hz, 1H), 7.18 (d, J = 7.6Hz, 1H), 4.19 (s, 1H), 3.65-3.23(m, 12H), 3.14(s, 3H); MS (*m/e*):431(M+1)

Compound 30:

^{1}H NMR (DMSO-d_6, 400 MHz):δ 9.78(s, 1H), 9.15 (s, 1H), 8.50 (s, 1H), 8.41 (s, 1H), 8.03 (s, 1H), 7.88 (d, J = 8Hz, 1H), 7.84 (d, J = 8.8Hz, 1H), 7.70 (d, J = 8.8Hz, 1H) ,7.38 (t, J = 8.0Hz, 1H), 7.20 (d, J = 7.6Hz, 1H), 6.45 (t, J = 2.4Hz, 1H), 4.19 (s, 1H), 2.38 (t, J = 6.4Hz, 6H), 1.52 (m, J = 5.2, 4H), 1.40(m, 2H), 1.23 (s, 2H); MS (*m/e*):415(M+1)

Compound 32:

^{1}H NMR (DMSO-d_6, 400 MHz):δ 9.77(s, 1H), 9.01 (s, 1H), 8.50 (s, 1H), 8.40(s, 1H), 8.02 (s, 1H), 7.85 (t, *J* = 8.0Hz, 2H), 7.71 (d, *J* = 8.8Hz, 1H), 7.39 (t, *J* = 8.0Hz, 1H), 7.20 (d, *J* = 6.8Hz, 1H), 6.44 (t, *J* = 2.4Hz, 1H), 4.19 (s, 1H), 3.27(m, 4H), 2.54 (m, 4H), 1.70 (s, 4H); MS (*m/e*):401(M+1)

Compound 33:

^{1}H NMR (DMSO-d_6, 400 MHz):δ 9.46 (s, 1H), 8.87 (s, 1H), 8.50 (s, 1H), 8.44 (s, 1H), 8.03 (s, 1H), 7.88 (d, *J* = 8Hz, 2H), 7.70(d, *J* = 5.2Hz, 1H), 7.38 (t, *J* = 8.0Hz, 2H), 7.20(d, *J* = 8Hz, 2H), 4.21(s, 1H), 3.20(m, 2H), 2.95 (m, 2H); MS (*m/e*):398 (M+1)

Compound 34:

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.79 (s, 1H), 8.50 (s, 1H), 8.45~8.36 (m, 2H), 8.05 (s, 1H), 7.97~7.95 (d, *J* = 8.4Hz, 1H), 7.92~7.90 (d, *J* = 8.4Hz, 1H), 7.68~7.65 (d, *J* = 8.8Hz, 1H), 7.38~7.34 (t, *J* = 7.6Hz, 1H), 7.19~7.17 (d, *J* = 7.6Hz, 1H), 4.19 (s, 1H), 3.58~3.56 (m, 2H), 1.74~1.60 (m, 4H), 1.26~1.23 (m, 6H), 0.91~0.86 (m, 6H); MS (*m/e*): 416.5 (M+1)

Compound 35:

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.86 (s,1H), 9.20 (s,1H), 8,56~8.56 (d, *J* = 2Hz, 1H), 8.53 (s, 1H), 8.06 (s,1H), 7.98~7.95 (dd, *J* = 2Hz, 8.8Hz, 1H), 7.93~7.91 (d, *J* = 8.4Hz, 1H), 7.73~7.70 (d, *J* = 8.8Hz, 1H), 7.39~7.35 (t, *J* = 7.2Hz, 1H), 7.20~7.18 (d, *J* = 7.6, 1H), 4.20(s, 1H), 3.79~3.75 (t, *J* = 6.8Hz, 4H), 2.85~2.82 (t, *J* = 6.8Hz, 4H); MS (*m/e*): 410.4 (M+1)

Compound 36:

^{1}H NMR ($CDCl_3$ MHz): δ 9.77(s, 1H), 8,69 (s, 1H), 8,53~8.51 (m, 2H), 8.05 (s, 1H), 7.95~7.89 (m, 2H), 7.69~7.67 (d, *J* = 8.8, 1H), 7.39~7.35 (t, *J* = 7.2Hz, 1H), 7.19~7.17 (d, *J* = 7.2Hz, 1H), 4.19 (s, 1H), 2.98 (s, 3H), 1.51~1.50 (m, 2H), 1.26~1.25 (m, 6H), 0.84 (s, 3H); MS (*m/e*): 402.5 (M+1)

Compound 37:

^{1}H NMR (CD3OD, 400 MHz): δ 8.50 (s, 1H), 8.40~8.40(d, *J* = 2.0Hz, 1H), 7.97 (s, 1H), 7.80~7.77 (m, 2H), 7.74~7.71 (d, *J* = 9.2Hz, 1H), 7.38~7.36 (t, *J* =

8.0Hz, 1H), 7.28~7.27 (d, J = 7.6Hz, 1H), 4.29~4.29 (d, J = 2.4Hz, 2H), 3.53 (s, 1H), 3.18 (s, 3H), 2.75~2.73 (t, J = 2.4Hz, 1H); MS (*m/e*): 356.4 (M+1)

Compound 38:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.51 (s, 1H), 8.49 (s, 1H), 7.94 (s, 1H), 7.91~7.88 (dd, J = 1.6Hz, 9.2Hz, 1H), 7.80~7.78 (d, J = 8.8Hz, 1H), 7.76~7.76 (d, J = 0.8Hz, 1H), 7.46~7.44 (t, J = 8.8Hz, 1H), 7.38~7.36 (t, J = 7.6Hz, 1H), 7.29~7.28 (m, 1H), 7.27~7.24 (t, J = 8.4Hz, 1H), 4.60 (s, 4H), 3.51 (s, 1H); MS (*m/e*): 382.4 (M+1)

Compound 39:

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.78 (s, 1H), 8.77 (s, 1H), 8.53~8.52 (d, J = 2Hz, 1H), 8.51 (s, 1H), 8.04 (s, 1H), 7.94~7.88 (m, 2H), 7.70~7.68 (d, J = 8.8Hz, 1H), 7.39~7.353 (t, J = 8Hz, 1H), 7.19~7.17 (d, J = 7.6Hz, 1H), 5.84~5.79 (m, 1H), 5.22~5.16 (m, 2H), 4,19 (s, 1H), 4.02~4.01 (d, J = 4.8Hz, 2H), 2,97 (s, 1H); MS (*m/e*): 357.4 (M+1)

Compound 40:

^{1}H NMR (DMSO-d_6, 400 MHz):δ 9.81 (s, 1H), 9.23 (s, 1H), 8.52 (s, 2H), 8.49 (s, 1H), 8.04(s, 1H), 7.90 (m, 2H), 7.70 (d, J = 8.8Hz,1H), 7.37 (t, J = 7.6Hz, 1H), 7.18 (d, J = 7.6Hz, 1H), 4.19(s, 1H), 3.87 (t, J = 8Hz, 2H), 3.59 (s, 2H), 2.06 (m, 2H)1.72 (s, 2H); MS (*m/e*): 408 (M+1).

Compound 41:

^{1}H NMR (DMSO-d_6, 400 MHz):δ 9.78(s, 1H), 9.11 (s, 1H), 8.51 (s, 2H), 8.04 (s, 1H), 7.90(d, J = 8.8Hz, 2H), 7.69 (d, J = 8.8Hz, 1H), 7.37 (t, J = 8.0Hz, 1H), 7.18 (d, J = 8.8Hz, 1H), 4.19 (s, 1H), 3.68(m, 4H),2.59 (m, 6H), 1.07 (m, 3H) ; MS (*m/e*): 401(M+1).

Compound 42:

^{1}H NMR (DMSO-d_6, 400 MHz):δ 9.77(s, 1H), 9.13 (s, 1H), 8.51 (s, 2H), 8.04 (s, 1H), 7.92(t, J = 7.6Hz, 2H), 7.69 (d, J = 8.8Hz, 1H), 7.37 (t, J = 8.0Hz, 1H), 7.18

(d, J = 6.0Hz, 1H), 4.19 (s, 1H), 3.88 (s, 4H), 3.59 (t, J = 5.2Hz, 4H), 1.64 (t, J = 5.2Hz, 4H) ; MS (*m/e*): 430(M+1).

Compound 43:

^{1}H NMR (DMSO-d_6, 400 MHz):δ 9.76(s, 1H), 9.92 (s, 1H), 8.51 (s, 2H), 8.04 (s, 1H), 7.90 (d, J = 8Hz, 2H), 7.68 (d, J = 8.8Hz, 1H), 7.37 (t, J = 8.0Hz, 1H), 7.17 (d, J = 8.8Hz, 1H), 4.19 (s, 1H), 2.76 (t, J = 12Hz, 1H), 2.41 (t, J = 10.8Hz, 6H), 1.66-1.42 (m, 6H), 1.22-1.07 (m, 8H) ; MS (*m/e*): 428(M+1).

Compound 44:

^{1}H NMR (DMSO-d_6, 400 MHz):δ 9.77(s, 1H), 8.90 (s, 1H), 8.51 (d, J = 6.8, 2H), 8.03 (s, 1H), 7.87(t, J = 8.8Hz, 2H), 7.71(d, J = 8.8Hz, 1H), 7.37 (t, J = 8.0Hz, 1H), 7.18 (d, J = 8Hz, 1H), 4.18(s, 1H), 3.67 (m, 8H), 1.15(d, J = 2.0Hz, 1H), 0.79(m, 4H); MS (*m/e*): 441(M+1).

Compound 45:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.79 (s, 1H), 9.18 (s, 1H), 8.54 (d, J = 4.4 Hz, 2H), 8.05 (s, 1H), 7.89 (m, 2H), 7.74~7.71 (d, J = 8.8 Hz, 1H), 7.41~7.37 (t, J = 8.0 Hz, 1H), 7.21~7.19 (d, J = 7.6 Hz, 1H), 4.20 (s, 1H), 3.65 (bs, 4H), 3.18 (bs, 4H), 2.94 (s, 3H); MS (*m/e*): 451.5 (M+1).

Compound 46:

^{1}H NMR (CD_3OD, 400 MHz): δ 8.51 (s 1H), 8.06 (s 1H), 8.05 (s, 1H), 7.68-7.80 (d, J = 9.2 Hz, 3H), 7.39-7.42 (t, J = 8.0 Hz, 1H), 7.29-7.31 (d, J = 3.2 Hz, 1H), 7.20-7.20 (d, J = 0.4 Hz, 1H), 4.08-4.12 (t, J = 8.0 Hz, 2H), 3.67-3.73 (t, J = 8.0 Hz, 2H); MS (*m/e*): 348.1 (M+1).

Compound 47:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.82 (s, 1H), 8.93 (s, 1H), 8.52~8.46 (m, 4H), 8.03 (s, 1H), 7.90~7.88 (m, 2H), 7.72~7.70 (m, 2H), 7.37 (s, 2H), 7.19~7.18 (m, 1H), 4.74 (s, 2H), 4.20 (s, 1H), 3.33~3.35 (m, 2H), 1.07~1.05 (m, 1H), 0.42~0.41 (m, 2H), 0.23~0.19 (m, 2H); MS (*m/e*): 449.5 (M+1)

Compound 48:

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.78 (s, 1H), 8.70 (s, 1H), 8.53~8.48 (m, 4H), 8.02~7.97 (m, 2H), 7.88~7.84 (m, 1H), 7.74~7.65 (m, 2H), 7.32 (s, 2H), 7.19 (s, 1H), 4.54 (s, 2H), 4.19 (s, 1H), 2.65~2.58 (m, 1H), 0.96~0.89 (m, 2H), 0.76~0.75 (m, 2H); MS (*m/e*): 435.5 (M+1)

Compound 49:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.79 (s, 1H), 9.04 (s, 1H), 8.50 (s, 1H), 8.41 (s, 1H), 8.03 (s, 1H), 7.90~7.84 (m, 2H), 7.71~7.69 (d, J = 8.8 Hz, 1H), 7.41~7.37 (t, J = 8.0 Hz, 1H), 7.21~7.19 (d, J = 7.6 Hz, 1H), 6.82~6.80 (d, J = 8.0Hz, 1H), 4.20 (s, 1H), 3.87~3.82 (m, 2H), 3.75~3.73 (bs, 1H), 3.43~3.38 (t, J = 9.2Hz, 2H), 1.85~1.81 (d, J = 5.6 Hz, 2H), 1.44~1.40 (m, 2H); MS (*m/e*): 388.4 (M+1).

Compound 50:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.79 (s, 1H), 9.09~9.05 (m, 1H), 8.50 (s, 1H), 8.41 (s, 1H), 8.03 (s, 1H), 7.89~7.84 (m, 2H), 7.72~7.70 (d, J = 9.2 Hz, 1H), 7.41~7.37 (t, J = 8.0 Hz, 1H), 7.21~7.19 (d, J = 7.2 Hz, 1H), 6.69~6.65 (m, 1H), 4.20 (s, 1H), 3.73~3.40 (t, J = 7.2Hz, 2H), 2.62~2.59 (t, J = 7.2Hz, 2H), 2.10 (s, 3H); MS (*m/e*): 378.4 (M+1).

Compound 51:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.79 (s, 1H), 9.02 (s, 1H), 8.50 (s, 1H), 8.41 (s, 1H), 8.03 (s, 1H), 7.89~7.84 (m, 2H), 7.71~7.69 (d, J = 8.8 Hz, 1H), 7.41~7.37 (t, J = 8.8 Hz, 1H), 7.21~7.19 (d, J = 7.2 Hz, 1H), 6.69 (m, 1H), 4.20 (s, 1H), 3.24~3.20 (t, J = 6.8Hz, 2H), 2.55~2.53 (t, J = 7.2Hz, 2H), 2.06 (s, 3H), 2.55~2.53 (tt, J = 6.8Hz, 7.2Hz, 2H); MS (*m/e*): 392.5 (M+1).

Compound 52:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.83 (s, 1H), 9.37 (s, 1H), 8.54 (d, J = 8.8, 2H), 8.08 (s, 1H), 7.93 (t, J = 8.8Hz, 2H), 7.74 (d, J = 9.2Hz, 1H), 7.39 (t, J = 8.0Hz, 1H), 7.20 (d, J = 7.6Hz, 1H), 4.23(s, 1H), 3.55 (m, 8H); MS (*m/e*): 469(M+1).

Compound 53:

^{1}H NMR (DMSO-d_6, 400 MHz):δ 9.77(s, 1H), 9.01 (s, 1H), 8.52 (d, J = 6.8, 2H), 8.05 (s, 1H), 7.88(m, 2H), 7.72(d, J = 7.2Hz, 1H), 7.39 (t, J = 8.4Hz, 1H), 7.20

(d, J = 7.6Hz, 1H), 4.20(s, 1H),3.66 (d, J = 6.4Hz, 2H), 3.54 (t, J = 5.2Hz, 4H), 2.66(t, J = 4.8Hz, 4H); MS (*m/e*): 455(M+1).

Compound 54:

^{1}H NMR (CD3OD, 400 MHz): δ 8.49 (s, 1H), 8.37 (s, 1H), 7.96 (s, 1H), 7.81~7.79 (d, J=7.2 Hz, 1H), 7.74~7.73 (m, 2H), 7.40~7.36 (t, J = 8.0 Hz, 1H), 7.27~7.25 (d, J = 7.2 Hz, 1H), 3.64~3.62 (bs, 4H), 3.52 (s, 1H), 2.53~2.51 (bs, 4H), 2.35 (s, 3H); MS (*m/e*): 387.5 (M+1).

Compound 55:

^{1}H NMR (CD3OD, 400 MHz): δ 8.48 (s, 1H), 8.37 (s, 1H), 7.96 (s, 1H), 7.81~7.79 (d, J=7.2 Hz, 1H), 7.74~7.73 (m, 2H), 7.40~7.36 (t, J = 8.0 Hz, 1H), 7.27~7.25 (d, J = 7.2 Hz, 1H), 3.64~3.61 (bs, 4H), 3.52 (s, 1H), 2.77~2.74 (m, 1H), 2.64~2.62 (bs, 4H), 1.12~1.10 (d, J = 6.4 Hz, 3H); MS (*m/e*): 415.5 (M+1).

Compound 56:

^{1}H NMR (CD3OD, 400 MHz): δ 8.48 (s, 1H), 8.37 (s, 1H), 7.96 (s, 1H), 7.81~7.79 (d, J = 7.2 Hz, 1H), 7.74~7.73 (m, 2H), 7.40~7.36 (t, J = 8.0 Hz, 1H), 7.27~7.25 (d, J = 7.2 Hz, 1H), 4.34~4.31 (d, J = 13.6 Hz, 2H), 3.51 (s, 1H), 2.97~2.91 (t, J = 12.4 Hz, 2H), 2.52~2.48 (m, 1H), 2.33 (s, 6H), 2.00~1.97 (d, J = 11.6 Hz, 2H), 1.49~1.45 (m, 2H); MS (*m/e*): 415.5 (M+1).

