QUINAZOLINE DERIVATIVES FOR INHIBITING CANCER CELL GROWTH AND METHOD FOR THE PREPARATION THEREOF

Field of the Invention

The present invention relates to a novel quinazoline derivative and a pharmaceutically acceptable salt thereof for inhibiting the growth of cancer cells, a method for the preparation thereof and a pharmaceutical composition comprising same as an active ingredient.

Background of the Invention

Most of the traditional drugs used for treating cancers, e.g., taxanes such as paclitaxel and doxetaxel; vinca alkaloid such as vincristine, vinblastine and vinorelbin; anthracyclines such as daunomycin and doxorubicin; camptothecins such as topotecan, irinotecan; actinomycin; and etopocid are based on selective cytotoxicity, but such selectivity against cancer cells has been unsatisfactory to cause many side effects.

To overcome such a problem, recent studies have focused on specific molecular level targets in the cell to maximize the therapeutic effect of an anticancer agent without causing adverse side effects.

In cells, there are many signal transduction systems, which are fuctionally linked to each other to control the proliferation, growth, metastasis and apoptosis of cells. A breakdown of the intracellular controlling system by genetic and environmental influences may cause abnormal amplification or destruction of the signal transduction system so that the possibility for tumor cell generation occurs.

Protein tyrosine kinases play important roles in such cellular regulation, and their abnormal expression or mutation has been observed in cancer cells. Protein tyrosine kinase is an enzyme which catalyzes the transportation of phosphate groups from ATP to tyrosines located on the protein substrate. Many growth factor receptor proteins function as tyrosine kinases to transport

cellular signals. The interaction between growth factors and their receptors normally controls the cellular growth, but abnormal signal transduction caused by the mutation or overexpression of any of the receptors may induce tumor cells or cancers.

Protein tyrosine kinases have been classified into many families in terms of growth factors, and epithelial cell growth factors (EGFs)-related EGF receptor (EGFR) tyrosine kinase have been intensely studied. An EGFR tyrosine kinase is composed of a receptor and tyrosine kinase, and delivers extracellular signals to the cell nuclear through the cellular membrane. The EGFR tyrosine kinases are classified by their structural differences into EGFR (Erb-B1), Erb-B2, Erb-B3, Erb-B4, and all of the above members can form a homodimer- or heterodimer- signal delivery complex. Also, overexpression of more than one member of the above mentioned homodimers is often observed in malignant cells.

Therefore, the inhibition of mutated or overexpressed EGFR tyrosine kinases has been considered to be useful for treating tumors, and many drugs have been developed therefor, e.g., Gefitinib, Erlotinib, Carnertinib, Lapatinib.

International Patent Publications WO 96/033981, WO 96/033979, WO 97/038994 and WO 96/033980 each discloses a quinazoline derivative substituted with an alkoxyalkylamino or alkylaminoalkoxy group, International Patent Publications WO 97/030034 and WO 96/016960 each discloses quinazoline substituted with aryl or heteroaryl, and International Patent Publications WO 2003/040109 and WO 2003/040108 disclose compounds having aminoalkoxy substituents at position 5 of quinazoline (Normaclature of quinazoline is according to a reference [J.A. Joule, Chapman & Hall, *Heterocyclic chemistry*, 3rd Ed., 189]).

International Patent Publication WO 95/019970 and United States Patents 5,654,307 and 5,679,683 each discloses various tricyclic heteroarylcompounds, International Patent Publications WO 99/006396, WO 99/006378, WO 97/038983, WO 2000/031048, WO 98/050038, WO 99/024037 and WO 2000/006555, and European Patent 787722 each discloses quinazoline compounds that inhibit the tyrosine kinase irreversably, United States Patent 6,225,318, European Patents 0387063 and 01292591, and International Patent

Publications WO 2001/098277, WO 2003/045939 and WO 2003/049740 each discloses compounds having various alkenyl or alkynyl substituents at position 6 of quinazoline.

Also, International Patent Publications WO 98/043960, WO 2000/018761, WO 2001/047892, WO 2001/072711, WO 2003/050090, WO 99/09016, WO 2000/018740 and WO 2000/66583 disclose 3-cyanoquinoline compounds, International Patent Publications WO 98/002434, WO 98/002437, WO 99/035132, WO 99/035146, WO 2001/004111 and WO 2002/002552 each discloses various quinazoline compounds substituted with furan having various sulfonealkylamino substituents, and International Patent Publications WO 2003/053466 and WO 2001/094353 disclose specific thienopyrimidine compounds.

Further, International Patent Publications WO 2001/012227, WO 2004/014386, WO 2004/035057 and WO 2001/076586 disclose various methods for treating tumors that employ specific drugs that interact with EGFR tyrosine kinase in combination with radiation therapy.

However, the above mentioned conventional quinazoline derivatives have to be taken in large dose for intended treatments, which causes such side effects such as diarrhea and skin eruption. Accordingly, there has continued to exist a need to develop an effective drug that gives no adverse side effect.

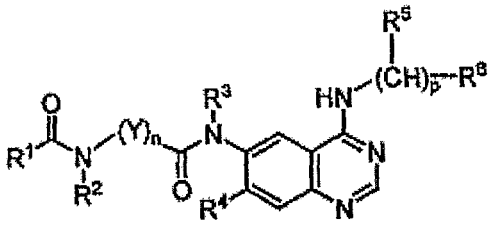
Summary of the Invention

Accordingly, it is an object of the present invention to provide a novel quinazoline derivative which selectively inhibits the cancer cell growth caused by epitherial growth factor without any side effects, and a method for the preparation thereof.

It is another object of the present invention to provide a phamarceutical composition for inhibiting cancer cell growth comprising the quinazoline derivative as an active ingredient.

In accordance with one aspect of the present invention, there is provided a quinazoline derivative of formula (I) or a pharmaceutically acceptable salt

thereof:



(I)

wherein,

R^1 is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkylamino, C_{1-6}dialkylamino, C_{1-6}alkylthio, aryl or heteroaryl which is optionally substituted with X;

R^2 and R^3 are each independently hydrogen, hydroxy, C_{1-6}alkyl, C_{3-7}cycloalkyl, hydroxyC_{1-5}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl or C_{1-6}dialkylaminoC_{1-6}alkyl;

Y is $-(CR^{11}R^{12})-$, aryl or heteroaryl, R^{11} and R^{12} being each independently hydrogen, halogen, hydroxy, amino, nitro, cyano, thiol, carboxylic acid, carbamoyl; C_{1-6}alkyl, C_{1-6}alkylamino, C_{1-6}dialkylamino, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, C_{1-6}alkyloxysulfonyl, C_{1-6}alkylaminosulfonyl, C_{1-6}dialkylaminosulfonyl, C_{1-6}alkanoyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkylcarbamoyl, C_{1-6}dialkylcarbamoyl, C_{1-6}alkylthiocarbonyl, C_{1-6}alkanoyloxy, C_{1-6}alkyloxycarbonyloxy, C_{1-6}alkylaminocarbonyloxy, C_{1-6}dialkylaminocarbonyloxy, C_{1-6}alkylthiocarbonyloxy, C_{1-6}alkanoylamino, C_{1-6}alkoxycarbonylamino, C_{1-6}alkyl or C_{1-6}dialkylureido, C_{1-6}alkyl, C_{1-6}dialkylguanidino, aryl, or heteroaryl which is optionally substitutied with substituent Z; or optionally fused to each other to form a 3 to 8-membered non-aromatic ring, or R^{11} or R^{12} may be fused to R^2 or R^3 to form together with the carbon and nitrogen they are attached to a 4 to 8-membered non-aromatic ring;

R^4 is hydrogen, halogen, hydroxy, amino, or C_{1-6}alkyl, C_{1-6}alkoxy or C_{1-6}alkylamino optionally substituted with R^{13}, R^{13} being halogen, cyano, trifluoromethyl, trifluoromethoxy, C_{1-6}alkoxy, C_{1-6}alkylamino, C_{1-5}dialkylamino, aryl or heteroaryl);

R^5 is hydrogen or C_{1-3}alkyl;

R^6 is R^{14}, aryl or heteroaryl optionally substituted with R^{15}, R^{14} and R^{15} being each independently hydrogen, halogen, trifluoromethyl, trifluoromethoxy, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylamino, C_{1-6}dialkylamino, or aryl, heteroaryl, arylalkyl, heteroarylalkyl, arylalkoxy, heteroarylalkoxy, aryloxy, heteroaryloxy, aryloxycarbonyl, heteroaryloxycarbonyl, arylcarbonyl, heteroarylcarbonyl, arylcarbamoyl, heteroarylcarbamoyl, arylsulfonyl or heteroarylsulfonyl optionally substituted with R^{16}, wherein R^{16} is halogen, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylamino or C_{1-6}dialkylamino;

n is an integer in the range of 1 to 6;

p is 0 or 1;

X and Z are each independently hydrogen, halogen, nitro, hydroxy, amino, cyano, thiol, carboxylic acid, carbamoyl, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkylamino, C_{1-6}dialkylamino, C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylcarbonyl, C_{1-6}alkylthiocarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbamoyl, C_{1-6}dialkylcarbamoyl, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, C_{1-6}alkoxycarbonyloxy, C_{1-6}alkylaminocarbonyloxy, C_{1-6}dialkylaminocarbonyloxy, C_{1-6}alkylthiocarbonyloxy, C_{1-6}alkanoylamino, C_{1-6}alkoxycarbonylamino, C_{1-6}alkylureido, C_{1-6}dialkylureido, C_{1-6}alkylguanidino, C_{1-6}dialkylguanidino, C_{1-6}alkoxysulfonyl, C_{1-6}alkylaminosulfonyl, C_{1-6}dialkylaminosulfonyl, C_{1-6}alkylsulfamoyl, C_{1-6}alkylaminosulfamoyl, C_{1-6}dialkylaminosulfamoyl, aryl or heteroaryl; wherein

aryl is C_{5-12} monocylic or bicyclic aryl;

heteroaryl is a 5 to 13-membered heteroaromatic or non-aromatic group containing one or more of the elements selected from the group consisting of N, O, S, SO and SO_2; and

The optionally substituted aryl and heteroaryl each has one or more substituents selected from the group consisting of halogen, hydroxy, amino, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylamino and C_{1-6}dialkylamino.

Detailed Description of the Invention

In the quinazoline derivative of formula (I) of the present invention, R^1 is preferably methyl, cyclopropyl, trifluoromethyl, cyanomethyl, chloromethyl, phenyl, methoxy, phenoxy, benzyloxy, methoxymethyl, acetoxymethyl, dimethylaminoethoxymethyl, methoxyethoxymethyl, methylthiomethyl, methanesulfinylmethyl, methanesulfonylmethyl, dimethylaminomethyl, morpholinomethyl, 4-methylpiperazinylmethyl, methanesulfonylethylaminomethyl, methoxyethylaminomethyl, ethoxycarbonyl, ethylamino, furan-3-yl, furan-2-yl-methylamino, benzamino, benzylamino, *t*-buthoxy, 3-methyl-isoxazol-5-yl, 5-methyl-isoxazol-4-yl, 1*H*-pyrazol-4-yl, vinyl, penta-1,3-dienyl, cyclopentenyl, 2-phenylvinyl, 2-methylvinyl, 2,2-dimethylvinyl, 1-methylvinyl, 2-phenylethynyl, 2-methylethynyl, 2-(bromomethyl)vinyl, 2-(dimethylaminomethyl)vinyl, 2-(morpholinomethyl)vinyl, 2-(4-methylpiperazinylmethyl)vinyl, 2-((*N*-methyl-(2-hydroxyethyl)amino)methyl)vinyl or 2-(methanesulfonylethylaminomethyl)vinyl;

R^2 and R^3 are preferably each independently hydrogen, methyl, ethyl or 3-(*N,N*-dimethylamino)propyl;

R^4 is preferably hydrogen, amino, hydroxyl, fluoro, chloro, methoxy, ethoxy, methoxyethoxy, methoxypropoxy, ethylsulfanyl, cyclopropylmethoxy, cyclopentyloxy, 2,2,2-trifluoroethoxy, 2-fluoroethoxy, *N,N*-dimethylamino, morpholinopropoxy or 4-methylpiperadinylmethoxy;