Compound 57:

^{1}H NMR (CD3OD, 400 MHz): δ 8.48 (s, 1H), 8.37 (s, 1H), 7.96 (s, 1H), 7.81~7.79 (d, J = 7.2 Hz, 1H), 7.74~7.73 (m, 2H), 7.40~7.36 (t, J = 8.0 Hz, 1H), 7.27~7.25 (d, J = 7.2 Hz, 1H), 4.34~4.31 (d, J = 13.6 Hz, 2H), 3.51 (s, 1H), 2.98~2.91 (t, J = 13.2 Hz, 3H), 2.73 (m, 4H), 1.96~1.93 (d, J = 12.4 Hz, 2H), 1.56~1.53 (m, 2H), 1.14~1.10 (t, J=7.6 Hz, 6H); MS (*m/e*): 443.5 (M+1).

Compound 58:

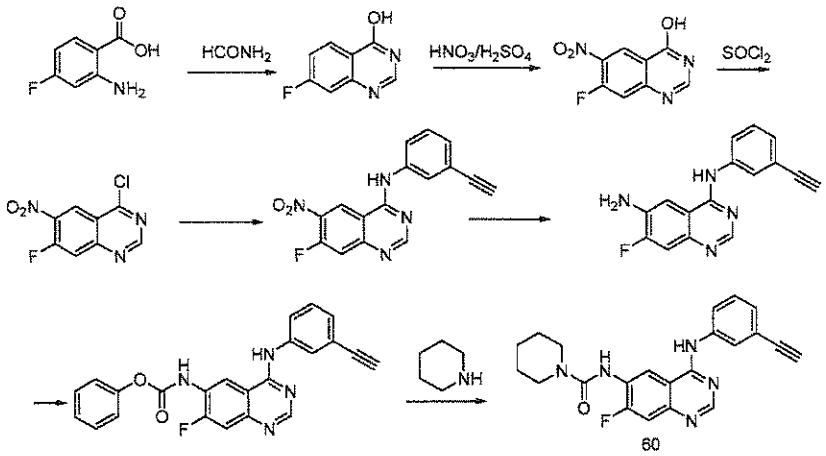
MS (*m/e*): 443 (M+1).

Compound 59:

MS (*m/e*): 45.2 (M+1).

Example 60: Synthesis of N-(4-(3-ethynylphenylamino)-7 –fluoroquinazolin -6-yl) piperidine-1-carboxamide (Compound 60)

The synthetic route to Compound 60 is shown below:



2-Amino-4-fluorobenzoic acid (1.55 g, 10 mmol) in formamide (5 mL) was heated to 150°C for 6 h. The mixture was cooled to room temperature with stirring. The precipitate was filtered out and washed with ethyl ether to give 1.3 g of 7-fluoroquinazolin-4-ol (78%).

7-Fluoroquinazolin-4-ol (1 g, 6.0 mmol) was dissolved in concentrated H_2SO_4 (3 mL) at 0°C. Concentrated HNO_3 (3 mL) was added dropwise with stirring in 15 min. The mixture was heated to 100°C for 3 h, and poured into ice-water with stirring after cooled to room temperature. The precipitate was filtered out and recrystallized with HOAc to give 0.60 g of 7-fluoro-6-nitroquinazolin-4-ol (38%).

7-Fluoro-6-nitroquinazolin-4-ol (518 mg, 2 mmol) was dissolved into thionyl chloride (3 mL) contain 2 drops of DMF. The solution was refluxed for 3 h and then the solvent was removed under reduced pressure. The residue, 4-chloro-7-fluoro-6-nitroquinazoline, was used directly in the next step without purification.

4-Chloro-7-fluoro-6-nitroquinazoline and 3-ethynylbenzenamine (234 mg, 2 mmol) was dissolved into isopropanol (5 mL) and refluxed for 3h. After cooled to room temperature, the precipitate was filtered out and washed with water to give 0.59g of N-(3-ethynylphenyl)-7-fluoro-6-nitroquinazolin-4-amine (95%).

A mixture of N-(3-ethynylphenyl)-7-fluoro-6-nitroquinazolin-4-amine (310 mg, 1 mmol) and $SnCl_2 \cdot 2H_2O$ (171mg, 4.5mmol) in ethyl acetate (35 mL) was refluxed for 2 h. After cooled to room temperature, the mixture was treated with 5% aqueous $NaHCO_3$ to adjust its pH value to 9-10. It was then subjected to extraction with EtOAc. The combined organic layers were washed with saturated brine and H_2O and dried. The solvent was removed under reduced pressure to give 225 mg (81%) N4-(3-ethynylphenyl)-7-fluoroquinazoline-4,6-diamine as a yellow solid.

N4-(3-ethynylphenyl)-7-fluoroquinazoline-4,6-diamine (100 mg, 0.36 mmol) was dissolved into DMF (3 mL) containing pyridine (35 μL, 0.432 mmol). Phenyl chloroformate (46 μL, 0.36 mmol) was dropped into the mixture at room temperature and heated to 70°C for 1 h to give phenyl 4-(3-ethynylphenylamino)-7-fluoroquinazolin-6-ylcarbamate. The obtained compound was used in the next step directly without purification. Then the amine (0.36 mmol) was added and stirred at 70°C for 2.5 h. After cooled to room temperature, the reaction mixture was diluted with ethyl acetate and washed with water. The combined organic layers were concentrated and purified with silica column to give Compound 60 (105 mg, 75% yield).

^{1}H NMR (DMSO-d_6, 400 MHz):δ 10.22 (s, 1H), 8.70(s, 1H), 8.66(s, 1H), 8.63(s 1H), 8.02 (s,1H), 7.90 (d, J = 8Hz,1H), 7.62(d, J = 12Hz, 1H), 7.42 (t, J = 8.4Hz, 1H), 7.25(d, J = 7.6Hz, 1H), 4.23(s, 1H), 3.49 (m, 4H), 1.53 (m, 6H); MS (*m/e*): 390 (M+1).

Examples 61-65: Synthesis of Compounds 61-65

Compounds 61-65 were prepared in a manner similar to that described in Example 60.

Compound 61:

^{1}H NMR (DMSO-d_6, 400 MHz):δ 9.88(s, 1H), 8.71(s, 1H), 8.59(d, J = 6.4Hz,2H), 8.05(s 1H), 7.90 (d, J = 9.2Hz,1H), 7.61 (d, J = 7.6Hz,1H), 7.41 (t, J = 8.0Hz, 1H), 7.24(d, J = 8.8Hz, 1H), 4.22(s, 1H), 3.65 (m, 4H),3.49(m, 6H); MS (*m/e*): 392 (M+1).

Compound 62:

^{1}H NMR (DMSO-d_6, 400 MHz):δ 10.04 (s, 1H), 8.79(s, 1H), 8.67(d, *J* = 0.4Hz,1H), 8.56(s, 1H), 8.07(s, 1H), 7.92 (d, *J* = 8.8Hz, 1H), 7.60 (d, *J* = 10.8Hz, H), 7.41 (m, 2H), 7.23 (d, *J* = 7.6Hz, 1H), 7.12 (m, 3H), 4.62 (s, 1H), 4.23(s, 1H), 3.01(s, 1H); MS (*m/e*): 444(M+1).

Compound 63:

^{1}H NMR (DMSO-d_6, 400 MHz):δ 10.00 (s, 1H), 8.83 (s, 1H), 8.73 (d, *J* = 4Hz, 1H), 8.56 (s, 1H), 8.00 (s, 1H), 7.78 (d, *J* = 8Hz, 1H), 7.61(d, *J* = 12Hz, 1H), 7.40 (m, *J* = 7.6Hz, 1H), 7.23 (d, *J* = 7.2Hz, 1H), 4.22 (s, 1H), 3.57 (s, 8H), 3.37 (s, 6H); MS (*m/e*): 438(M+1).

Compound 64:

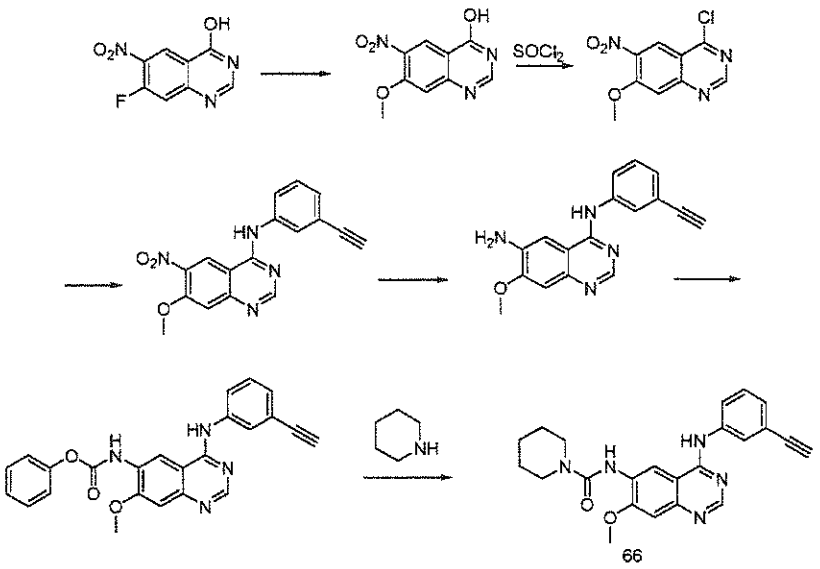
^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.96 (s, 1H), 8.67 (s, 1H), 8.59 (s,1H), 8.60(s, 1H), 8.39 (s, 1H), 8.05 (d, *J* = 8.4Hz, 1H), 7.91 (d, *J* = 8.8Hz, 1H), 7.59 (d, *J* = 10.8Hz, 1H), 7.39 (d, *J* = 7.6Hz, 1H), 7.22 (d, *J* = 6Hz, 1H), 7.13 (d, *J* = 2.0Hz, 1H), 4.22 (s, 1H), 3.68 (m, 4H), 2.22 (s, 6H), 1.80 (m, 2H); MS (*m/e*): 419 (M+1).

Compound 65:

^{1}H NMR (DMSO-d_6, 400 MHz):δ 9.93 (s, 1H), 8.73 (s, 1H), 8.58 (s,2H), 8.06(s, 1H), 7.91 (d, *J* = 8.0Hz, 1H), 7.58 (d, *J* = 8.8Hz, 1H), 7.40 (t, *J* = 6.8Hz, 1H), 7.23(d, *J* = 8Hz, 1H), 4.22 (s, 1H), 2.92(t, *J* = 5.2Hz, 2H), 2.51(m, 4H), 1.99-1.91(m, 4H), 1.72-1.42(m, 4H),1.23-1.16(m, 4H); MS (*m/e*): 459(M+1).

Example 66: Synthesis of N-(4-(3-ethynylphenylamino)-7 –methoxyquinazolin -6-yl)piperidine-1-carboxamide (Compound 66)

The synthetic route to Compound 62 is shown below:



66

Sodium (92 mg, 4 mmol) was dissolved in methanol (4 mL) under nitrogen at 0°C. 7-Fluoro-6-nitroquinazolin-4-ol (418 mg, 2 mmol) was added. The mixture was refluxed for 3 h and then cooled to room temperature, and treated with 2N HCl to adjust its pH to 3-4. The solution was concentrated, and the residue was diluted with ethyl acetate, and washed with water twice. The organic solution was concentrated to give 7-methoxy-6-nitroquinazolin-4-ol (405 mg, yield: 92%).

7-Methoxy-6-nitroquinazolin-4-ol was transformed to Compound 66 in a manner similar to that described in Example 60.

^{1}H NMR (DMSO-d6, 400 MHz):9.81 (s, 1H), 8.59(s, 1H), 8.53 (s, 1H), 8.02 (s, 1H), 7.98 (s, 1H), 7.89 (d, J = 8.8Hz, 1H), 7.38 (t, J = 8Hz, 1H), 7.25(s, 1H), 7.19 (d, J = 7.6Hz, 1H), 4.21 (s, 1H), 3.98 (s, 3H), 3.53-3.51(m, 4H), 1.60-1.53 (s, 6H); MS (*m/e*):402 (M+1).

Examples 67-84: Synthesis of Compounds 67-84

Compounds 67-84 were prepared in a manner similar to that described in Example 66.

Compound 67:

^{1}H NMR (DMSO-d_6, 400 MHz):9.69 (s, 1H), 8.58 (s, 1H), 8.54 (s, 1H), 8.10 (s, 1H), 8.04 (s, 1H), 7.90 (d, J = 8.8Hz, 1H), 7.38 (t, J = 8Hz, 1H), 7.26 (s, 1H), 7.19

(d, J = 7.2Hz, 1H), 4.19 (s, 1H), 3.99 (s, 3H), 3.64 (t, J = 4.8Hz, 4H), 3.49 (s, J = 4.8Hz, 4H); MS (*m/e*): 404 (M+1).

Compound 68:

^{1}H NMR (DMSO-d_6, 400 MHz):9.71 (s, 1H), 8.57 (s, 1H), 8.52(s, 1H), 8.07 (s, 1H), 8.04 (s, 1H), 7.91 (d, J = 8.8Hz, 1H), 7.37 (t, J = 6.4Hz, 1H), 7.24 (s, 1H), 7.18(d, J = 5.2Hz, 1H), 4.19(s, 1H), 3.98 (s, 3H), 3.50(m, 4H), 2.48 (m, 6H), 1.04 (s, 3H); MS (*m/e*): 431 (M+1).

Compound 69:

^{1}H NMR (DMSO-d_6, 400 MHz):9.65 (s, 1H), 8.73 (s, 1H), 8.57(s, 1H), 8.49 (s, 1H), 8.00 (s, 1H), 7.87 (d, J = 7.6Hz, 1H), 7.37 (t, J = 8Hz, 1H), 7.24 (s, 1H), 7.17 (d, J = 7.6Hz, 1H), 4.19 (s, 1H), 4.01 (s, 3H), 3.56 (s, 8H), 3.36 (s, 6H); MS (*m/e*): 450 (M+1).

Compound 70:

^{1}H NMR (DMSO-d_6, 400 MHz):9.73 (s, 1H), 8.66 (s, 1H), 8.53(s, 1H), 8.49 (s, 1H), 8.03 (s, 1H), 7.98 (s, 1H), 7.89 (d, J = 7.2Hz, 1H), 7.46-7.36 (m, 3H), 7.25-7.13 (m, 6H), 4.63 (s, 2H), 4.19 (s, 1H), 3.98 (s, 3H), 3.04 (s, 3H); MS (*m/e*): 456 (M+1).

Compound 71:

^{1}H NMR (DMSO-d_6, 400 MHz):9.66 (s, 1H), 8.88 (s, 1H), 8.48(s, 1H), 8.41 (s, 1H), 7.98 (s, 1H), 7.85 (d, J = 8.0Hz, 1H), 7.37 (t, J = 8.0Hz, 1H), 7.12 (s, 1H), 7.15 (d, J = 7.2Hz, 1H), 4.18(s, 1H), 4.03 (s, 3H), 3.43-3.30 (m, 7H); MS (*m/e*): 392 (M+1).

Compound 72:

^{1}H NMR (DMSO-d_6, 400 MHz):9.76 (s, 1H), 8.62 (s, 1H), 8.51(s, 1H), 8.36 (s, 1H), 8.00 (s, 1H), 7.87 (d, J = 7.6Hz, 1H), 7.37 (t, J = 8.0Hz, 1H), 7.26 (s, 1H), 7.18 (d, J = 7.6Hz, 1H), 4.21 (s, 1H), 4.01 (s, 3H), 3.54 (dd, J = 4.0Hz, 4.0Hz, 4H), 3.46 (s, 3H), 3.16 (s, 3H); MS (*m/e*): 406 (M+1).

Compound 73:

^{1}H NMR (DMSO-d_6, 400 MHz):9.68 (s, 1H), 8.57 (s, 1H), 8.50(s, 1H), 8.04 (s, 1H), 8.00 (s, 1H), 7.89 (d, J = 7.6Hz, 1H), 7.35 (t, J = 8.0Hz, 1H), 7.24 (s, 1H), 7.17 (d, J = 7.6Hz, 1H), 4.20 (s, 1H), 3.98 (s, 3H), 3.42-3.40 (m, 2H), 2.99 (s, 3H), 2.80-2.74 (m, 6H), 1.09 (m,6H); MS (*m/e*): 447 (M+1).