R^5 is preferably hydrogen;

R^6 is preferably 1-phenyl-ethyl, 3-ethynyl-phenyl, biphenyl, 3-chloro-4-fluoro-phenyl, 3-chloro-4-(3-fluoro-benzyloxy)-phenyl, 3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenyl, 4-[2-(6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-phenyl, *N*-phenyl-benzamid-4-yl, 3-chloro-4-(pyridin-2-ylmethoxy)-phenyl, 3-chloro-4-(pyridin-3-ylmethoxy)-phenyl, 3-chloro-4-(6-methyl-pyridin-2ylmethoxy)-phenyl, 3-chloro-4-(pyridin-4-ylmethoxy)-phenyl, 3-methyl-4-(pyridin-2-ylmethoxy)-phenyl, 1-pyridin-2-ylmethyl-1*H*-indazol-5-yl, 1-(3-fluoro-benzyl)-1*H*-indazol-5-yl, 1-penta-2,4-dienyl-1*H*-indazol-5-yl, 3-chloro-4-(2-fluoroethoxy)-phenyl, 2-methyl-1*H*-indol-5-yl or 1-benzyl-1*H*-indazol-5-yl;

Y is preferably $-(CR^{11}R^{12})-$, aryl or heteroaryl, R^{11} and R^{12} being each

independently hydrogen, amino, hydroxyl, halogen, C_{1-6}alkyl, C_{1-3}alkenyl, C_{1-6}alkylC_{1-6}alkyl, hydroxylC_{1-3}alkyl, diC_{1-3}alkylaminoC_{1-3}alkyl, C_{1-3}alkoxyC_{1-3}alkyl, C_{1-3}alkylsulfonylC_{1-3}alkyl, C_{1-3}alkylsulfinylC_{1-3}alkyl, C_{1-3}alkylsulfanylC_{1-3}alkyl, carboxyC_{1-3}alkyl, C_{1-3}alkoxycarbonylC_{1-3}alkyl, diC_{1-3}alkylamino, C_{1-3}alkoxy, C_{1-6}alkanoyloxy, C_{1-6}alkylcarbamoyl, aryl, heteroaryl, or C_{1-3}alkylsubstitutied with aryl or heteroaryl, the aryl or heteroaryl is phenyl, naphtyl, furan, thiophene, imidazole, triazole, pyridine, oxazole, isoxazole, thiazole, indole, quinoline, isoquinoline, quinazoline, aziridine, azetidine, pyrrolidine, piperidine, morpholine, piperazine, thiomorpholine or 4-pyridone, or optionally fused to each other to form a 3 to 8-membered non-aromatic ring, or R^{11} or R^{12} may be fused to R^2 or R^3 to form together with the carbon and nitrogen they are attached to a 4 to 8-membered non-aromatic ring; and

Preferable n is an integer in the range of 1 to 4.

In the present invention, the term 'halo' refers to fluoro, chloro, bromo or iodo, unless otherwise indicated.

In the present invention, the term 'alkyl' refers to a monovalent saturated hydrocarbon compound having linear, circular or branced residue, 'alkenyl' and 'alkynyl' refer to the said alkylcompound having carbon-carbon double bond and triple bond, respectively, when the alkyl is composed of 2 or more carbon atoms.

In the present invention, the term 'alkoxy' refers to an oxygen derivative of the said alkyl, unless otherwise indicated.

In the present invention, the term 'aryl' refers to an aromatic hydrocarbon such as phenyl or naphtyl, unless otherwise indicated.

Examples of more preferred compounds of formula (I) according to the present invention are:

1) ({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-methyl)-carbamic acid *t*-butylester;

2) *N*-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-methyl)-2-methoxy-acetamide;

3) *N*-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-methyl)-2-methanesulfonyl-acetamide;

4) *N*-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-methyl)-acrylamide;

5) (2*S*)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-(2-methoxy-acetylamino)-3-phenyl-propionamide;

6) (1*S*)-(1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-3-methanesulfanyl-propyl)-carbamic acid *t*-butylester;

7) (2*S*)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-(2-methoxy-acetylamino)-4-methanesulfanyl-butyramide;

8) (2*S*)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-(2-methanesulfonyl-acetamino)-4-methanesulfanyl-butyramide;

9) (2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-methanesulfanyl-butyramide;

10) (1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-cyclopropyl)-carbamic acid *t*-butylester;

11) (2*S*)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-(2-methoxy-acetylamino)-2-phenyl-acetamide;

12) (4*S*)-4-*t*-buthoxycarbonylamino-4-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-butyric acid methylester;

13) 4-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-4-(2-methoxy-acetylamino)-butyric acid methylester;

14) 4-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-4-(2-methoxy-acetylamino)-butyric acid;

15) 2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-pyrrolidine-1-carboxylic acid *t*-butylester;

16) 1-(2-methoxy-acetyl)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide;

17) 1-(2-methanesulfonyl-acetyl)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide;

18) 1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide;

19) (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid *t*-butylester;

20) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-propionamide;

21) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-propionamide;

22) *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

23) 3-phenyl-propionylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

24) hexa-2,4-dienonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

25) cyclopent-1-en carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

26) *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-3-phenyl-acrylamide;

27) but-2-ynoylic acid(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

28) but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

29) 3-methyl-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

30) *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-2-methyl-acrylamide;

31) *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-2-cyano-acetamide;

32) 3-methyl-isoxazol-5-carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

33) furan-3-carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

34) 1*H*-pyrazol-4-carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

35) *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-benzamide;

36) *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-oxalamic acid ethylester;

37) cyclopropylcarboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

38) acetic acid 2-*t*-buthoxycarbonylamino-1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethylester;

39) acetic acid 1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-2-(2-methoxy-acetylamino)-ethylester;

40) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-hydroxyl-3-(2-methoxy-acetylamino)-propionamide;

41) (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-carbamic acid *t*-butylester;

42) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-2-methyl-propionamide;

43) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-2-methyl-propionamide;

44) *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-acrylamide;

45) (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-1-phenyl-ethyl)-carbamic acid *t*-butylester;

46) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-3-phenyl-propionamide;

47) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-3-phenyl-propionamide;

48) 3-(2-methoxy-acetylamino)-thiophene-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide;

49) (2-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid *t*-butylester;

50) 3-(2-methanesulfonyl-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-propionamide;

51) *N*-(2-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

52) {2-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-carbamic acid *t*-butylester;

53) *N*-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-3-(2-methanesulfonyl-acetylamino)-propionamide;

54) *N*-{2-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide;

55) 4-bromo-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

56) 4-dimethylamino-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

57) 4-morpholin-4-yl-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

58) 4-(4-methyl-piperazin-1-yl)-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

59) 4-[(2-hydroxyl-ethyl)-methyl-amino]-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

60) 4-(2-methanesulfonyl-ethylamino)-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

61) 3-(2-chloro-acetylamide)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide;

62) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-morpholin-4-yl-acetylamino)-propionamide;

63) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-dimethylamino-acetylamino)-propionamide;

64) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(4-methyl-piperazin-1-yl)-acetylamino]-propionamide;

65) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(2-methoxy-ethylamino)-acetylamino]-propionamide;

66) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(2-methanesulfonyl-ethylamino)-acetylamino]-propionamide;

67) 3-(2-chloro-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-propionamide;

68) *N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-3-(2-morpholin-4-yl-acetylamino)-propionamide;

69) 3-(2-dimethylamino-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-propionamide;

70) *N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(4-methyl-piperazin-1-yl)-acetylamino]-propionamide;

71) 3-[2-(2-methoxy-ethylamino)-acetylamino]-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-methylamino]-quinazolin-6-yl}-propionamide;

72) 3-[2-(2-methanesulfonyl-ethylamino)-acetylamino]-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-propionamide;

73) *N*-{2-[4-(2-methyl-1*H*-indol-5-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide;

74) 3-(2-methanesulfonyl-acetylamino)-*N*-[4-(1-phenyl-ethylamino)-quinazolin-6-yl]-propionamide;

75) *N*-{2-[4-(1-phenyl-ethylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide;

76) *N*-[2-(4-{4-[2-(6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-phenylamino}-quinazolin-6-ylcarbamoyl)-ethyl]-acrylamide;

77) {2-[4-(1-benzyl-1*H*-indazol-5-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-carbamic acid *t*-butylester;

78) *N*-[4-(1-benzyl-1*H*-indazol-5-ylamino)-quinazolin-6-yl]-3-(2-methanesulfonyl-acetylamino)-propionamide;

79) *N*-{2-[4-(1-benzyl-1*H*-imidazol-5-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide;

80) {2-[4-(4-phenylcarbamoyl-phenylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-carbamic acid *t*-butylester;

81) 4-{6-[3-(2-methanesulfonyl-acetylamino)-propionylamino]-quinazolin-4-ylamino}-*N*-phenyl-benzamide;

82) 4-[6-(3-acryloylamino-propionylamino)-quinazolin-4-ylamino]-*N*-phenyl-benzamide;

83) *N*-[4-(biphenyl-4-ylamino)-quinazolin-6-yl]-3-(2-methanesulfonyl-acetylamino)-propionamide;

84) *N*-{2-[4-(biphenyl-4-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide;

85) *N*-{2-[4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide;

86) (3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-carbamic acid *t*-butylester;

87) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-methoxy-acetylamino)-butyramide;

88) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-methanesulfonyl-acetylamino)-butyramide;

89) 4-acryloylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-butyramide;

90) *N*-(3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-benzamide;

91) *N*-(3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-oxalamic acid ethylester;

92) cyclopropylcarboxylic acid (3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-amide;

93) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-cyano-acetylamino)-butyramide;

94) furan-3-carboxylic acid (3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-amide;

95) 1*H*-pyrazol-4-carboxylic acid (3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-amide;

96) {3-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-ylcarbamoyl]-propyl}-carbamic acid *t*-butylester;

97) *N*-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-4-(2-methanesulfonyl-acetylamino)-butyramide;

98) 4-acryloylamino-*N*-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-butyramide;

99) (3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-ylcarbonyl}-propyl)-carbamic acid *t*-butylester;

100) 4-(2-methanesulfonyl-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide;

101) 4-acryloylamino-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide;

102) 4-(2-chloro-acetylamino)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-butyramide;

103) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-morpholin-4-yl-acetylamino)-butyramide;

104) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-dimethylamino-acetylamino)-butyramide;

105) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-[2-(4-methyl-piperazin-1-yl)-acetylamino]-butyramide;

106) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-[2-(2-methoxy-ethylamino)-acetylamino]-butyramide;

107) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-[2-(2-methanesulfonyl-ethylamino)-acetylamino]-butyramide;

108) 4-(2-chloro-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide;

109) *N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-4-(2-morpholin-4-yl-acetylamino)-butyramide;

110) 4-(2-dimethylamino-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide;

111) *N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-4-[2-(4-methyl-piperazin-1-yl)-acetylamino]-butyramide;

112) 4-[2-(2-methanesulfonyl-ethylamino)-acetylamino]-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide;

113) 4-[2-(2-methoxy-ethylamino)-acetylamino]-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide;

114) (4-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-butyl)-carbamic acid *t*-butylester;

115) 5-(2-methoxy-acetylamino)-pentanoic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide;

116) 5-(2-methanesulfonyl-acetylamino)-pentanoic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-pentylamino]-quinazolin-6-yl}-amide;

117) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfanyl-acetylamino)-propionamide;

118) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfinyl-acetylamino)-propionamide;

119) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2,2,2-trifluoro-acetylamino)-propionamide;

120) 3-acetylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide;

121) acetic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethylcarbamoyl)-methylester;

122) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(2-dimethylamino-ethoxy)-acetylamino]-propionamide;

123) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(3-ethyl-ureido)-propionamide;

124) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(3-phenyl-ureido)-propionamide;

125) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(3-furan-2-ylmethyl-ureido)-propionamide;

126) (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid methylester;

127) (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid phenylester;

128) (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid benzylester;

129) *N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-propionamide;

130) *N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-propionamide;