Compound 74:

^{1}H NMR (DMSO-d_6, 400 MHz):9.69 (s, 1H), 8.56 (s, 1H), 8.53 (s, 1H), 8.05 (s, 1H), 8.04 (s, 1H), 7.90 (d, J = 7.6Hz, 1H), 7.38 (t, J = 8Hz, 1H), 7.26 (s, 1H), 7.19 (d, J = 7.6Hz, 1H), 4.21 (s, 1H), 3.99 (s, 3H), 3.58 (m, 4H), 2.36 (m, 4H), 2.23(s, 3H); MS (*m/e*): 417 (M+1).

Compound 76:

^{1}H NMR (DMSO-d_6, 400 MHz):9.70 (s,1H), 8.57 (s, 1H), 8.53 (s, 1H), 8.04 (s, 2H), 7.90 (d, J = 8.0Hz, 1H), 7.38 (t, J = 8.0Hz, 1H), 7.25 (s, 1H), 7.19 (d, J = 8.0Hz, 1H), 4.21 (s, 1H), 3.99 (s, 3H), 3.50 (m, 4H), 2.49 (m, 4H), 2.24 (m, 2H), 0.85-0.11 (m, 5H); MS (*m/e*): 457 (M+1).

Compound 77:

^{1}H NMR (DMSO-d_6, 400 MHz):9.69 (s, 1H), 8.56 (s, 1H), 8.53 (s, 1H), 8.04 (s, 2H), 7.90 (d, J = 8.0Hz,1H), 7.38 (t, J = 8.0Hz, 1H), 7.25 (s, 1H), 7.19 (d, J = 7.6Hz, 1H), 4.21 (s, 1H), 4.11 (m, 2H), 4.03 (s, 3H), 2.95 (m, 2H), 2.73 (m, 4H), 2.21 (m, 1H), 1.88 (m, 2H), 1.71 (m, 4H), 1.41 (m, 2H); MS (*m/e*): 458 (M+1).

Compound 79:

^{1}H NMR (DMSO-d_6, 400 MHz):9.69 (s, 1H), 8.56 (s, 1H), 8.53 (s, 1H), 8.04 (s, 2H), 7.90 (d, J = 7.6Hz, 1H), 7.38 (t, J = 8.0Hz, 1H), 7.25 (s, 1H), 7.19 (d, J = 7.6Hz, 1H), 4.21(s, 1H), 4.14 (m, 2H), 3.99 (s, 3H), 2.86 (m, 2H), 2.20 (s, 6H), 1.78 (m, 2H), 1.35 (m, 2H), 1.24 (m, 1H); MS (*m/e*): 445 (M+1).

Compound 80:

^{1}H NMR (DMSO-d_6, 400 MHz):9.66 (s, 1H), 8.61 (s, 1H), 8.52 (s, 2H), 8.04 (s, 1H), 7.91 (d, *J* = 7.2Hz, 1H), 7.38 (t, *J* = 8.0Hz, 1H), 7.22 (s, 1H), 7.21 (d, *J* =7.2Hz, 1H), 4.26 (m, 2H), 4.18 (s, 1H), 3.50 (m, 4H), 2.51 (m, 2H), 2.41 (m, 4H), 1.49 (m, 3H), 1.04 (m, 3H); MS (*m/e*): 445 (M+1).

Compound 81:

^{1}H NMR (DMSO-d6, 400 MHz):8.53 (s, 1H), 8.34-8.31 (m, 3H), 7.83 (dd, *J* = 2.0Hz, *J* = 1.6Hz, 1H), 7.60 (d, *J* = 9.2Hz, 1H), 7.47 (s,1H), 7.7.45 (s,1H), 7.31 (t, *J* = 7.6Hz, 2H), 7.21 (t, *J* = 7.2Hz,1H), 5.61-5.58 (m,1H), 3.79-3.77 (m,1H), 3.66-3.64 (m,1H), 3.39-3.37 (m,2H), 3.18-3.17 (m, 2H), 2.40 (s, 6H), 2.25-2.24(m, 1H), 1.58 (d, *J* = 7.6Hz, 3H); MS (*m/e*): 405 (M+1).

Compound 82:

^{1}H NMR (DMSO, 400 MHz): 8.52 (s, 1H), 8.28 (s, 2H), 7.63 (s,1H), 7.48 (d, *J* = 7.6Hz, 2H), 7.24-7.14 (m, 4H), 5.80-5.77 (m,1H), 3.99(s,3H), 3.78-3.89 (m, 4H), 3.29-3.22 (m, 2H), 2.33(s, 6H), 2.25-2.24(m, 1H), 1.56 (d, *J* = 7.2Hz, 3H); MS (*m/e*): 453 (M+1).

Compound 83:

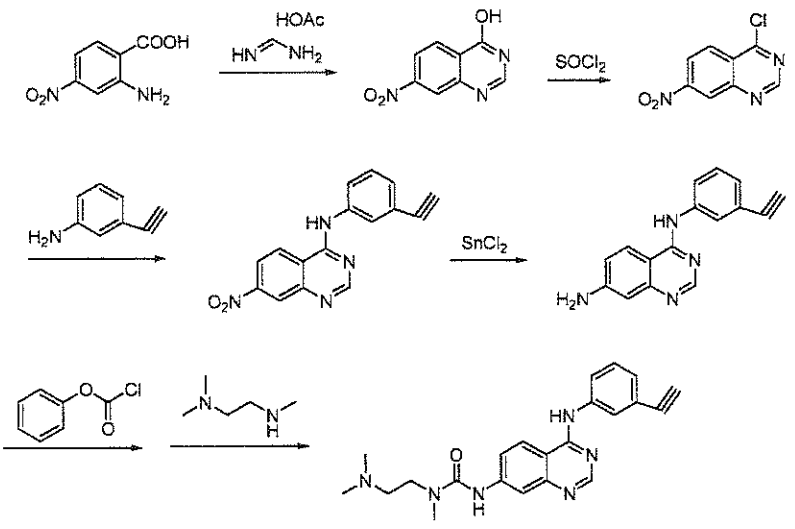
^{1}H NMR (DMSO-d6, 400 MHz): 8.74 (s, 1H), 8.48 (s, 1H), 8.29 (s, 1H), 7.56 (s, 1H), 7.23-7.15 (m, 6H), 3.96 (s,3H), 3.72-3.57 (m, 3H), 3.32-3.29 (m, 2H),2.82-2.78 (m, 2H), 2.23 (s, 6H), 1.34(s, 4H); MS (*m/e*): 447 (M+1).

Compound 84:

^{1}H NMR (DMSO-d6, 400 MHz): 9.54 (s, 1H), 8.61 (s, 1H), 8.44 (s, 1H), 7.69 (s, 2H), 7.48 (d, *J* = 8.0Hz, 2H), 7.23-7.19 (m, 3H), 3.99 (s,3H), 3.80-3.66 (m, 2H), 3.45-3.40 (m, 2H),3.18-3.06 (m, 3H), 2.90-2.83 (m, 6H), 2.08-2.01 (m, 3H), 1.24-1.18 (m, 3H); MS (*m/e*): 447 (M+1).

Example 85: Synthesis of 1-(2-(dimethylamino)ethyl)-3- (4-(3-ethynylphenylamino)quinazolin-7-yl)-1-methylurea (Compound 85)

The synthetic route to Compound 85 is shown below:



85

To a solution of 2-amino-4-nitrobenzoic acid (6.00 g, 32.94 mmol) in ethanol (40 mL) was added formamidin acetate (6.80 g, 65.32 mmol). The reaction mixture was refluxed for 5 h. The reaction mixture was cooled to room temperature and refrigerated. The precipitate was filtered out, washed with several portions of cooled ethanol, and then dried in vacuo to give 5.60g (89%) of 7-nitroquinazolin-4-ol as a yellow solid.

A mixture of 7-nitroquinazolin-4-ol (3.4g, 17.79mmol), thionyl chloride (20mL), and DMF (0.5mL) was refluxed for 48 h. After the mixture was cooled, excess thionyl chloride was removed by evaporation and the residue was azeotroped with toluene to afford 2.61g (70%) of 4-chloro-7-nitroquinazoline as a yellowish solid.

A mixture of 4-chloro-7-nitroquinazoline (2.0 g, 9.54 mmol), isopropanol (30 mL), and 3-ethynylbenzenamine (1.2 g, 10.00 mmol) was refluxed for 5 h. The reaction mixture was cooled to room temperature and refrigerated. The solid was filtered, washed with cold isopropanol several times, and dried in vacuo to give 2.6g (94%) of N-(3-ethynylphenyl)-7-nitroquinazolin-4-amine as a yellow solid.

A mixture of N-(3-ethynylphenyl)-7-nitroquinazolin-4-amine (2.0g, 6.89mmol), $SnCl_2$ (5.0g, 26.37mmol), and ethyl acetate (50mL) was refluxed for 3 h, and then subeject to extraction with ethyl acetate (20 mL) twice. The combined organic layers were washed with brine (20 mL) twice, dried over Na_2SO_4, and concentrated in vacuo to afford 1.6 g (86%) of N4-(3-ethynylphenyl)quinazoline-4,7-diamine as a yellow solid.

A mixture of N4-(3-ethynylphenyl)quinazoline-4,7-diamine (48 mg, 0.18 mmol), phenyl carbonochloridate (25.2 μL), pyridine (32 μL), and DMF (2 mL) was stirred at room temperature for 1.5 h. N, N, N-trimethylethane-1, 2-diamine (20 mg, 0.19 mmol) was added. The mixture was stirred at 80°C for 3 h. Then the resulting solution was poured into water and extracted with ethyl acetate (20 mL) 3 times. The combined organic layers were washed with brine (10 mL) twice, dried over Na_2SO_4, and concentrated in vacuo to afford 55mg (78%) of Compound 85 as a yellow solid.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.92 (s, 1H), 9.66 (s, 1H), 8.69~8.58 (d, J = 8.8Hz, 1H), 8.52 (s, 1H), 8.15 (s, 1H), 8.00~7.98 (dd, J = 0.8Hz, 8.8Hz, 1H), 7.92~7.91 (d, J = 1.6Hz, 1H), 7.72~7.70 (d, J = 9.2Hz, 1H), 7.39~7.35 (t, J = 7.6Hz, 1H), 7.19~7.17 (d, J = 7.6Hz, 1H), 4.20 (s, 1H), 3.48~3.45 (m, 2H), 3.00 (s, 3H), 2.53~2.48 (m, 2H), 2.28 (s, 6H); MS (*m/e*): 389.5 (M+1)

Examples 86-90: Synthesis of Compounds 86-90

Compounds 86-90 were prepared in a manner similar to that described in Example 85.

Compound 86:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.85 (s,1H), 8.56~8.54 (d, J = 9.2, 1H), 8.52 (s, 1H), 8.13 (s, 1H), 7.98~7.96 (d, J = 8.8Hz, 1H), 7.84 (s, 1H), 7.69~7.66 (d, J = 9.6Hz, 1H), 7.40~7.36 (t, J = 7.6Hz, 1H), 7.20~7.18 (d, J = 7.5Hz, 1H), 4.20 (s, 1H), 2.99 (s, 3H), 2.87~2.85 (m, 2H), 2.66~2.56 (m, 6H), 1.03~0.99 (t, J = 7.2Hz, 6H); MS (*m/e*): 417.5 (M+1).

Compound 87:

^{1}H NMR (DMSO-d_6, 400 Hz): δ 9.90 (s, 1H), 8.97 (s, 1H), 8.59~8.457 (d, J = 9.2Hz, 1H), 8.53 (s, 1H), 8.15 (s, 1H), 8.02~8.02 (d, J = 1.6Hz, 1H), 8.00~7.98 (d, J = 7.6Hz, 1H), 7.85~7.83 (dd, J = 1.6Hz, 8.8Hz, 1H), 7.39~7.35 (t, J = 8.0Hz, 1H), 7.20~7.18 (d, J = 7.6Hz, 1H), 5.88~5.79 (m, 1H), 5.21~5.16 (m, 2H), 4.20 (s, 1H), 4.03~4.02 (d, J = 5.2Hz, 2H), 3.15 (s, 3H); MS (*m/e*): 358.4 (M+1).

Compound 88:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.13 (s, 1H), 9.86 (s, 1H), 8.56~8.54 (d, *J* = 9.2Hz, 1H), 8.52 (s, 1H), 8.12 (s, 1H), 7.97 (s, 1H), 7.95 (s, 1H), 7.58~7.56 (d, *J* = 9.2Hz, 1H), 7.49~7.46 (t, *J* = 6.4Hz, 1H), 7.39~7.33 (m, 5H), 7.27~7.23 (m, 1H), 7.20~7.18 (d, *J* = 7.2Hz, 1H), 4.36~4.34 (d, *J* = 6.0Hz, 2H), 4.21 (s, 1H); MS (*m/e*): 394.4 (M+1).

Compound 89:

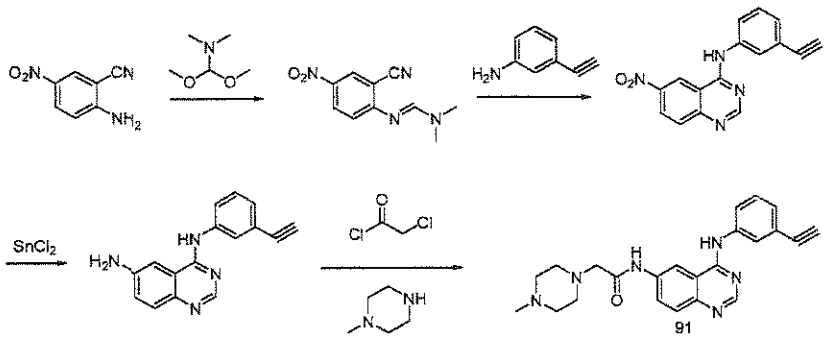
^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.91 (s, 1H), 8.59~8.57 (d, *J* = 9.2Hz, 1H), 8.53 (s, 1H), 8.14 (s, 1H), 8.02~8.01 (d, *J* = 2.0Hz, 1H), 7.99~7.98 (d, *J* = 7.6Hz, 1H), 7.85~7.82 (dd, *J* = 1.6Hz, 8.8Hz, 1H), 7.39~7.35 (t, *J* = 8Hz, 1H), 7.20~7.18 (d, *J* = 8Hz, 1H), 4.21 (s, 1H), 3.64~3.62 (m, 4H), 3.54~3.52 (m, 4H); MS (*m/e*): 374.4 (M+1)

Compound 90:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.73 (s, 1H), 8.79 (s, 1H), 8.54 (s, 1H), 8.46~8.44 (d, *J* = 9.6Hz, 1H), 8.11 (s, 1H), 7.96 (s, 1H), 7.95~7.93 (d, *J* = 8Hz, 1H), 7.80~7.77 (t, *J* = 1.2Hz, 9.2), 7.41~7.37 (t, *J* = 15.2Hz, 1H), 7.21~7.19 (d, *J* = 8Hz, 1H), 4.21 (s, 1H), 3.55~3.51 (m, 2H), 3.30 (s, 1H), 3.04 (s, 1H); MS (*m/e*): 376.4 (M+1).

Example 91: Synthesis of N-(4-(3-ethynylphenylamino)quinazolin-6-yl) -2-(4-methylpiperazin-1-yl)acetamide (Compound 91)

The synthetic route to Compound 91 is shown below.



To a solution of 5-nitroanthranilonitrile (1.00 g, 6.13 mmol) in dioxane (25 mL) was added dimethylformamide dimethylacetal (0.88 g, 7.36 mmol). The reaction mixture was stirred at 100°C for 2h and then cooled to room temperature and refrigerated. The precipitate was filtered out, washed with cold ether several times, and then dried in vacuo to give 1.30 g (97%) of (E)-N'-(2-cyano-4- nitrophenyl)- N,N-dimethylformamidine as a yellow solid.

(E)-N'-(2-cyano-4-nitrophenyl)-N,N-dimethylformamidine (1.00 g, 4.58 mmol) and 3-aminophenylacetylene (0.64 g, 5.49 mmol) was dissolved in HOAc (15 mL). After stirred at 100°C for 3 h, the resulting mixture was cooled to room temperature. The precipitate was filtered out, washed with ether, and dried in vacuo to give 1.23 g (93%) of N-(3-ethynylphenyl)-6-nitroquinazolin-4-amine as a yellow solid.

A mixture of N-(3-ethynylphenyl)-6-nitroquinazolin-4-amine (1.00 g, 3.45 mmol) and $SnCl_2 \cdot 2H_2O$ (3.10 g, 13.8 mmol) in ethyl acetate (35 mL) was refluxed for 2 h and then cooled to room temperature. The pH was adjusted to 9-10 by treatment with 5% aqueous $NaHCO_3$. The mixture was subjected to extraction with EtOAc. The combined organic layers were washed with saturated brine and H_2O and dried. The solvent was removed under reduced pressure to give 0.79g (89%) of N4-(3-ethynylphenyl) quinazoline-4,6-diamine as a yellow solid.

To a solution of N4-(3-ethynylphenyl)quinazoline-4,6-diamine (100 mg, 0.38 mmol) in DMF (2 mL) containing N,N-diisopropylethylamine (124 μL, 0.76 mmol) was added chloroacetyl chloride (32 μL, 0.38 mmol) at room temperature. After 10 min, 1-methylpiperazine (209 μL, 1.90 mmol) was added and the reaction mixture was stirred at 80°C for 5 h. The reaction mixture was concentrated and the residue was purified by PTLC to give Compound 91 as a yellow solid in 94% yield.

^{1}H NMR (CD_3OD, 400 MHz): δ 8.65 (s, 1H), 8.54 (s, 1H), 7.99~7.97 (m, 2H), 7.84~7.79 (m, 2H), 7.43~7.39 (t, J = 8.0Hz, 1H), 7.31~7.29 (d, J = 8.0Hz, 1H), 4.62 (s, 2H), 3.54 (s, 1H), 2.75~2.67 (bs, 8H), 2.41 (s, 3H); MS (*m/e*): 401.5 (M+1).

Examples 92-125: Synthesis of Compounds 92-125

Compounds 92-125 were prepared in a manner similar to that described in Example 91.

Compound 92:

^{1}H NMR (CD3OD, 400 MHz): 8.59 (d, J = 2.0Hz, 1H), 8.37 (s, 1H), 7.93 (dd, J = 2.4Hz, J = 2.4Hz, 1H), 7.72 (d, J = 8.8Hz, 1H), 7.47 (t, J = 6.8Hz, 1H), 7.28-7.25 (m, 1H), 7.11 (q, 1H), 5.87-5.84 (m, 1H), 3.38 (s, 2H), 3.04 (m, 4H), 2.86 (m, 4H), 2.66 (s, 3H), 1.71 (d, J = 7.2Hz, 3H), MS (*m/e*): 423 (M+1).

Compound 93:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.99 (s, 1H), 9.88 (s, 1H), 8.66 (s, 1H), 8.57 (s, 1H), 8.06 (d, J = 9.2Hz, 1H), 8.03 (s, 1H), 7.89 (d, J = 8.0Hz, 1H), 7.78 (d, J = 8.8Hz, 1H), 7.41 (t, J = 8.0Hz, 1H), 7.23 (d, J = 7.2Hz, 1H), 4.23(s, 1H), 3.20 (d, 2H), 3.17 (d, J = 4.4Hz, 1H), 2.60 (m, 8H), 2.6 (m, 8H), 2.35 (t, J = 6.8Hz, 3H); MS (*m/e*): 415 (M+1).

Compound 94:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.97 (s, 1H), 9.88 (s, 1H), 8.66 (d, J = 1.6Hz, 1H), 8.57 (s, 1H), 8.06 (d, J = 9.2Hz, 1H), 8.03 (s, 1H), 7.89 (d, J = 8.0Hz, 1H), 7.78 (d, J = 9.2Hz, 1H), 7.41 (t, J = 8.0Hz, 1H), 7.23 (d, J = 8.0Hz, 1H), 4.23(s, 1H), 3.19 (d, 2H), 2.6 (m, 8H), 0.99 (d, J = 6.8Hz, 6H); MS (*m/e*): 429 (M+1).

Compound 95:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.96 (s, 1H), 8.79 (s, 1H), 8.58 (s, 1H), 8.12 (d, J = 8.8Hz, 1H), 8.07 (s, 1H), 7.92 (d, J = 7.6Hz, 1H), 7.80 (d, J = 8.4Hz, 1H), 7.40 (t, J = 7.2Hz, 1H), 7.22 (d, J = 7.2Hz, 1H), 4.23 (s, 1H), 3.39 (s, 2H), 2.98 (m, 8H), 1.13 (s, 6H); MS (*m/e*): 417 (M+1).

Compound 96:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.94 (s, 1H), 8.73 (s, 1H), 8.57 (s, 1H), 8.11 (d, J = 6.4Hz, 1H), 8.05 (s, 1H), 7.90 (d, J = 8.0Hz, 1H), 7.79 (d, J = 9.2Hz, 1H), 7.39 (t, J = 7.6Hz, 1H), 7.21 (d, J = 7.6Hz, 1H), 4.21 (s, 1H), 3.39 (s, 2H), 3.34 (m, 4H), 2.79 (s, 6H); MS (*m/e*): 389 (M+1).

Compound 97:

MS (*m/e*): 413.2 (M+1).

Compound 98:

^{1}H NMR (DMSO, 400 MHz): δ10.09 (s, 1H), 9.92 (s, 1H), 8.62 (s, 1H), 8.57 (s, 1H), 8.10 (d, *J* = 8.8Hz, 1H), 8.02 (s, 1H), 7.99 (d, *J* = 8.0Hz, 1H), 7.81 (d, *J* = 8.8Hz, 1H), 7.41 (t, *J* = 8.0Hz, 1H), 7.22 (d, *J* = 7.6Hz, 1H), 4.21 (s, 1H), 3.47 (t, *J* = 4.2Hz, 4H), 3.39 (s, 2H), 3.26 (s, 6H) , 2.85 (t, *J* = 3.9Hz, 4H); MS (*m/e*): 434 (M+1).

Compound 99:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.98 (s, 1H), 9.85 (s, 1H), 8.62 (d, *J* = 2.0Hz, 1H), 8.57 (s, 1H), 8.10 (dd, *J* = 8.8, 2.0Hz 1H), 8.03 (s, 1H), 7.88 (dd, *J* = 8.4, 1.2Hz 1H), 7.78 (d, *J* = 9.2Hz, 1H), 7.41 (t, *J* = 7.6Hz, 1H), 7.23 (d, *J* = 8.0Hz, 1H), 4.23 (s, 1H), 3.18 (s, 2H), 2.90 (d, *J* = 12.0Hz, 2H), 2.48 (s, 3H), 2.22 (t, *J* = 11.2Hz, 2H), 1.97 (t, *J* = 9.6Hz, 1H), 1.85 (d, *J* = 12.0Hz, 2H), 1.67 (d, 4H), 1.55 (m, 2H); MS (*m/e*): 455 (M+1).

Compound 100:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.98 (s, 1H), 9.86 (s, 1H), 8.64 (d, *J* = 1.6Hz, 1H), 8.57 (s, 1H), 8.05 (dd, *J* = 8.8, 2.0Hz 1H), 8.03 (s, 1H), 7.89 (dd, *J* = 8.4, 1.2Hz 1H), 7.78 (d, *J* = 9.2Hz, 1H), 7.41 (t, *J* = 8.0Hz, 1H), 7.23 (d, *J* = 8.0Hz, 1H), 4.23 (s, 1H), 3.20 (s, 2H), 2.56 (m, 8H), 2.37 (m, 4H), 2.14 (s, 6H); MS (*m/e*): 458 (M+1).

Compound 102:

MS (*m/e*): 475 (M+1).

Compound 103:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.97 (s, 1H), 9.86 (s, 1H), 8.64 (d, *J* = 1.6Hz, 1H), 8.57 (s, 1H), 8.06 (dd, *J* = 9.2, 2.0Hz 1H), 8.03 (s, 1H), 7.89 (dd, *J* = 8.4, 1.2Hz 1H), 7.78 (d, *J* = 8.4Hz, 1H), 7.41 (t, *J* = 8.0Hz, 1H), 7.23 (d, *J* = 7.6Hz, 1H), 4.23 (s, 1H), 3.21 (s, 2H), 2.56 (m, 8H), 2.20 (d, *J* = 6.4Hz, 2H), 1.24 (s, 1H), 0.83 (m, 1H), 0.46 (m, 2H), 0.80 (m, 2H); MS (*m/e*): 441 (M+1).

Compound 104:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.99 (s, 1H), 9.86 (s, 1H), 8.65 (d, *J* = 1.2Hz, 1H), 8.57 (s, 1H), 8.06 (dd, *J* = 8.8, 2.0Hz 1H), 8.03 (s, 1H), 7.89 (dd, *J* = 8.4, 1.2Hz 1H), 7.79 (d, *J* = 9.2Hz, 1H), 7.41 (t, *J* = 8.0Hz, 1H), 7.23 (d, *J* = 7.6Hz, 1H), 4.23 (s, 1H), 3.38 (s, 2H), 3.17 (d, *J* = 5.2Hz, 1H), 2.86 (t, *J* = 5.6Hz, 4H), 2.62 (d, *J* = 4.8Hz, 4H) 2.31 (s, 3H), 1.80 (m, 2H), 1.24 (s, 1H); MS (*m/e*): 415 (M+1)

Compound 105:

MS (*m/e*): 431(M+1).

Compound 106:

MS (*m/e*): 427.2(M+1).

Compound 107:

^{1}H NMR (DMSO-d_6, 400MHz): δ 9.94 (s, 1H), 9.84 (s, 1H), 8.63 (s, 1H), 8.55 (s, 1H), 8.03 (m, 2H), 7.88 (d, *J* = 8.0Hz, 1H), 7.77 (d, *j* = 9.2Hz, 1H), 7.37 (t, *J* = 8.0Hz, 1H), 7.20 (d, *j* = 7.6Hz, 1H), 4.20 (s, 1H), 3.16 (s, 2H), 2.95 (d, *j* = 11.2Hz, 2H), 2.39 (m, 5H), 2.17 (t, *j* = 8.8Hz, 2H), 1.62 (m, 4H), 1.35 (m, 4H), 0.83 (t, *j* = 7.6Hz, 6H); MS (m/e): 485.3 (M+1).

Compound 108:

^{1}H NMR (DMSO-d_6, 400MHz): δ10.09 (s, 1H), 9.86 (s, 1H), 8.68 (s, 1H), 8.57 (s, 1H), 8.02 (m, 2H), 7.88 (d, *J* = 8.0Hz, 1H), 7.79 (d, *j* = 9.2Hz, 1H), 7.41 (t, *J* = 8.0Hz, 1H), 7.23 (d, *J* = 7.6Hz, 1H), 4.20 (s, 1H), 3.78 (s, 2H), 3.58 (s, 2H), 3.28 (s, 2H), 2.63 (s, 2H), 2.51 (s, 2H), 1.99 (s, 1H), 0.73 (m, 4H); MS (m/e): 455.2 (M+1).

Compound 109:

^{1}H NMR (DMSO-d_6, 400MHz): δ 9.96 (s, 1H), 9.84 (s, 1H), 8.62 (s, 1H), 8.57 (s, 1H), 8.09 (d, *J* = 8.8Hz, 1H), 8.02 (s, 1H), 7.88 (d, *J* = 8.0Hz, 1H), 7.79 (t, *J* = 8.8Hz, 1H), 7.41 (t, *J* = 8.0Hz, 1H), 7.23 (d, *J* = 8.0Hz, 1H), 4.22 (s, 1H), 3.57 (m, 1H), 3.17 (s, 2H), 2.80 (m, 2H), 2.30 (m, 2H), 1.78 (m, 2H), 1.54 (m, 2H); MS (m/e): 402.1 (M+1).

Compound 110:

^{1}H NMR (DMSO-d_6, 400MHz): δ 9.95 (s, 1H), 9.84 (s, 1H), 8.61 (s, 1H), 8.55 (s, 1H), 8.09 (m, 2H), 7.86 (d, *j* = 8.8Hz, 1H), 7.76 (d, *j* = 9.2Hz, 1H), 7.79 (t, *j* = 8.0Hz, 1H), 7.21 (d, *j* = 7.6Hz, 1H), 4.21 (s, 1H), 3.42 (t, *j* = 6.0Hz, 2H), 3.22 (s, 3H), 3.17 (s, 2H), 2.49 (m,10H); MS (m/e): 445.2 (M+1).

Compound 111:

^{1}H NMR (DMSO-d_6, 400MHz): δ 9.95 (s, 1H), 9.84 (s, 1H), 8.64 (s, 1H), 8.57 (s, 1H), 8.08 (d, *j* = 8.8Hz, 1H), 8.03 (s, 1H), 7.89 (d, *j* = 8.1Hz, 1H), 7.78 (d, *j* = 9.2Hz, 1H), 7.40 (t, *j* = 8.4Hz, 1H), 7.23 (d, *j* = 7.6Hz, 1H), 4.21 (s, 1H), 3.18 (s, 2H), 2.95 (d, *j* = 10.8Hz, 2H), 2.40 (s, 3H), 2.30 (m, 4H), 2.18 (m, 7H), 1.76 (m, 2H), 1.56 (m, 2H); MS (m/e): 484.0 (M+1).

Compound 112:

^{1}H NMR (CD3OD, 400 MHz): δ8.69 (s, 1H), 8.51 (s, 1H), 7.94 (s, 1H), 7.81~7.75 (m, 3H), 7.40~7.36 (t, *J* = 8.0Hz, 1H), 7.28~7.26 (d, *J* = 8.0Hz, 1H), 3.51 (s, 1H), 2.86~2.82 (m, 2H), 2.69~2.65 (m, 10H), 1.11~1.09 (d, *J* = 6.0Hz, 6H); MS (*m/e*): 443.5 (M+1).

Compound 113:

^{1}H NMR (CD3OD, 400 MHz): δ8.65 (s, 1H), 8.52 (s, 1H), 7.95~7.89 (m, 2H), 7.81~7.77 (m, 2H), 7.40~7.36 (t, *J* = 8.0Hz, 1H), 7.29~7.27 (d, *J* = 8.0Hz, 1H), 3.50 (s, 1H), 2.72 (m, 8H), 1.38~1.36 (d, *J* = 6.8Hz, 3H), 1.12~1.01 (d, *J* = 6.4Hz, 6H); MS (*m/e*): 443.5 (M+1).

Compound 114:

^{1}H NMR (DMSO-d_6, 400 MHz):10.27 (s,1H), 10.04 (s,1H), 9.28 (s,1H), 8.58 (s,1H), 8.44(d, *J* = 7.2Hz,1H), 8.29 (s,1H), 8.16(d, *J* = 7.6Hz,1H), 7.78 (d, *J* = 8.8Hz,1H), 7.39 (t, *J* = 7.6Hz,1H), 7.21 (d, *J* = 7.2Hz,1H), 4.22 (s,1H), 2.51(s,8H), 1.26(s, 6H), 1.21 (s,3H); MS (*m/e*): 429 (M+1).

Compound 115:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.97 (s,1H), 9.84 (s,1H), 8.78 (s,1H), 8.56 (s,1H), 8.16 (d, *J* = 9.2Hz,1H), 8.07 (s,1H), 7.93 (d, *J* = 8.4Hz,1H), 7.78 (d, *J* =

9.2Hz,1H), 7.41 (t, *J* = 8.4Hz,1H), 7.22 (d, *J* = 8.0Hz,1H), 4.23 (s,1H), 2.61(s,8H), 1.24(s, 6H), 1.01 (d, *J* = 10.8Hz,1H), 0.98-0.96 (m, 1H); MS (*m/e*): 457 (M+1).

Compound 116:

^{1}H NMR (DMSO-d_6, 400 MHz):9.99 (s,1H), 9.87 (s,1H), 8.73 (s,1H), 8.56 (s,1H), 8.15(d, *J* = 7.6Hz,1H), 8.08 (s,1H), 8.7.95(d, *J* = 7.2Hz,1H), 7.78 (d, *J* = 10.2Hz,1H), 7.41 (t, *J* = 7.6Hz,1H), 7.22 (d, *J* = 8.0Hz,1H), 4.23 (s,1H),3.15(d, *J* = 4.8Hz,1H) 2.55(s,8H), 1.25(s, 6H), 1.02-0.971 (m, 3H); MS (*m/e*): 443 (M+1).

Compound 117:

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.86 (s,1H), 9.42 (s,1H), 8.68 (s,1H), 8.57 (s,1H), 8.18(d, *J* = 7.2Hz,1H), 8.05 (s,1H), 7.92(d, *J* = 7.6Hz,1H), 7.58 (d, *J* = 7.2Hz,1H), 7.39 (t, *J* = 6.0Hz,1H), 7.22 (d, *J* = 7.6Hz,1H), 6.14 (s,1H), 4.22 (s,1H), 3.09-3.06 (m, 2H), 1.49(s,3H), 1.32(s, 6H); MS (*m/e*): 374 (M+1).

Compound 118:

^{1}H NMR (DMSO-d_6, 400 MHz): δ10.00 (s, 1H), 9.82 (s, 1H), 9.04 (s, 1H), 8.52 (s, 1H), 7.96 (s, 1H), 7.85~7.83 (d, *J* = 7.2Hz, 1H), 7.40~7.36 (t, *J* = 8.0Hz, 1H), 7.19 (s, 1H), 4.20 (s, 1H), 4.07 (s, 3H), 3.34 (s, 2H), 2.61~2.58 (m, 4H), 2.48~2.36 (m, 4H), 1.05~1.02 (t, *J* = 9.6Hz, 3H); MS (*m/e*): 445.5 (M+1).