131) *N*-(2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

132) *N*-{4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-propionamide;

133) *N*-{4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-propionamide;

134) *N*-(2-{4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

135) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(2-methoxy-ethoxy)-acetylamino]-propionamide;

136) 5-methyl-isoxazol-4-carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

137) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-methanesulfanyl-acetylamino)-butyramide;

138) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-methanesulfinyl-acetylamino)-butyramide;

139) *N*-[2-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-methyl-carbamoyl)-ethyl]-acrylamide;

140) *N*-[2-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-ethyl-carbamoyl)-ethyl]-acrylamide;

141) *N*-{2-[{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-(3-dimethylamino-propyl)-carbamoyl]-ethyl}-acrylamide;

142) *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-*N*-methyl-acrylamide;

143) *N*-(2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-*N*-methyl-acrylamide;

144) *N*-(2-{4-[3-chloro-4-(6-methyl-pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

145) (2*S*)-1-acryloyl-pyrrolidin-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

146) (2*S*)-1-(1-oxo-butyn-2-yl)-pyrrolidin-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

147) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(6-methyl-pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

148) (3*R*,5*S*)-acetic acid 1-acryloyl-5-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-pyrrolidin-3-ylester;

149) (2*S*,4*R*)-1-acryloyl-4-hydroxyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

150) (2*S*,4*R*)-1-acryloyl-4-ethylsulfanyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

151) (2*S*,4*R*)-1-acryloyl-4-dimethylamino-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

152) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

153) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-4-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

154) 2-(1-acryloyl-pyrrolidin-2-yl)-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-acetamide;

155) 1-acryloyl-pyrrolidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

156) 1-acryloyl-piperidine-4-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

157) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-amide;

158) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-(3-ethynyl-phenylamino)-quinazolin-6-yl]-amide;

159) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-amide;

160) (2*S*,4*R*)-1-acryloyl-4-ethanesulfonyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

161) (2*S*,4*R*)-1-acryloyl-4-methoxy-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

162) 1-acryloyl-piperidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

163) 1-acryloyl-azetidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

164) 1-acryloyl-piperidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

165) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-fluoro-quinazolin-6-yl}-amide;

166) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

167) *N*-(2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

168) (2*S*)-1-acryloyl-pyrrolidin-2-carboxylic acid {7-methoxy-4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

169) 2-(1-acryloyl-pyrrolidin-2-yl)-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-acetamide;

170) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-ethoxy-quinazolin-6-yl}-amide;

171) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-ethylsulfanyl-quinazolin-6-yl}-amide;

172) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-cyclopropylmethoxy-quinazolin-6-yl}-amide;

173) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-cyclopentyloxy-quinazolin-6-yl}-amide;

174) *N*-(2-{4-[3-chloro-4-(pyridin-4-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

175) (2*S*)-1-(4-dimethylamino-buten-2-oyl)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

176) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {7-chloro-4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

177) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {7-fluoro-4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

178) *N*-(2-{7-fluoro-4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

179) (2*S*)-1-acryloyl-2,5-dihydro-1*H*-pyrrol-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

180) (4*R*)-3-acryloyl-thiazolidin-4-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

181) 1-acryloyl-azetidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

182) 1-acryloyl-azetidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

183) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2,2,2-trifluoro-ethoxy)-quinazolin-6-yl]-amide;

184) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-dimethylamino-quinazolin-6-yl}-amide;

185) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [7-methoxy-4-(1-pyridin-2-ylmethyl-1*H*-indazol-5-ylamino)-quinazolin-6-yl]-amide;

186) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenylamino]-7-ethoxy-quinazolin-6-yl}-amide;

187) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2-fluoro-ethoxy)-quinazolin-6-yl]-amide;

188) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[1-(3-fluoro-benzyl)-1*H*-indazol-5-ylamino]-7-methoxy-quinazolin-6-yl}-amide;

189) (1*R*)-*N*-(1-{4-[3chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

190) (1*S*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

191) (1*S*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}ethyl)-N-methyl-acrylamide;

192) *N*-(2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-fluoro-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

193) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [7-methoxy-4-(1-penta-2,4-dienyl-1*H*-indazol-5-ylamino)-quinazolin-6-yl]-amide;

194) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(6-methyl-pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

195) 1-acryloyl-azetidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-fluoro-quinazolin-6-yl}-amide;

196) 1-acryloyl-piperidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

197) 1-acryloyl-piperidine-4-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

198) 1-acryloyl-pyrrolidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

199) 1-acryloyl-azetidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-ethoxy-quinazolin-6-yl}-amide;

200) 1-acryloyl-azetidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

201) (3S)-1-acryloyl-piperidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

202) *N*-((1*S*)-1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-ethyl)-*N*-ethyl-acrylamide;

203) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(2-fluoro-ethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

204) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

205) (2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-butyramide;

206) *N*-(2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-2-fluoro-ethyl)-acrylamide;

207) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-7-(1-methyl-piperidin-4-ylmethoxy)-quinazolin-6-yl}-amide;

208) (1*R*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2-methoxy-ethoxy)-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

209) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-yl}-amide;

210) *N*-({4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-methyl)-acrylamide

211) *N*-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-methyl)-acrylamide;

212) (3*S*)-3-acryloylamino-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-butyramide;

213) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-yl]-amide;

214) (1*S*)-*N*-{1-[4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide;

215) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-yl]-amide;

216) (1*S*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

217) *N*-{[4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-ylcarbamoyl]-methyl}-acrylamide;

218) *N*-({4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-ylcarbamoyl}-methyl]-acrylamide;

219) (1*S*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylemthoxy)-phenylamino]-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-ylcarbamoyl}-ethyl-acrylamide;

220) (1*S*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(3-methoxypropoxy)-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

221) (2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-4-methylsulfanyl-butyramide;

222) (2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-yl}-4-methylsulfanyl-butyramide;