Compound 119:

^{1}H NMR (DMSO-d_6, 400 MHz): δ10.04 (s, 1H), 9.82 (s, 1H), 9.04 (s, 1H), 8.52 (s, 1H), 7.96 (s, 1H), 7.85~7.83 (d, *J* = 7.2Hz, 1H), 7.40~7.36 (t, *J* = 8.0Hz, 1H), 7.19 (s, 1H), 4.20 (s, 1H), 4.07 (s, 3H), 3.2 (s, 2H), 2.61~2.58 (m, 4H), 2.48~2.36 (m, 8H), 1.10 (bs, 6H); MS (*m/e*): 459.5 (M+1).

Compound 120:

^{1}H NMR (DMSO-d_6, 400 MHz): 10.00 (s, 1H), 9.83 (s, 1H), 9.04 (s, 1H), 8.53 (s, 1H), 7.96 (s, 1H), 7.84 (d, *J* = 7.6Hz, 1H), 7.38 (t, *J* = 8.0Hz, 1H), 7.32 (s, 1H), 7.20 (d, *J* = 7.6Hz, 1H), 4.21 (s, 1H), 4.08 (s, 3H), 3.22 (s, 2H), 2.60 (m, 8H), 2.23 (s, 3H); MS (*m/e*): 431 (M+1).

Compound 121:

^{1}H NMR (DMSO-d_6, 400 MHz): δ10.16 (s, 1H), 9.81 (s, 1H), 9.08 (s, 1H), 8.52 (s, 1H), 7.97 (s, 1H), 7.84 (d, J = 8.8Hz, 1H), 7.38 (t, J = 8.0Hz, 1H), 7.32 (s, 1H), 7.20 (d, J = 8.0Hz, 1H), 4.21 (s, 1H), 4.06 (s, 3H), 3.46 (t, J = 5.2Hz, 1H), 3.26 (s, 3H), 2.76 (t, J = 5.2Hz, 1H) , 1.24 (s, 1H); MS (*m/e*): 406 (M+1).

Compound 123:

^{1}H NMR (CD3OD, 400 MHz): δ8.93 (s,1H), 8.48 (s,1H), 7.93 (s,1H), 7.77 (d, J = 8.0Hz,1H), 7.38 (t, J = 7.6Hz,1H), 7.27 (t, J = 7.2Hz,2H), 4.14 (s,3H), 3.37(s,1H), 3.25 (s,2H), 3.12-3.09 (m, 3H), 2.42-2.37 (m, 2H), 2.02-2.00 (m, 2H), 1.80-1.77 (m, 2H), 1.31-1.25 (m, 4H),1.20 (s, 6H); MS (*m/e*): 487 (M+1).

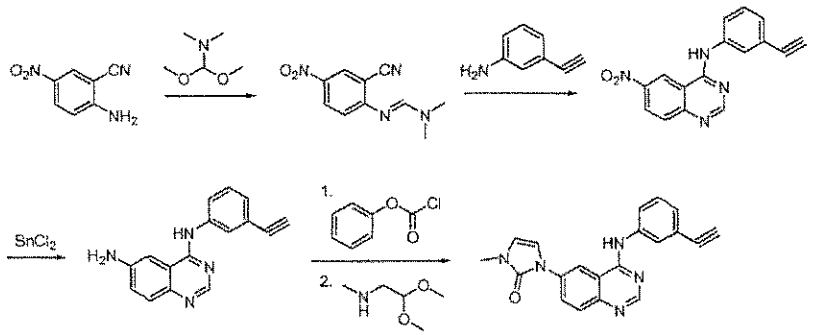
Compound 124:

^{1}H NMR (DMSO-d_6, 400 MHz): δ10.04 (s,1H), 9.81 (s,1H), 9.02 (s,1H), 8.53 (s,1H), 7.97 (s,1H), 7.85 (d, J = 8.0Hz,1H), 7.38 (t, J = 8.0Hz,1H), 7.32 (s,1H), 7.20 (d, J = 7.6Hz,1H), 4.19 (s,1H), 4.07(s,3H), 3.21 (s,2H), 2.68-2.60 (m, 4H), 1.22 (s, 3H), 1.02-0.97(m, 6H); MS (*m/e*): 445 (M+1).

Compound 125:

^{1}H NMR (DMSO-d_6, 400 MHz): δ10.52 (s,1H), 9.94 (s,1H), 8.95(s,1H), 8.57 (s,1H), 7.99 (s,1H), 7.86 (d, J = 9.2Hz,1H), 7.39 (t, J = 8.4Hz,1H), 7.33 (s,1H), 6.76 (d, J = 7.6Hz,1H), 4.23 (s,1H), 4.04(s,3H), 2.98 (s,8H), 2.78-2.75 (m, 3H), 2.34-2.30 (m, 2H), 1.37 (s, 6H); MS (*m/e*): 473 (M+1).

Example 126: Synthesis of 1-(4-(3-ethynylphenylamino)quinazolin -6-yl)-3- methyl-1H-imidazol-2(3H)-one (Compound 126)



To a solution of 5-nitroanthranilonitrile (1.00 g, 6.13 mmol) in dioxane (25 mL) was added dimethylformamide dimethyl acetal (0.88 g, 7.36 mmol). Th reaction mixture was stirred at 100°C for 2 h and then cooled to room temperature and refrigerated. The precipitate was filtered out, washed with cold ether several time, and then dried in vacuo to give 1.30 g (97%) of N'-(2-cyano-4-nitrophenyl)-N,N-dimethylformamidine as a yellow solid.

A mixture of N'-(2-cyano-4-nitrophenyl)-N,N-dimethylformamidine (1.00 g, 4.58 mmol) and 3-aminophenylacetylene (0.64 g, 5.49 mmol) in HOAc (15 mL) was stirred at 100°C for 3 h and cooled to room temperature. The precipitate was filtered, washed with ether, and was dried in vacuo to give 1.23 g (93%) of N-(3-ethynylphenyl)-6-nitroquinazolin-4-amine as a yellow solid.

N-(3-ethynylphenyl)-6-nitroquinazolin-4-amine (1.00 g, 3.45 mmol) and $SnCl_2 \cdot 2H_2O$ (3.10 g, 13.8 mmol) in ethyl acetate (35mL) were refluxed for 2 h. After cooled to room temperature, the mixture was treated with 5% aqueous $NaHCO_3$ to adjust its pH to 9-10 and then subjected to extraction with EtOAc. The combined organic layers were washed with saturated brine and H_2O, dried, and concentrated under reduced pressure to give 0.79 g (89%) of N4-(3-ethynylphenyl)quinazoline-4,6-diamine as a yellow solid.

To a solution of N4-(3-ethynylphenyl)quinazoline-4,6-diamine (100 mg, 0.38 mmol) in DMF (2 mL) containing pyridine (37 μL, 0.46 mmol) was added phenyl chloroformate (49 μL, 0.38 mmol) dropwise at room temperature. After 10min, (methylamino)acetaldehyde dimethylacetal (45.2 mg, 0.38 mmol) was added and the reaction mixture was heated to 100°C for 1 h. After cooled to room temperature, the reaction mixture was diluted with ethyl acetate and washed with water. The combined organic layers were concentrated and purified with a silica column to give Compound 126 as a yellow solid in 83% yield.

^{1}H NMR (CD_3OD, 400 MHz): 8.84 (s, 1H), 8.83~8.82 (d, J = 2.0Hz, 1H), 8.60~8.57 (dd, J = 2.0Hz, 9.6Hz, 1H), 7.98~7.96 (d, J = 9.2Hz, 1H), 7.95 (s, 1H), 7.81~7.79 (dd, J = 1.6Hz, 7.2Hz, 1H), 7.52~7.49 (m, 2H), 7.17~7.16 (d, J = 2.8Hz, 1H), 6.82~6.81 (d, J = 2.8Hz, 1H), 3.64 (s, 1H), 3.38 (s, 3H); MS (*m/e*): 342.3 (M+1).

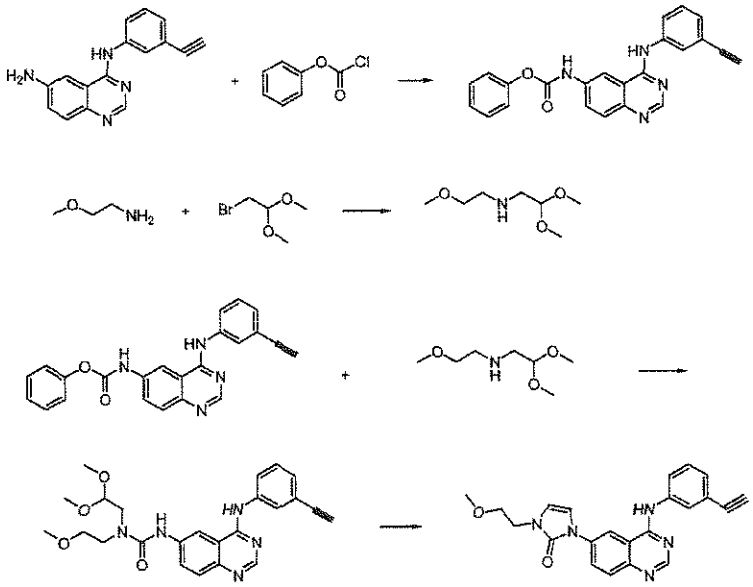
Example 127: Synthesis of 1-(4-(3-ethynylphenylamino)quinazolin -6-yl)- 1H-imidazol-2(3H)-one

Compound 127 was prepared in a manner similar to that described in Example 126.

^{1}H NMR (CD3OD, 400 MHz): 8.55 (s, 2H), 8.24~8.22 (dd, J = 2.8Hz, 9.2Hz, 1H), 7.97 (s, 1H), 7.88~7.86 (d, J = 8.8Hz, 1H), 7.82-7.81 (d, J = 2.4Hz, 1H), 7.40~7.36 (t, J = 8.0Hz, 1H), 7.28~7.26 (d, J = 8.8Hz, 1H), 7.09~7.08 (d, J = 3.2Hz, 1H), 6.79~6.78 (d, J = 3.2Hz, 1H), 3.52 (s, 1H); MS (*m/e*): 327.9(M+1).

Example 128: Synthesis of 1-(4-(3-ethynylphenylamino)quinazolin -6-yl)-3- (2-methoxy- ethyl)-1H-imidazol-2(3H)-one (Compound 128)

The synthetic route to Compound 128 is shown below:



To a solution of N4-(3-ethynylphenyl)quinazoline-4,6-diamine (100 mg, 0.38 mmol) in DMF (2 mL) containing pyridine (37 μL, 0.46 mmol) was added phenyl chloroformate (49 μL, 0.38 mmol) dropwise at room temperature for 1 h. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The

combined organic layers were concentrated to give phenyl 4-(3-ethynylphenylamino)quinazolin-6-ylcarbamate as a yellow solid in 95% yield and used in the next step without purification.

To a solution of 2-methoxyethanamine (100 mg, 1.33 mmol) in DMF (2 mL) was added K_2CO_3 (276 mg, 1.99 mmol) and 2-bromo-1,1-dimethoxyethane (236 mg, 1.39 mmol). The mixture was stirred at 80°C for 3 h. After cooled to room temperature, the reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was concentrated to give 2,2-dimethoxy-N-(2-methoxyethyl)ethanamine as a yellow oil in 91% yield and used in the next step without purification.

To a solution of phenyl 4-(3-ethynylphenylamino)quinazolin-6-ylcarbamate (50 mg, 0.13 mmol) in DMF (2 mL) was added 2,2-dimethoxy-N-(2-methoxyethyl)ethanamine (22.0 mg, 0.13 mmol). The mixture was stirred at 80°C for 0.5 h and then p-toluenesulfonic acid (28.5 mg, 0.15 mmol) was added. After stirred at 80°C for additional 1 h, the mixture was cooled to room temperature and diluted with ethyl acetate and washed with water and brine. The organic layer was concentrated and purified with silica column to give Compound 128 as yellow solid in 82% yield.

^{1}H NMR (CD_3OD, 400 MHz): 8.57 (s, 2H), 8.24~8.22 (dd, J = 2.8Hz, 9.2Hz, 1H), 7.98 (s, 1H), 7.89~7.87 (d, J = 8.8Hz, 1H), 7.82-7.81 (d, J = 2.4Hz, 1H), 7.40~7.36 (t, J = 8.0Hz, 1H), 7.29~7.27 (d, J = 8.8Hz, 1H), 7.09~7.08 (d, J = 3.2Hz, 1H), 6.79~6.78 (d, J = 3.2Hz, 1H), 3.92~3.90 (t, J = 5.2Hz, 2H), 3.68~3.66 (t, J = 5.2Hz, 2H), 3.52 (s, 1H), 3.40 (s, 3H); MS (*m/e*): 386.4(M+1).

Examples 129-156: Synthesis of Compounds 129-156

Compounds 129-156 were prepared in a manner similar to that described in Example 128.

Compound 129:

^{1}H NMR (DMSO-d6, 400 MHz): 10.06 (s, 1H), 8.71 (s, 1H), 8.7-0 (s, 1H), 8.51~8.48 (dd, J = 1.6Hz, 8.4Hz, 1H), 8.09 (s, 1H), 7.99~7.97 (d, J = 8.0Hz, 1H), 7.89-7.8 7 (d, J = 8.8Hz, 1H), 7.45~7.41 (t, J = 8.0Hz, 1H), 7.34~7.33 (d, J = 3.2Hz, 1H), 7.26~7.24 (d, J = 7.2Hz, 1H), 6.93~6.92 (d, J = 3.2Hz, 1H), 4.23 (s, 1H),

3.77~3.74 (t, J = 6.4Hz, 2H), 3.61~3.55 (m, 4H), 2.61~2.56 (t, J = 6.4Hz, 2H), 2.48~2.24 (m, 4H); MS (*m/e*): 441.5(M+1).

Compound 130:

^{1}H NMR (DMSO-d6, 400 MHz): 10.04 (s, 1H), 8.69 (s, 1H), 8.63 (s, 1H), 8.49~8.46 (dd, J = 1.6Hz, 8.4Hz, 1H), 8.08 (s, 1H), 7.99~7.97 (d, J = 8.0Hz, 1H), 7.89-7.8 7 (d, J = 8.8Hz, 1H), 7.45~7.41 (t, J = 8.0Hz, 1H), 7.34~7.33 (d, J = 3.2Hz, 1H), 7.26~7.24 (d, J = 7.2Hz, 1H), 6.96~6.95 (d, J = 3.2Hz, 1H), 4.23 (s, 1H), 3.86~3.83 (t, J = 6.8Hz, 2H), 2.84~2.80 (t, J = 6.8Hz, 2H), 2.12 (s, 3H); MS (*m/e*): 402.5(M+1).

Compound 131:

^{1}H NMR (DMSO-d6, 400 MHz): 9.74 (s, 1H), 8.67 (s, 1H), 8.63 (s, 1H), 8.45~8.43 (dd, J = 2.4Hz, 8.8Hz, 1H), 8.07 (s, 1H), 7.97~7.95 (d, J = 8.0Hz, 1H), 7.89-7.87 (d, J = 8.8Hz, 1H), 7.45~7.41 (t, J = 8.0Hz, 1H), 7.31~7.30 (d, J = 3.2Hz, 1H), 7.26~7.24 (d, J = 7.2Hz, 1H), 7.08~7.07 (d, J = 3.2Hz, 1H), 4.23 (s, 1H), 4.14~4.10 (m, 1H), 3.99~3.96 (m, 2H), 3.50~3.45 (t, J = 8.4Hz, 2H), 1.91~1.86 (m, 2H), 1.79~1.75 (m, 2H); MS (*m/e*): 412.4(M+1).

Compound 132:

^{1}H NMR (DMSO-d6, 400 MHz): 9.74 (s, 1H), 8.67 (s, 1H), 8.63 (s, 1H), 8.45~8.43 (dd, J = 2.4Hz, 8.8Hz, 1H), 8.07 (s, 1H), 7.97~7.95 (d, J = 8.0Hz, 1H), 7.89-7.87 (d, J = 8.8Hz, 1H), 7.45~7.41 (t, J = 8.0Hz, 1H), 7.31~7.30 (d, J = 3.2Hz, 1H), 7.26~7.24 (d, J = 7.2Hz, 1H), 7.08~7.07 (d, J = 3.2Hz, 1H), 4.23 (s, 1H), 3.98~3.97 (m, 1H), 3.25~3.24 (m, 2H), 3.03~2.99 (m, 2H), 2.29 (s, 3H), 1.95~1.80 (m, 4H); MS (*m/e*): 425.2(M+1).

Compound 133:

^{1}H NMR (DMSO-d6, 400 MHz): 9.93 (s, 1H), 8.63 (s, 2H), 8.46~8.43 (dd, J = 2.8Hz, 8.8Hz, 1H), 8.06 (s, 1H), 7.96~7.94 (d, J = 8.4Hz, 2H), 7.45~7.41 (t, J = 8.0Hz, 1H), 7.26~7.24 (m, 2H), 6.93 (s, 1H), 4.24 (s, 1H), 3.65~3.62 (t, J = 6.8Hz, 2H), 1.67~1.64 (m, 2H), 1.35~1.24 (m, 2H), 0.95~0.91 (t, J = 7.2Hz,3H); MS (*m/e*): 384.4(M+1).

Compound 134:

MS (*m/e*): 466.5(M+1).

Compound 135:

^{1}H NMR (CD3OD, 400 MHz): 8.79 (s, 1H), 8.62 (s, 1H), 8.55~8.33 (d, *J* = 8.8Hz, 1H), 8.13 (s, 1H), 8.04~8.02 (d, *J* = 8.0Hz, 1H), 7.88~7.85 (d, *J* = 8.0Hz, 1H), 7.46~7.40 (m, 2H), 6.91~6.90 (d, *J* = 3.2Hz, 1H), 4.23 (s, 1H), 3.74~3.71 (t, *J* = 6.4Hz, 2H), 2.57~2.54 (t, *J* = 6.4Hz, 2H), 2.27 (s, 6H); MS (*m/e*): 399.4(M+1).

Compound 136:

^{1}H NMR (DMSO-d6, 400 MHz): 10.41 (s, 1H), 8.84 (s, 1H), 8.62 (s, 1H), 8.06 (s, 1H), 8.57~8.54 (dd, *J* = 2.4Hz, 8.8Hz, 1H), 8.17 (s, 1H), 8.07~8.05 (d, *J* = 8.8Hz, 1H), 7.87~7.85 (d, *J* = 9.2Hz, 1H), 7.58~7.57 (d, *J* = 3.6Hz, 1H), 7.42~7.39 (t, *J* = 8.0Hz, 1H), 7.24~7.18 (m, 2H), 6.90 (s, 1H), 6.61 (d, *J* = 3.2Hz, 1H), 4.35~4.32 (t, *J* = 6.0Hz, 2H), 4.24 (s, 1H), 4.02~3.99 (t, *J* = 6.0Hz, 2H); MS (*m/e*): 422.5(M+1).

Compound 137:

^{1}H NMR (CD3OD, 400 MHz): 8.66~8.53 (m, 4H), 8.27~8.24 (dd, *J* = 2.0Hz, 9.2Hz, 1H), 7.91~7.79 (m, 4H), 7.50 (m, 1H), 7.43~7.39 (t, *J* = 8.0Hz, 1H), 7.31~7.29 (d, *J* = 7.6Hz, 1H), 7.18~7.17 (d, *J* = 3.2Hz, 1H), 6.90~6.89 (d, *J* = 3.2Hz, 1H), 5.02 (s, 2H), 3.38 (s, 1H); MS (*m/e*): 419.5(M+1).

Compound 138:

^{1}H NMR (DMSO-d6, 400 MHz): 9.96 (s, 1H), 8.66 (s, 1H), 8.63 (s, 1H), 8.45~8.43 (d, *J* = 8.4Hz, 1H), 8.05 (s, 1H), 7.95~7.87 (m, 2H), 7.45~6.99 (m, 8H), 6.99 (s, 1H), 6.61 (d, *J* = 3.2Hz, 1H), 4.88 (s, 2H), 4.24(s, 1H); MS (*m/e*): 436.5(M+1).

Compound 139:

^{1}H NMR (DMSO-d6, 400 MHz): 10.04 (s, 1H), 8.68 (s, 1H), 8.62 (s, 1H), 8.46~8.44 (d, J = 9.2Hz, 1H), 8.07 (s, 1H), 7.97~7.95 (d, J = 7.6Hz, 1H), 7.88-7.86 (d, J = 9.2Hz, 1H), 7.44~7.40 (t, J = 8.0Hz, 1H), 7.28 (s, 1H), 7.25~7.23 (d, J = 7.2Hz, 1H), 6.81 (s, 1H), 4.24 (s, 1H), 3.07 (s, 1H), 0.90 (bs, 4H); MS (*m/e*): 368.4(M+1).

Compound 140:

^{1}H NMR (CD3OD, 400 MHz): 8.60 (s, 1H), 8.58~8.57 (d, J = 2.4Hz, 1H), 8.25~8.22 (dd, J = 2.0Hz, 9.2Hz, 1H), 8.01 (s, 1H), 7.90~7.88 (d, J = 9.2Hz, 1H), 7.86-7.84 (d, J = 8.4Hz, 1H), 7.43~7.39 (t, J = 8.0Hz, 1H), 7.31~7.29 (d, J = 7.6Hz, 1H), 7.12 (s, 1H), 6.86 (s, 1H), 4.59~4.57 (m, 1H), 3.56 (s, 1H), 2.16~2.12 (m, 2H), 1.92~1.76 (m, 6H); MS (*m/e*): 396.4(M+1).

Compound 141:

^{1}H NMR (DMSO-d6, 400 MHz): 9.92 (s, 1H), 8.63 (s, 2H), 8.42~8.39 (dd, J = 2.4Hz, 9.2Hz, 1H), 8.01 (s, 1H), 7.95~7.93 (d, J = 9.2Hz, 1H), 7.88-7.86 (d, J = 9.2Hz, 1H), 7.44~7.40 (t, J = 8.0Hz, 1H), 7.25~7.23 (m, 2H), 7.03 (s, 1H), 4.23 (s, 1H), 4.10(bs, 1H), 3.04 (s, 2H), 1.88 (bs, 8H), 1.03 (bs, 3H); MS (*m/e*): 439.4(M+1).

Compound 142:

^{1}H NMR (CD3OD, 400 MHz): 9.88 (s, 1H), 8.64 (s, 1H), 8.61 (s, 1H), 8.42~8.40 (d, J = 8.8Hz, 1H), 8.04 (s, 1H), 7.93~7.88 (m, 2H), 7.50~7.49 (d, J = 4.8Hz, 1H), 7.45~7.41 (t, J = 7.6Hz, 1H), 7.26~7.24 (d, J = 7.6Hz, 1H), 7.23~7.22 (d, J = 2.8Hz, 1H), 7.15 (s, 1H), 7.04~7.02 (t, J = 4.0Hz, 1H), 6.97~6.96 (d, J = 2.8Hz, 1H), 5.04 (s, 2H), 4.24 (s, 1H); MS (*m/e*): 424.5 (M+1).

Compound 143:

^{1}H NMR (DMSO-d6, 400 MHz): 9.93 (s, 1H), 8.64 (s, 1H), 8.63 (s, 1H), 8.44~8.42 (dd, J = 2.0Hz, 8.8Hz, 1H), 8.05 (s, 1H), 7.95~7.93 (d, J = 8.4Hz, 1H), 7.90~7.88 (d, J = 8.8Hz, 1H), 7.45~7.43 (t, J = 8.0Hz, 1H), 7.27~7.25 (m, 2H), 6.86~6.85 (d, J = 3.2Hz, 1H), 6.00~5.93 (m, 1H), 5.24~5.16 (m, 2H), 4.29~4.27 (d, J = 5.2Hz, 2H), 4.24 (s, 1H); MS (*m/e*): 368.4 (M+1).

Compound 144:

^{1}H NMR (DMSO-d6, 400 MHz): 9.89 (s, 1H), 8.62 (bs, 2H), 8.42 (bs, 1H), 8.05 (s, 1H), 7.91~7.80 (m, 2H), 7.44 (bs, 1H), 7.25~7.14 (m, 2H), 6.99 (s, 1H), 4.25 (s, 1H), 3.61 (bs, 2H), 3.26 (bs, 2H), 3.04~2.90 (m, 2H), 2.08 (bs, 2H), 1.93~1.88 (m, 4H); MS (*m/e*): 453.5 (M+1).

Compound 145:

^{1}H NMR (CD3OD, 400 MHz): 9.91 (s, 1H), 8.64 (s, 1H), 8.63~8.62 (d, J = 2.0Hz, 1H), 8.39~8.36 (dd, J = 1.6Hz, 9.2Hz, 1H), 8.04 (s, 1H), 7.93~7.89 (m, 2H), 7.46~7.42 (t, J = 8.0Hz, 1H), 7.27 (s, 1H), 7.25~7.24 (d, J = 3.2Hz, 1H), 6.97~6.96 (d, J = 3.2Hz, 1H), 4.52~4.51 (d, J = 2.0Hz, 2H), 4.25 (s, 1H), 3.44 (s, 1H); MS (*m/e*): 366.4 (M+1).

Compound 146:

^{1}H NMR (CD3OD, 400 MHz): 9.88 (s, 1H), 8.63 (s, 1H), 8.60 (s, 1H), 8.43~8.41 (d, J = 8.8Hz, 1H), 8.03 (s, 1H), 7.93~7.87 (m, 2H), 7.46~7.42 (t, J = 7.6Hz, 1H), 7.26~7.24 (d, J = 8.0Hz, 1H), 7.21~7.20 (d, J = 3.2Hz, 1H), 6.94~6.93 (d, J = 2.8Hz, 1H), 4.25 (s, 1H), 3.66~3.63 (t, J = 6.8Hz, 2H), 2.48~2.39 (m, 6H), 1.79~1.76 (m, 2H), 0.96~0.93 (t, J = 7.2Hz, 6Hz); MS (*m/e*): 441.5 (M+1).

Compound 147:

^{1}H NMR (DMSO-d6, 400 MHz):10.11 (s,1H), 8.72 (d, J = 2.0Hz, 1H), 8.63 (s,1H), 8.59 (dd, J = 2.0Hz, J = 2.0Hz, 1H), 8.10 (s,1H), 7.99 (d, J = 8.0Hz,1H), 7.88 (d, J = 9.2Hz,1H),7.43 (t, J = 8.0Hz,1H), 7.35 (d, J = 2.8Hz,1H), 7.24 (d, J = 7.6Hz,1H), 6.88 (d, J = 2.8Hz,1H), 4.23 (s,1H), 3.80-3.78 (m, 2H), 3.65-3.62 (m, 2H), 3.51-3.48 (m, 2H),1.14-1.08 (m, 3H); MS (*m/e*): 400 (M+1).

Compound 148:

^{1}H NMR (CD_3OD, 400 MHz): 9.88 (s, 1H), 8.62 (s, 1H), 8.60 (s, 1H), 8.03 (s, 1H), 7.93~7.91 (d, J = 8.0Hz, 1H), 7.89~7.87 (d, J = 9.2Hz, 1H), 7.45~7.43 (t, J = 8.0Hz, 1H), 7.26~7.24 (d, J = 7.2Hz, 1H), 7.18~7.17 (d, J = 3.2Hz, 1H), 6.91~6.90 (d,

J = 2.8Hz, 1H), 4.23 (s, 1H), 3.75~3.72 (t, *J* = 6.4Hz, 2H), 2.59~2.56 (t, *J* = 6.4Hz, 2H), 2.51~2.40 (m, 4H), 2.38~2.32 (m, 4H), 2.14 (s, 3H); MS (*m/e*): 454.5 (M+1).

Compound 149:

^{1}H NMR (CD_3OD, 400 MHz): 9.92 (s, 1H), 8.63 (s, 1H), 8.60 (s, 1H), 8.44~8.42 (d, *J* = 8.8Hz, 1H), 8.04 (s, 1H), 7.96~7.87 (m, 2H), 7.46~7.42 (t, *J* = 7.6Hz, 1H), 7.26~7.24 (d, *J* = 7.6Hz, 1H), 7.18~7.17 (d, *J* = 2.8Hz, 1H), 6.91~6.90 (d, *J* = 2.4Hz, 1H), 4.25 (s, 1H), 3.37~3.69 (m, 1H), 3.52~3.47 (m, 1H), 2.30~2.26 (m, 2H), 2.19~2.06 (m, 2H), 1.78~1.71 (m, 2H), 1.65~1.59 (m, 2H), 1.42~1.45 (m, 1H), 1.07~1.10 (m, 3H); MS (*m/e*): 439.5 (M+1).

Compound 150:

^{1}H NMR (CD_3OD, 400 MHz): 8.57 (s, 1H), 8.53 (s, 1H), 8.22~8.20 (dd, *J* = 1.6Hz, 9.2Hz, 1H), 7.99 (s, 1H), 7.89~7.87 (d, *J* = 8.8Hz, 1H), 7.84~7.82 (d, *J* = 8.0Hz, 1H), 7.39~7.37 (t, *J* = 7.6Hz, 1H), 7.29~7.27 (d, *J* = 7.2Hz, 1H), 7.03~7.02 (d, *J* = 2.8Hz, 1H), 6.82~6.81 (d, *J* = 3.2Hz, 1H), 4.16~4.12 (t, *J* = 6.8Hz, 2H), 3.56 (s, 1H), 2.59~2.56 (t, *J* = 6.4Hz, 2H); MS (*m/e*): 400.4(M+1).

Compound 151:

^{1}H NMR (CD_3OD, 400 MHz): 8.58~8.57 (m, 2H), 8.25~8.22 (dd, *J* = 2.0Hz, 8.8Hz, 1H), 7.98 (s, 1H), 7.92~7.89 (d, *J* = 8.8Hz, 1H), 7.86~7.84 (d, *J* = 8.0Hz, 1H), 7.43~7.39 (t, *J* = 7.6Hz, 1H), 7.31~7.29 (d, *J* = 7.2Hz, 1H), 7.09~7.08 (d, *J* = 2.8Hz, 1H), 6.80~6.79 (d, *J* = 3.2Hz, 1H), 3.86~3.83 (t, *J* = 6.4Hz, 2H), 3.53 (s, 1H), 2.91~2.88 (t, *J* = 6.8Hz, 2H), 2.26~2.22 (m, 2H), 1.85~1.66 (m, 5H); MS (*m/e*): 425.1(M+1).

Compound 152:

^{1}H NMR (CD_3OD, 400 MHz): 8.61 (s, 1H), 8.53 (s, 1H), 8.22~8.20 (dd, *J* = 1.6Hz, 9.2Hz, 1H), 7.99 (s, 1H), 7.89~7.87 (d, *J* = 8.8Hz, 1H), 7.84~7.82 (d, *J* = 8.0Hz, 1H), 7.39~7.37 (t, *J* = 7.6Hz, 1H), 7.29~7.27 (d, *J* = 7.2Hz, 1H), 7.03~7.02 (d, *J* = 2.8Hz, 1H), 6.83~6.82 (d, *J* = 2.8Hz, 1H), 4.08~4.05 (t, *J* = 6.8Hz, 2H), 3.55 (s, 1H), 3.52~3.40 (m, 4H), 2.85~2.82 (t, *J* = 6.8Hz, 2H), 2.00~1.89 (m, 4H); MS (*m/e*): 453.4(M+1).

Compound 153:

^{1}H NMR (CD_3OD, 400 MHz): 8.59 (s, 1H), 8.57~8.56 (d, J = 2.0Hz, 1H), 8.24~8.21 (dd, J = 2.4Hz, 8.8Hz, 1H), 7.99 (s, 1H), 7.90~7.88 (d, J = 8.8Hz, 1H), 7.84~7.82 (d, J = 7.2Hz, 1H), 7.42~7.38 (t, J = 8.0Hz, 1H), 7.30~7.28 (d, J = 7.6Hz, 1H), 7.10~7.09 (d, J = 3.2Hz, 1H), 6.81~6.80 (d, J = 3.6Hz, 1H), 3.90~3.87 (t, J = 5.6Hz, 2H), 3.54 (s, 1H), 3.45~3.42 (t, J = 6.0Hz, 2H), 2.94 (s, 3H); MS (*m/e*): 449.5 (M+1).

Compound 154:

^{1}H NMR (CD_3OD, 400 MHz): 8.58 (s, 1H), 8.56~8.55 (d, J = 2.0Hz, 1H), 8.23~8.20 (dd, J = 2.4Hz, 8.8Hz, 1H), 7.99 (s, 1H), 7.89~7.87 (d, J = 8.8Hz, 1H), 7.84~7.82 (d, J = 8.0Hz, 1H), 7.41~7.37 (t, J = 8.0Hz, 1H), 7.29~7.27 (d, J = 7.6Hz, 1H), 7.08~7.07 (d, J = 2.8Hz, 1H), 6.80~6.79 (d, J = 3.6Hz, 1H), 3.96~3.93 (t, J = 5.6Hz, 2H), 3.53 (s, 1H), 3.52~3.48 (t, J = 5.6Hz, 2H), 2.94 (s, 3H), 2.84 (s, 3H); MS (*m/e*): 463.5 (M+1).