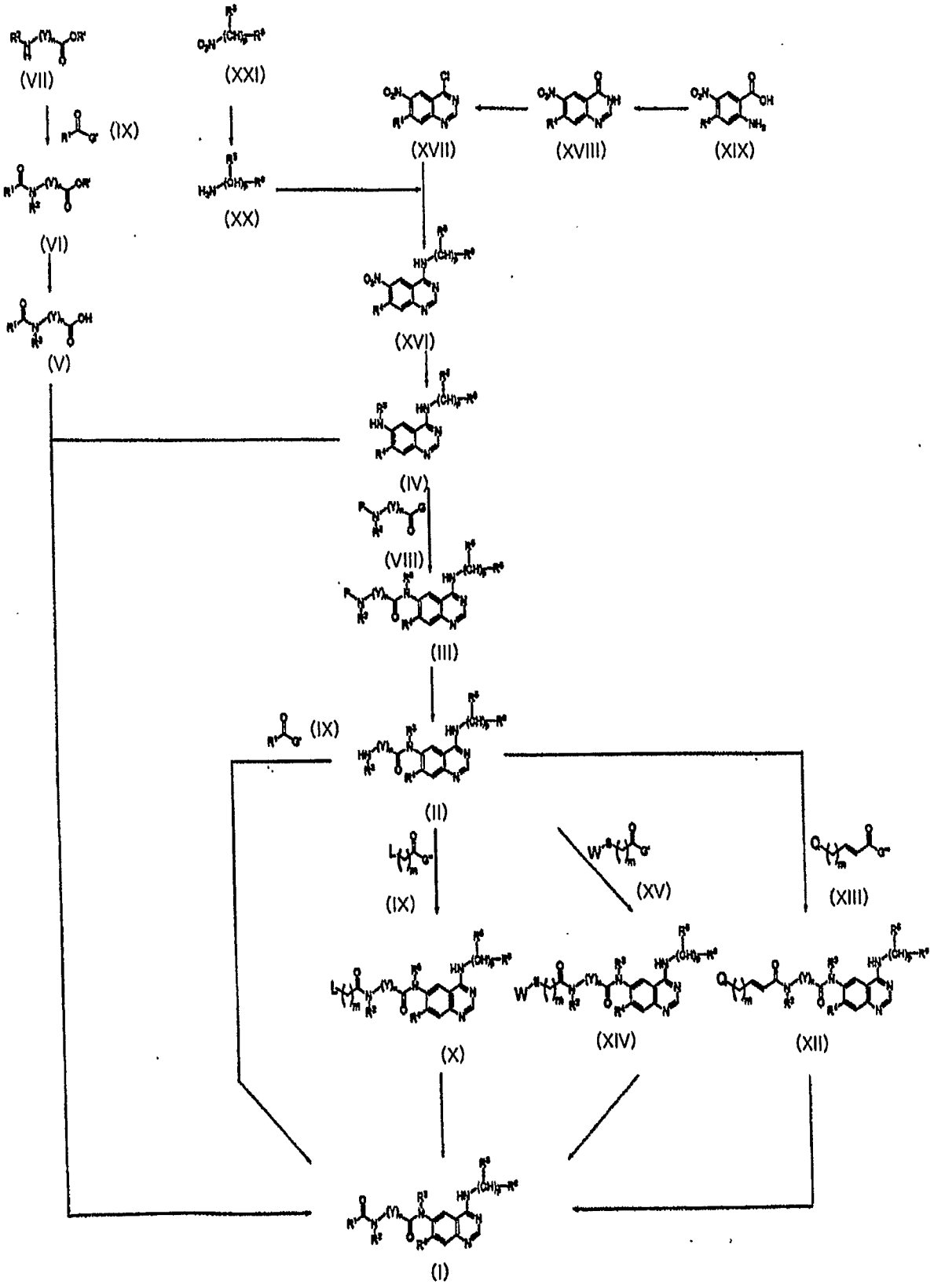
223) (2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-4-methylsulfinyl-butyramide;

224) (2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-methyl-butyramide; and

225) (2*S*)-2-acryloylamino-4-methyl-pentanoic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide.

The compound of formula (I) of the present invention may be prepared by the procedure shown in Reaction Scheme (I):

Reaction Scheme (I)


(VII)
(IX)
(XXI)
(XVII)
(XVIII)
(XIX)
(XX)
(VI)
(XVI)
(V)
(IV)
(VIII)
(III)
(IX)
(II)
(IX)
(XV)
(XIII)
(X)
(XIV)
(XII)
(I)

wherein,

R^1, R^2, R^3, R^4, R^5, R^6, Y, n and p have the same meanings as defined preveiously while;

R' and W are each independently C_{1-6}alkyl;

G, G' and G" are each independently halogen, hydroxy or C_{1-6}alkanoyloxy;

L is halogen, C_{1-6}alkylsulfonyloxy or arylsulfonyloxy;

Q is halogen;

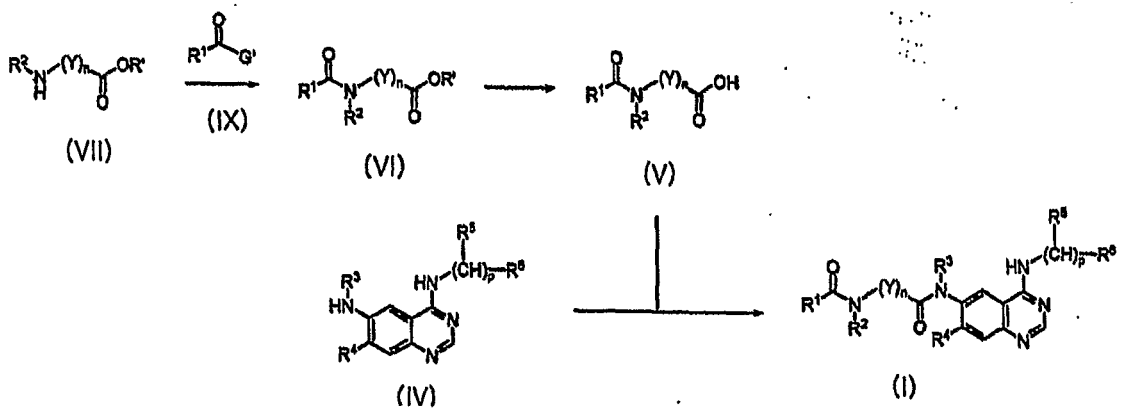
G"' is halogen, hydroxy or tri(C_{1-6}alkyl)silyloxy;

P is a *t*-buthoxycarbonyl or benzyloxycarbonylate amine protecting group; and

M is an integer in the range of 1 to 5.