Compound 155:

^{1}H NMR (CD_3OD, 400 MHz): 8.58 (s, 1H), 8.56~8.55 (d, J = 2.0Hz, 1H), 8.23~8.20 (dd, J = 2.0Hz, 8.8Hz, 1H), 7.98 (s, 1H), 7.89~7.87 (d, J = 9.2Hz, 1H), 7.84~7.82 (d, J = 8.0Hz, 1H), 7.41~7.37 (t, J = 7.6Hz, 1H), 7.29~7.27 (d, J = 8.0Hz, 1H), 7.07~7.06 (d, J = 2.8Hz, 1H), 6.73~6.72 (d, J = 2.8Hz, 1H), 3.85~3.82 (t, J = 5.6Hz, 2H), 3.55~3.52 (t, J = 6.0Hz, 2H), 3.52 (s, 1H), 1.56~1.52 (m, 1H), 0.83~0.81 (m, 2H), 074~0.71 (m, 2H); MS (*m/e*): 439.5 (M+1).

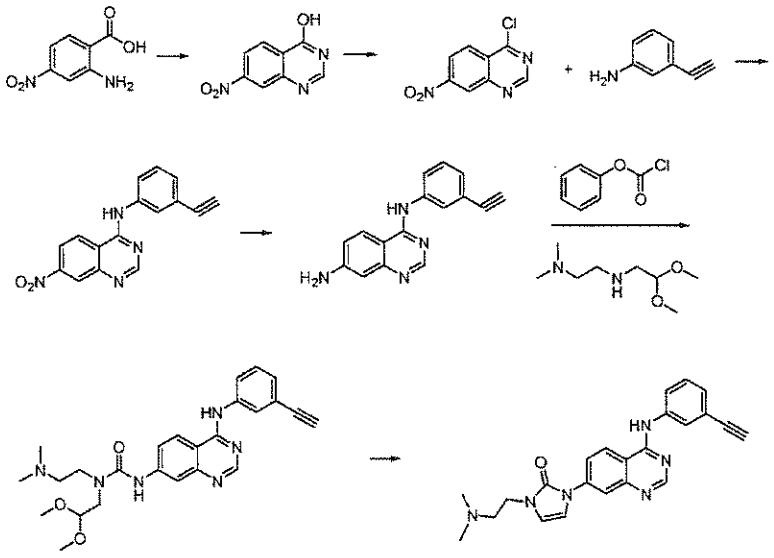
Compound 156:

^{1}H NMR (CD_3OD, 400 MHz): 8.61 (d, J = 2.0Hz, 1H), 8.60~8.56 (dd, J = 2.0Hz, 1H), 8.24~8.21 (dd, J = 2.0Hz, 9.2Hz, 1H), 8.01~7.99 (dd, J = 2.0Hz, 4.4Hz, 1H), 7.92~7.91 (dd, J = 2.4Hz, 9.2Hz, 1H), 7.86~7.84 (d, J = 8.0Hz, 1H), 7.43~7.39 (t, J = 8.0Hz, 1H), 7.32~7.30 (d, J = 8.0Hz, 1H), 4.05~4.02 (t, J = 5.6Hz, 1H), 3.98~3.96 (t, J = 5.6Hz, 1H), 3.94~3.92 (t, J = 5.6Hz, 1H), 3.78~3.75 (t, J = 5.6Hz,

1H), 3.55 (s, 1H), 3.27 (s, 1.5H), 3.05 (s, 1.5H), 1.92~1.85 (m, 1H), 0.82~0.77 (m, 3H), 0.69~0.65 (m, 1H); MS (*m/e*): 453.5 (M+1).

Example 157: Synthesis of 3-(2-(dimethylamino)ethyl)-1- (4-(3-ethynylphenylamino)quinazolin-7-yl)-1H-imidazol-2(3H)-one (Compound 157)

The Synthetic route to Compound 157 is shown below:



To a solution of 2-amino-4-nitrobenzoic acid (6.00 g, 32.94 mmol) in ethanol (40 mL) was added formamidin acetate (6.80 g, 65.32 mmol). The reaction mixture was refluxed for 5 h and cooled to room temperature and refrigerated. The precipitate was filtered out, washed with several portions of cooled ethanol, and then dried in vacuo to give 5.60 g (89%) of 7-nitroquinazolin-4-ol as a yellow solid.

A mixture of 7-nitroquinazolin-4-ol (3.4 g, 17.79 mmol), thionyl chloride (20 mL), and DMF (0.5 mL) was refluxed for 48h. After the mixture was cooled to room temperature, excess thionyl chloride was removed by evaporation and the residue was azeotroped with toluene to afford 2.61g (70%) of product 4-chloro-7-nitroquinazoline as a yellowish solid.

A mixture of 4-chloro-7-nitroquinazoline (2.0 g, 9.54 mmol), isopropanol (30 mL), and 3-thynylbenzenamine (1.2 g, 10.00 mmol) was refluxed for 5 h. The resulting mixture was cooled to room temperature and refrigerated. The precipitate

was filtered out, washed with cold isopropanol several times, and dried in vacuo to give 2.6 g (94%) of N-(3-ethynylphenyl)-7-nitroquinazolin-4-amine as a yellow solid.

N-(3-ethynylphenyl)-7-nitroquinazolin-4-amine (2.0 g, 6.89 mmol), $SnCl_2$ (5.0 g, 26.37 mmol), and ethyl acetate (50 mL) was refluxed for 3h. The mixture was subjected to extraction with ethyl acetate (20 mL). The combined organic layers were washed with brine (20 mL×2), dried over Na_2SO_4, and concentrated in vacuo to afford 1.6 g (86%) of N4-(3-ethynylphenyl)quinazoline-4,7-diamine as a yellow solid.

A mixture of N4-(3-ethynylphenyl)quinazoline-4,7-diamine (48mg, 0.18mmol), phenyl carbonochloridate (25.2uL, 0.18mmol), pyridine (32 μL), and DMF (2 mL) was stirred at room temperature for 1.5 h. To this was added N1-(2,2-dimethoxyethyl)-N2,N2-dimethylethane-1,2-diamine (33.5 mg, 0.19 mmol). The mixture was stirred at 80°C for 1 h and then p-toluenesulfonic acid (35.6 mg, 0.20 mmol) was added. The mixture was stirred at 80°C for additional 1 h. After cooled to room temperature, it was diluted with ethyl acetate and washed with water and brine. The combined organic layers were concentrated and purified with silica column to give Compound 157 as a yellow solid in 75% yield.

^{1}H NMR (CD_3OD, 400 MHz): 8.57 (s, 1H), 8.48~8.47 (d, J = 3.6Hz, 1H), 8.46 (s, 1H), 8.09 (s, 1H), 8.07 (s, 1H), 7.98 (s, 1H), 7.83~7.81 (d, J = 8.0Hz, 1H), 7.42~7.38 (t, J = 8.0Hz, 1H), 7.31~7.29 (d, J = 7.6Hz, 1H), 7.13~7.12 (d, J = 2.8Hz, 1H), 6.83~6.82 (d, J = 2.8Hz, 1H), 3.89~3.85 (t, J = 6.8Hz, 2H), 3.56 (s, 1H), 2.72~2.69 (t, J = 6.4Hz, 2H), 2.35 (s, 6H); MS (*m/e*): 399.4 (M+1).

Examples 158-163: Synthesis of Compounds 158-163

Compounds 158-163 were prepared in a manner similar to that described in Example 157.

Compound 158:

^{1}H NMR (CD_3OD, 400 MHz): 8.59 (s, 1H), 8.52~8.49 (d, J = 8.8Hz, 1H), 8.11~8.08 (d, J = 2.4Hz, 1H), 8.09~8.08 (d, J = 2.4Hz, 1H), 7.98 (s, 1H), 7.83~7.81 (d, J = 8.0Hz, 1H), 7.43~7.39 (t, J = 7.6Hz, 1H), 7.32~7.30 (d, J = 7.6Hz, 1H), 7.18~7.17 (d, J = 2.8Hz, 1H), 6.85~6.84 (d, J = 3.2Hz, 1H), 3.81~3.77 (t, J = 6.8Hz, 2H), 3.56 (s, 1H), 2.74~2.67 (m, 6H), 2.02~1.95 (m, 2H), 1.14~1.10 (t, J = 7.2Hz, 6H); MS (*m/e*): 441.5 (M+1).

Compound 159:

^{1}H NMR (MeOD, 400 MHz): 8.58 (s, 1H), 8.48~8.45 (dd, J = 1.6Hz, 8.0Hz, 1H), 8.09~8.08 (d, J = 2.4Hz, 1H), 8.07 (s, 1H), 7.98 (s, 1H), 7.83~7.81 (d, J = 8.0Hz, 1H), 7.42~7.38 (t, J = 8.0Hz, 1H), 7.31~7.29 (d, J = 7.2Hz, 1H), 7.12~7.11 (d, J = 2.8Hz, 1H), 6.84~6.83 (d, J = 3.2Hz, 1H), 3.90~3.85 (m, 1H), 3.67~3.64 (m, 1H), 3.55 (s, 1H), 3.23~3.18 (m, 1H), 3.01~2.94 (m, 1H), 2.86~2.82 (m, 1H), 2.44~2.38 (m, 1H), 2.32~2.26 (m, 1H), 1.98~1.91 (m, 1H), 1.75~1.69 (m, 1H), 1.18 (s, 3H); MS (*m/e*): 439.5 (M+1).

Compound 160:

^{1}H NMR (CD_3OD, 400 MHz): 8.59 (s, 1H), 8.51~8.49 (dd, J = 2.0Hz, 7.6Hz, 1H), 8.13~8.12 (d, J = 2.0Hz, 1H), 8.11~8.10 (d, J = 2.0Hz, 1H), 7.98 (s, 1H), 7.83~7.81 (d, J = 8.0Hz, 1H), 7.43~7.39 (t, J = 8.4Hz, 1H), 7.32~7.30 (d, J = 8.0Hz, 1H), 7.16~7.15 (d, J = 3.6Hz, 1H), 6.82~6.81 (d, J = 3.2Hz, 1H), 3.82~3.78 (t, J = 7.2Hz, 2H), 3.61 (s, 1H), 2.73~2.33 (m, 10H), 2.28 (s, 3H), 2.00~1.93 (m, 2H); MS (*m/e*): 468.5 (M+1).

Compound 161:

^{1}H NMR (CD_3OD, 400 MHz): 8.59 (s, 1H), 8.51~8.49 (d, J = 9.6Hz, 1H), 8.11~8.08 (m, 2H), 7.98 (s, 1H), 7.83~7.81 (d, J = 8.0Hz, 1H), 7.43~7.39 (t, J = 7.6Hz, 1H), 7.32~7.30 (dd, J = 1.6Hz, 6.8Hz, 1H), 7.17~7.16 (d, J = 3.2Hz, 1H), 6.86~6.85 (d, J = 2.8Hz, 1H), 3.85~3.78 (t, J = 6.8Hz, 2H), 3.55 (s, 1H), 3.12~3.07 (m, 1H), 2.38 (s, 3H), 2.30~2.12 (m, 4H), 1.85~1.78 (m, 2H), 1.69~1.55 (m, 2H); MS (*m/e*): 439.5 (M+1).

Compound 162:

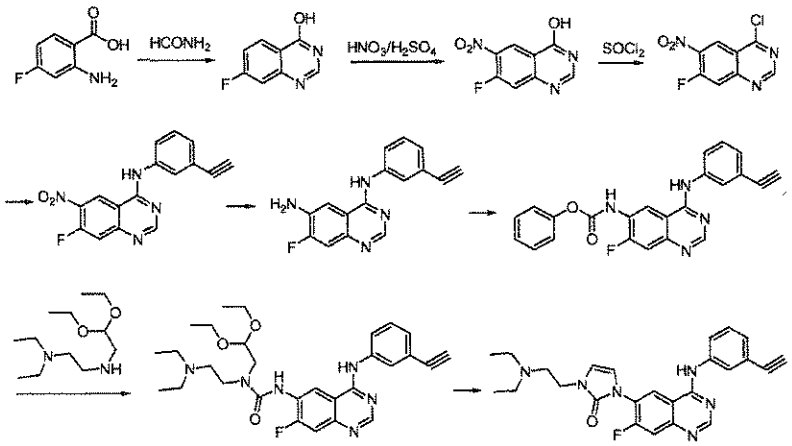
^{1}H NMR (CD_3OD, 400 MHz): 8.59 (s, 1H), 8.51~8.48 (d, J = 10.0Hz, 1H), 8.11~8.09 (m, 2H), 7.98 (s, 1H), 7.84~7.81 (d, J = 8.8Hz, 1H), 7.43~7.39 (t, J = 8.0Hz, 1H), 7.32~7.30 (d, J = 7.6Hz, 1H), 7.15~7.14 (d, J = 3.2Hz, 1H), 6.88~6.87 (d, J = 2.8Hz, 1H), 3.77~3.73 (t, J = 7.2Hz, 2H), 3.54 (s, 1H), 3.54~3.50 (t, J = 7.2Hz, 2H), 3.42~3.39 (t, J = 7.2Hz, 1H), 2.44~2.40 (t, J = 7.6Hz, 2H), 2.12~2.07 (m, 2H), 2.04~1.99 (m, 2H); MS (*m/e*): 453.5 (M+1).

Compound 163:

^{1}H NMR (CD_3OD, 400 MHz): 8.60 (s, 1H), 8.53~8.50 (d, J = 10.0Hz, 1H), 8.12~8.10 (m, 2H), 7.99 (s, 1H), 7.84~7.82 (d, J = 8.0Hz, 1H), 7.84~7.82 (d, J = 8.0Hz, 1H), 7.44~7.41 (t, J = 7.6Hz, 1H), 7.33~7.31 (d, J = 7.2Hz, 1H), 7.19~7.18 (d, J = 2.8Hz, 1H), 6.86~6.85 (d, J = 3.6Hz, 1H), 3.94~3.91 (t, J = 6.8Hz, 2H), 3.56 (s, 1H), 3.26~3.23 (m, 2H), 3.03 (s, 3H), 2.30~2.26 (m, 2H); MS (*m/e*): 448.4(M+1).

Example 164: Synthesis of 3-(2-(diethylamino)ethyl)-1- (4-(3-ethynylphenylamino)-7-fluoroquinazolin-6-yl)-1H-imidazol-2(3H)-one (Compound 164)

The synthetic route to Compound 164 is shown below:



2-amino-4-fluorobenzoic acid (1.55 g, 10 mmol) was dissolved into formamide (5 mL) and stirred at 150°C for 6 h. The mixture was cooled to room temperature with stirring. The precipitate was filtered out and washed with diethyl ether to give 1.3 g of 7-fluoroquinazolin-4-ol (78%).

7-Fluoroquinazolin-4-ol (1g, 6.0 mmol) was dissolved in concentrated H_2SO_4 (3 mL) at 0°C. Concentrated HNO_3 (3 mL) was added dropwise with stirring in 15min. The mixture was stirred at 100°C for 3 h and cooled to room temperature. The mixture was poured into ice-water with stirring. The precipitate was filtered and recrystallized in HOAc to give 0.60 g of 7-fluoro-6-nitroquinazolin-4-ol (38%).

7-Fluoro-6-nitroquinazolin-4-ol (518mg, 2mmol) was dissolved into thionyl chloride (3 mL) containing 2 drops of DMF. The solution was refluxed for 3 h. The

solvent was removed under reduced pressure to afford 4-chloro-7-fluoro-6-nitroquinazoline, which was used directly in the next step without purification.

4-Chloro-7-fluoro-6-nitroquinazolineand 3-ethynylbenzenamine (234 mg, 2 mmol) was dissolved into isopropanol (5 mL). The mixture was refluxed for 3 h and cooled to room temperature. The precipitate was filtered and washed with water to give 0.59 g of N-(3-ethynylphenyl)-7-fluoro-6-nitroquinazolin-4-amine (95%).

A mixture of N-(3-ethynylphenyl)-7-fluoro-6-nitroquinazolin-4-amine (310 mg, 1 mmol) and $SnCl_2 \cdot 2H_2O$ (171 mg, 4.5 mmol) in ethyl acetate (35 mL) was refluxed for 2 h. After cooled to room temperature, the mixture was treated with 5% aqueous $NaHCO_3$ to adjust its pH to 9-10, and then subjected to extraction with EtOAc. The organic layers were washed with saturated brine and H_2O and dried. The solvent was removed under reduced pressure to give 225 mg (81%) N4-(3-ethynylphenyl)-7-fluoroquinazoline-4,6-diamine as a yellow solid.