Specifically, The compound of formula (I) of the present invention may be prepared by the procedure shown in Reaction Schemes (II) to (VI):

Reaction Scheme (II)



wherein,

R^1, R^2, R^3, R^4, R^5, R^6, Y, n, p, R' and G' have same meanings as defined above.

In Reaction Scheme (II), a compound of formula (IV), the preparative procedure thereof is explained in Reacion Scheme (VII) in detail, is subjected to a condensation reaction with a compound of formula (V) to obtain a compound of formula (I). The condensation agent which may be used in this reaction is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, *N,N*-dicyclohexyldiimide, C_{1-6}alkylchloroformate, carbonyldiimidazole or *O*-(1*H*-benzotriazol-1-yl)-

N,N,N',N'-tetramethyluronium tetrafluoroborate, and the agent may be employed in an amount of 1 to 10 equivalentss, preferably 1 to 5 equivalentss based on the compound of formula (IV). The compound of formula (V) may be employed in an amount of 1 to 10 equivalentss, preferably 1 to 4 equivalentss based on the compound of formula (IV).

N,N-dimethylaminopyridine, *N,N*-hydroxysuccinimide or *N*-hydroxybenzotriazole can be added as a catalyst in an amount of 0.05 to 1 equivalent based on the compound of formula (IV). Also, triethylamine, *N,N*-diisopropylethylamine, pyridine or *N*-methylmorpholine can be added as a base in an amount of 1 to 5 equivalentss based on the compound of formula (IV).

The solvent used in this reaction may be methylene chloride, chloroform, *N,N*-dimethylformamide, tetrahydrofuran (THF), 1,4-dioxane or acetonitrile, and the reaction can be carried out at a temperature ranging from -20℃ to the boiling point of the solvent used, preferably 0 to 40℃.

The compound of formula (V) is commercially availavle and it can be prepared by hydrolysis of the compound of formula (VI). In this hydrolysis step, lithium hydroxide, sodium hydroxide, potassium hydroxide or barium hydroxide may be used in an amount of 1 to 20 equivalentss, preferably 1 to 10 equivalents based on the compound of formula (VI). The hydrolysis can be carried out at a temperature ranging from -20℃ to 100℃, preferably 0 to 30℃ in a solvent selected from the group consisting of water, alcohol, ether and a mixture thereof.

The compound of formula (VII) is subjected to a condensation reaction with the compound of formula (IX) to obtain the compound of formula (VI), and the compound of formula (IX) may be employed in an amount of 1 to 10 equivalents, preferably 1 to 3 equivalents based on the compound of formula (VII). In case that the G' is halogen or alkanoyloxy, the compound of formula (VI) may be prepared by just adding a base without a condensation reagent, and in case that the G' is hydroxy, the compound of formula (VI) may be prepared by using a condensation reagent selected from the group consisting of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, *N,N*-dicyclohexyldiimide, C_{1-6}alkylchloroformate and *O*-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate in an amount of 1 to 10 equivalents,

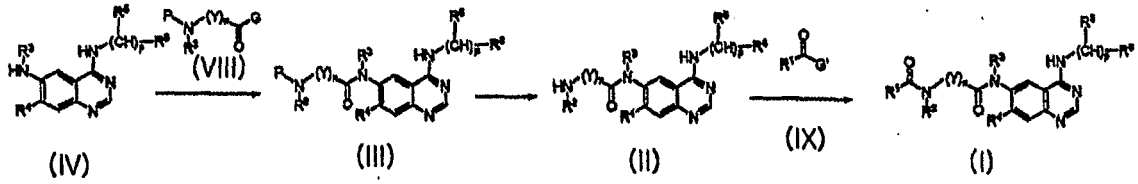
preferably 1 to 5 equivalents based on the compound of formula (VII).

In this reaction, a solvent such as *N,N*-dimethylaminopyridine, *N,N*-hydroxysuccinimide and *N*-hydroxybenzotriazole may be optionally used in an amount of 0.05 to 1 equivalent based on the compound of formula (VII). Further, a base such as triethylamine, *N,N*-diisopropylethylamine, pyridine and *N*-methylmorpholine may be optionally used in an amount of 1 to 5 equivalents. The solvent used in this reaction may be selected from the group consisting of methylene chloride, chloroform, *N,N*-dimethylformamide, THF, 1,4-dioxane, acetonitrile and a mixture thereof, and the reaction can be carried out at a temperature ranging from -20℃ to the boiling point of the solvent used, preferably 10 to 40℃.

The compound of formula (VII) is commercially available and it can be prepared in accordance with the method described by Dieter Seebach *et al.*, [*Helvetica Chimica Acta*, 2003, *86*:1852].

The compound of formula (IX) is commercially available and it can be prepared in accordance with the method described by Hwei-Ru Tsou *et al.*, [*Journal of Medicinal Chemistry*, 2001, *44*:2719].

Reaction Scheme (III)



wherein,

R^1, R^2, R^3, R^4, R^5, R^6, Y, n, p, G, G' and P have same meanings as defined above.

In Reaction Scheme (III), the compound of formula (II) is subjected to a condensation reaction with a compound of formula (IX) to obtain the compound of formula (I). The compound of formula (IX) may be employed in an amount of 1 to 10 equivalents, preferably 1 to 5 equivalents based on the compound of formula (II). In case that the G' is halogen or alkanoyloxy, the compound of formula (I) may be prepared by just adding a base without a condensation reagent, and in case that the G' is hydroxy, the compound of formula (I) may be

prepared by using a condensation reagent selected from the group consisting of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, *N,N*-dicyclohexyldiimide, C_{1-6}alkylchloroformate and *O*-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate in an amount of 1 to 10 equivalents, preferably 1 to 5 equivalents based on the compound of formula (II).