N4-(3-ethynylphenyl)-7-fluoroquinazoline-4,6-diamine (50 mg, 0.18 mmol) was dissolved into DMF (2 mL) containing pyridine (17.5μL, 0.21mmol). Phenyl chloroformate (23 μL, 0.18 mmol) was added to the mixture at room temperature and stirred at 70°C for 1 h to give phenyl 4-(3-ethynylphenylamino) -7-fluoroquinazolin-6-ylcarbamate. N1-(2,2-diethoxyethyl)-N2,N2 -diethylethane-1,2-diamine (42mg, 0.18mmol) was added and stirred at 70°C for 2.5 h. After cooled to room temperature, the reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was concentrated and purified with a silica column to give 45 mg (70%) of 1-(2,2-diethoxyethyl)-1-(2-(diethylamino) ethyl)-3-(4-(3-ethynylphenylamino)-7-fluoroquinazolin-6-yl)urea.

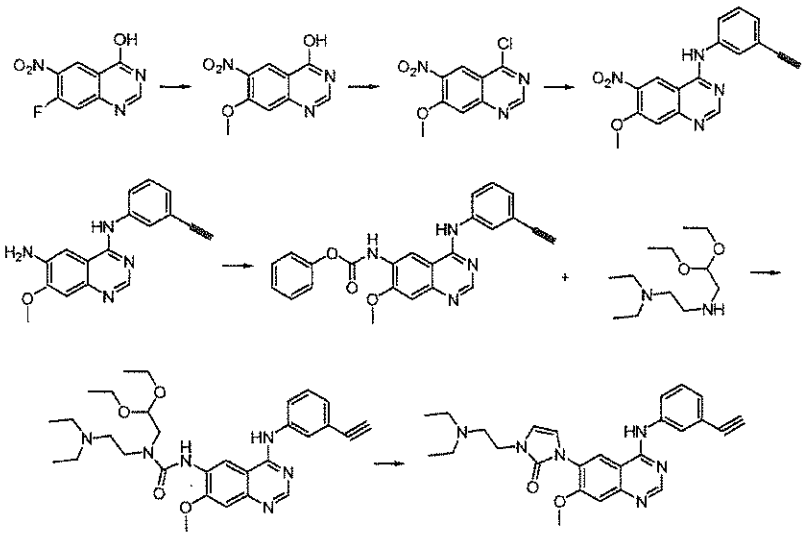
To a solution of 1-(2,2-diethoxyethyl)-1-(2- (diethylamino)ethyl) -3-(4-(3-ethynylphenylamino)-7-fluoroquinazolin-6-yl)urea (45 mg, 0.08 mmol) in DMF (2 mL) was added p-toluenesulfonic acid (28.5 mg, 0.15 mmol). The mixture was stirred at 80°C for 1 h and then cooled to room temperature. It was diluted with ethyl acetate and washed with water and brine. The organic layer was concentrated and purified with a silica column to give Compound 164 as yellow solid in 90% yield.

^{1}H NMR (DMSO-d6, 400 MHz):10.18 (s,1H), 8.89 (d, J = 8.0Hz, 1H), 8.67 (s,1H), 8.06 (s,1H), 7.93(d, J = 7.6Hz,1H), 7.65(d, J = 11.2Hz,1H), 7.42 (t, J = 8.0Hz,1H), 7.25 (d, J = 7.2Hz, 1H),6.88 (s, 1H) 6.87 (d, J=2.8Hz, 1H), 4.24 (s,1H),

3.66 (t, *J*=2.8Hz, 2H), 2.66 (t, *J*=6.4Hz, 2H), 2.49-2.53 (m,4H), 0.98-0.93 (m,6H); MS (*m/e*): 445 (M+1).

Example 165: Synthesis of 3-(2-(diethylamino)ethyl)-1-(4- (3-ethynylphenylamino)-7-methoxyquinazolin-6-yl)-1H-imidazol-2(3H)-one (Compound 165)

The synthetic route to Compound 165 is shown below:



Sodium (92 mg, 4 mmol) was dissolved in methanol (4 mL) under nitrogen at 0°C. 7-Fluoro-6-nitroquinazolin-4-ol (418mg, 2mmol) was added. The mixture was refluxed for 3 h and cooled to room temperature and treated with 2N HCl to adjust its pH to 3-4. After the mixture was concentrated, the residue was diluted with ethyl acetate and washed with water twice. The organic layer was concentrated to give 405 mg (92%) of 7-methoxy-6-nitroquinazolin-4-ol.

7-Methoxy-6-nitroquinazolin-4-ol was converted to Compound 165 in a manner similar to that described in Example 160.

^{1}H NMR (DMSO-d6, 400 MHz):9.98 (s,1H), 8.69 (s,1H), 8.63 (s,1H), 8.05 (s,1H), 7.92 (d, *J* = 7.2Hz,1H), 7.35-7.29 (m, 2H), 7.21 (d, *J* = 7.6Hz, 1H), 6.75 (d, *J*=2.0Hz, 1H), 6.58 (d, *J*=2.8Hz, 1H), 4.15 (s,1H), 3.91 (s,3H), 3.64 (t, *J*=7.6Hz, 2H), 2.65 (t, *J*=7.2Hz, 2H),2.58 (m,4H), 0.97 (m,6H); MS (*m/e*): 457 (M+1).

Examples 166-170: Synthesis of Compounds 166-170

Compounds 166-170 were prepared in a manner similar to that described in Example 165.

Compound 166:

^{1}H NMR (DMSO-d6, 400 MHz):9.90 (s,1H), 8.67 (s,1H), 8.62 (s,1H), 8.08 (s,1H), 7.92 (d, *J* = 8.4Hz,1H), 7.42-7.37 (m, 2H), 7.21 (d, *J* = 7.6Hz, 1H), 6.72 (s,2H), 4.22 (s,1H), 3.95 (s,3H), 3.77 (t, *J*=2.8Hz, 2H), 3.59 (t, *J*=4.8Hz, 2H),3.31 (s,3H); MS (*m/e*): 416 (M+1).

Compound 167:

^{1}H NMR (DMSO-d6, 400 MHz):9.94 (s,1H), 8.69 (s,1H), 8.62 (s,1H), 8.09 (s,1H), 7.93 (d, *J* = 7.6Hz,1H), 7.42-7.37 (m, 2H), 7.21 (d, *J* = 7.6Hz, 1H), 6.79 (d, *J*=2.4Hz, 1H), 6.73 (d, *J*=2.4Hz, 1H), 4.22 (s,1H), 3.94 (s,3H), 3.75 (t, *J*=2.8Hz, 2H), 3.68-3.57(m,4H), 3.59 (t, *J*=4.8Hz, 2H), 2.51-2.48(m,4H); MS (*m/e*): 471(M+1).

Compound 168:

^{1}H NMR (DMSO-d6, 400 MHz):9.90 (s,1H), 8.66 (s,1H), 8.62 (s,1H), 8.08 (s,1H), 7.92 (d, *J* = 8.0Hz,1H), 7.42-7.37 (m, 2H), 7.21 (d, *J* = 7.2Hz, 1H), 6.76 (d, *J*=2.8Hz, 1H), 6.70 (d, *J*=2.8Hz, 1H), 4.24 (s,1H), 3.94 (s,3H), 3.71 (t, *J*=6.0Hz, 2H), 2.56 (t, *J*=8.4Hz, 2H), 2.42 (s,8H), 2.34(s,3H); MS (*m/e*): 484 (M+1).

Compound 169:

^{1}H NMR (DMSO-d6, 400 MHz):9.94 (s,1H), 8.69 (s,1H), 8.62 (s,1H), 8.08 (s,1H), 7.92 (d, *J* = 8.0Hz,1H), 7.41-7.35 (m, 2H), 7.21 (d, *J* = 7.6Hz, 1H), 6.76 (d, *J*=2.4Hz, 1H), 6.72 (d, *J*=2.4Hz, 1H), 4.24 (s,1H), 3.93 (s,3H), 3.72 (t, *J*=6.8Hz, 2H), 2.46-2.50 (m, 6H), 1.80 (t, *J*=7.2Hz, 2H), 1.00-0.96 (m, 6H); MS (*m/e*): 471 (M+1).

Compound 170:

^{1}H NMR (DMSO-d6, 400 MHz):9.92 (s,1H), 8.67 (s,1H), 8.65 (s,1H), 8.07 (s,1H), 7.91 (d, *J* = 8.8Hz,1H), 7.43-7.39 (m, 2H), 7.22 (d, *J* = 7.2Hz, 1H), 6.78 (s, 2H), 4.49 (d, *J* = 2.0Hz, 2H), 4.23 (s,1H), 3.95(s,3H); MS (*m/e*): 396 (M+1).

Example 171: Inhibition of EGFR activity

A431 cells (human epidermoid carcinoma) were seeded in DMEM at 2.5×10^4 cells/well in 96-well plates and incubated overnight. The DMEM medium was

discarded and the plates were washed with 200 μL of serum-free DMEM medium. After the medium was discarded, 90 μL serum-free DMEM medium was added to each well. The plates were incubated again overnight.

Each test compound was dissolved in DMSO-containing (5%) FBS-free DMEM to prepare a series of solutions at the concentrations of 10, 3.3, 1.1, 0.37, 0.12, 0.04, 0.013, and 0.004 μM. Solutions of compounds at various concentrations were added to wells (10 μL/well) except controls. The plates were incubated under 5% CO_2 at 37°C for 60 min. 10 μL of 200 ng/ml EGF (Biosource, PHG0064) was added to each of the compound-treated wells and some of the controls, followed by incubation under 5% CO_2 at 37°C again for 45 min.

After removal of the medium, to each well was added 100 μL of cell lysis buffer containing 50 mM Tris-Cl (pH 8.0), 0.5 M NaCl and 0.2 mM EDTA, 0.1% Triton X-100, and protease inhibitors (1 μg/ml aprotinin, 0.75 μg/ml leupeptin, 1 μg/ml pepstatin, 1 mM DTT, 500 μM sodium vanadate, and 1 mM PMSF). Note that the protease inhibitors were added immediately before use. The cell lysate was kept at -80°C overnight

100 μL of 0.5 μg/ml anti-EGFR antibody (Perkin Elmer, AF231) in PBS was added to a 96-well DELFIA yellow plate (Perkin Elmer, AAAND-0001) and incubated at 25°C overnight with gentle shaking. The medium was discarded and the plate was washed with 200 μL of DELFIA wash buffer 3 times. 200 μL of blocking buffer (PBS buffer containing 0.137 M NaCl, 0.0027 M KCl, 0.01 M Na_2PO_4-$12H_2O$, 0.0015 M KH_2PO_4, pH=7.4, and 1% BSA) was added to initiate the blocking procedure. The plate was incubated at 25°C for 1 h with gentle shaking.

The blocking buffer was discarded and the plate was washed with 200 μL of DELFIA wash buffer (PBS buffer containing 0.05% Tween-20) 3 times. 80 μL of sample diluent (20 mM Tris-Cl/pH7.3, 150 mM NaCl, 0.1% BSA, and 0.05% Tween-20) and 20 μL of the above-obtained cell lysate were then added to each well. Incubation was continued at 25°C for 1 h with gentle shaking.

The plate was washed again with 200 μL of DELFIA wash buffer 3 times. 100 μL of 0.5 μg/ml Eu-PT66 antibody (Perkin Elmer, AD0040) in DELFIA assay buffer (Perkin Elmer, 1244-106) was added and incubated at 25°C for 1 h with gentle shaking. After washing with 200 μL of DELFIA wash buffer 3 times, 100 μL of

DELFIA enhancement (Perkin Elmer, 4001-0010) was added. The incubation was continued at 25°C for 30 min with gentle shaking.

Fluorescence was measured at 620 nm by Victor^3 (340 nm excitation and 620 nm emission)

Inhibition rates were calculated as follows:

$$\text{Inhibition (\%)} = 100 - \frac{\text{signal of compound well - signal of cell well}}{\text{signal of EGF well - signal of cell well}} \text{ X } 100\%$$

where "signal of compound well" represents the fluorescence detected from the well which contained cells, a test compound, and EGF; "signal of cell well" represents the fluorescence detected from the well which contained cells, but not a test compound and EGF; and "signal of EGF well" represents the fluorescence detected from the well which contained cells and EGF, but not a test compound.

IC_{50} values (concentration required to inhibit EGFR activity by 50%) were subsequently calculated using the XL-Fit 2.0 software.

The results show that all of Compounds 1-170 inhibited EGFR activity. Their IC_{50} values ranged from 0.001 μM to 10 μM.

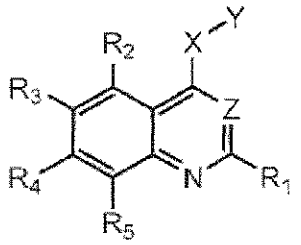
OTHER EMBODIMENTS

All of the features disclosed in this specification may be combined in any combination. Each feature disclosed in this specification may be replaced by an alternative feature serving the same, equivalent, or similar purpose. Thus, unless expressly stated otherwise, each feature disclosed is only an example of a generic series of equivalent or similar features.

From the above description, one skilled in the art can easily ascertain the essential characteristics of the present invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. For example, compounds structurally analogous to the compounds of this invention can be made and used to practice this invention. Thus, other embodiments are also within the claims.

WHAT IS CLAIMED IS:

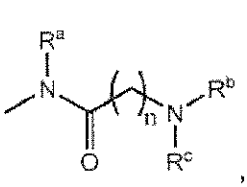
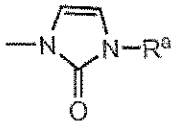
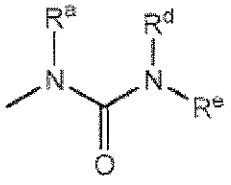
1. A compound of the following formula:



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;

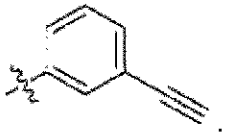
Y is phenyl substituted with alkynyl, or

fused with another 3-8 membered ring; and

Z is N or C-CN.

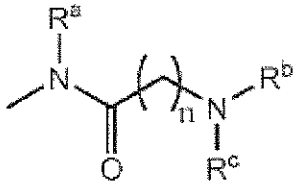
2. The compound of claim 1 and/or a pharmaceutically acceptable salt thereof, wherein Z is N.

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

4. The compound of claim 1 and/or a pharmaceutically acceptable salt thereof, wherein Y is .

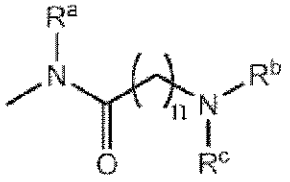
5. The compound of claim 4 and/or a pharmaceutically acceptable salt thereof, wherein X is O, NH, or N-CH_3 and Z is N.

6. The compound of claim 1 or 5 and/or a pharmaceutically acceptable salt thereof,



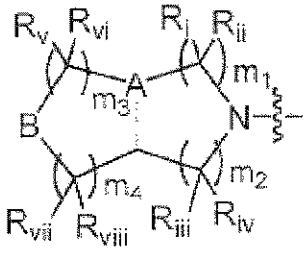
wherein one of R_3 and R_4 is , in which n is 1 and each of R^a, R^b, and R^c, independently, is H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

7. The compound of claim 1 or 5 and/or a pharmaceutically acceptable salt thereof,



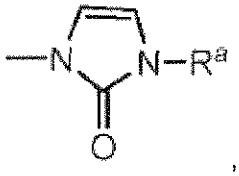
wherein one of R_3 and R_4 is ,in which n is 1 or 2; R^a is H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and R^b and R^c, together with the nitrogen atom to which they are attached, form a 3-12 membered saturated, unsaturated, or aromatic ring containing 1-3 heteroatoms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

8. The compound of claim 7 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:

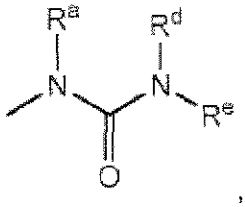


wherein each of m_1, m_2, m_3, and m_4, independently, is 0,1,2, or 3; A is N or CR; B is NR or CRR', each R and R', independently, being H, alkyl, or halo; and each of R_i, R_{ii}, R_{iii}, R_{iv}, R_v, R_{vi}, R_{vii}, and R_{viii}, independently, is H, alkyl, or halo.

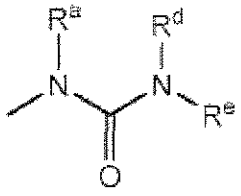
9. The compound of claim 1 or 5 and/or a pharmaceutically acceptable salt thereof,

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

10. The compound of claim 1 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. The compound of claim 1 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.

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

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

14. A compound of claim 1 and/or a pharmaceutically acceptable salt thereof for use in treating cancer.

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