In this reaction, a solvent such as *N,N*-dimethylaminopyridine, *N,N*-hydroxysuccinimide and *N*-hydroxybenzotriazole may be optionally used in an amount of 0.05 to 1 equivalent based on the compound of formula (II). Further, a base such as triethylamine, *N,N*-diisopropylethylamine, pyridine and *N*-methylmorpholine may be optionally used in an amount of 1 to 5 equivalents. The solvent used in this reaction may be selected from the group consisting of methylene chloride, chloroform, *N,N*-dimethylformamide, THF, 1,4-dioxane, acetonitrile and a mixture thereof, and the reaction can be carried out at a temperature ranging from -20℃ to the boiling point of the solvent used, preferably 0 to 40℃.

The compound of formula (IV), the preparative procedure thereof is explained in Reacion Scheme (VII) in detail, is subjected to a condensation reaction with a compound of formula (VIII) to obtain a compound of formula (III). Then, the compound of formula (III) is subjected to the deprotection (removing the protecting group 'P') to obtain the compound of formula (II).

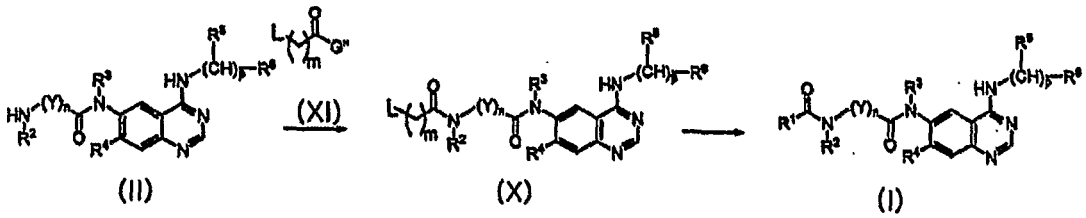
The compound of formula (VIII) is commercially available and it can be prepared in accordance with the method described by Dieter Seebach *et al.*, [*Helvetica Chimica Acta*, 2003, *86*:1852].

The condensation agents which may be used in this reaction is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, *N,N*-dicyclohexyldiimide, C_{1-6}alkylchloroformate, carbonyldiimidazole or *O*-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate. The compound of formula (VIII) may be employed in an amount of 1 to 10 equivalents, preferably 1 to 3 equivalents based on the compound of formula (IV). In case that the G' is halogen or alkanoyloxy, the compound of formula (VI) may be prepared by just adding a base without a condensation reagent, and in case that the G' is hydroxy, the compound of formula (VI) may be prepared by using the said condensation reagent. In this reaction, a solvent such as *N,N*-dimethylaminopyridine, *N,N*-

hydroxysuccinimide and *N*-hydroxybenzotriazole may be optionally used in an amount of 0.05 to 1 equivalent based on the compound of formula (IV). Also, triethylamine, *N,N*-diisopropylethylamine, pyridine and *N*-methylmorpholine can be optionally added as a base in an amount of 1 to 5 equivalents based on the compound of formula (IV). The solvent used in this reaction may be selected from the group consisting of methylene chloride, chloroform, *N,N*-dimethylformamide, THF, 1,4-dioxane, acetonitrile and a mixture thereof, and the reaction can be carried out at a temperature ranging from -20℃ to the boiling point of the solvent used, preferably 0 to 40℃.

While subjecting the compound of formula (III) to deprotection to obtain the compound of formula (II), hydrochloric acid, phosphoric acid, sulfuric acid or trifluoroacetic acid as a depretecting agent can be added or used as a solvent. Further, the compound of formula (II) can be obtained by using metal (for example, palladium, platinum or nickel) or metal oxide, carrying the reaction under hydrogen gas, or adding cyclohexene or cyclodihexene. The deprotection can be carried out at a temperature ranging from 0℃ to 10℃, preferably room temperature to 50℃ in accordance with the method described by Greene Wuts, [*Protective Groups in Organic Synthesis*, 3rd Ed., Wiley-Interscience].

Reaction Scheme (IV)



wherein,

R^1, R^2, R^3, R^4, R^5, R^6, Y, n, p, L, G" and m have same meanings as defined above.

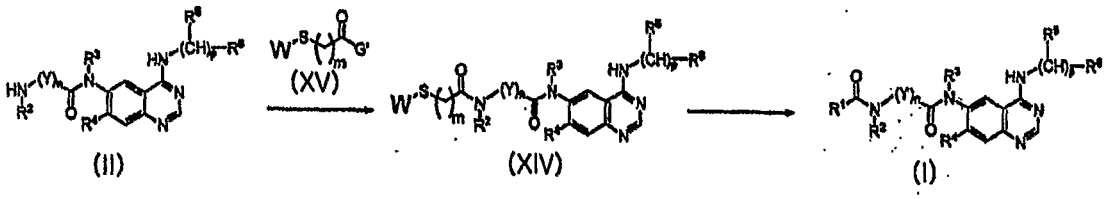
In Reaction Scheme (IV), when the R^1 is C_{1-6}alkylaminoC_{1-6}alkyl, C_{1-6}dialkylaminoC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl or C_{1-6}alkylthioC_{1-6}alkyl, the compound of formula (X) may be prepared by subjecting the compounds of

formula (II) and (XI) to condensation reaction, and then the compound of formula (I) may be prepared by adding amine, alcohol or thiol corresponding to R^1.

The condensation reaction to obtain the compoun (II) is carried out in similar condition of reaction to prepare the compound of formula (III) or by applying the reaction. The compound of formula (XI) is commercially available and it can be prepared in accordance with conventional methods.

The amine, alcohol or thiol added to the compound of formula (X) is commercially available and it can be prepared in accordance with conventional methods, and the compounds may be employed in an amount of 1 to 10 equivalents, preferably 1 to 3 equivalents based on the compound of formula (X). Further, an inorganic or organic base such as potassium carbonate, sodium carbonate, sodium hydride, triethylamine, 1,8-diazabicyclo[5.4.0]undec-7-en (DBU) and *N,N*-diisopropylethylamine may be used in an amount of 1 to 5 equivalents based on the compound of formula (X). The solvent used in this reaction may be selected from the group consisting of THF, 1,4-dioxane, toluene, *N,N*-dimethylformamide, dimethoxyethane and a mixture thereof, and the reaction can be carried out at a temperature ranging from 0℃ to 150℃, preferably 0℃ to 100℃.

Reaction Scheme (V)



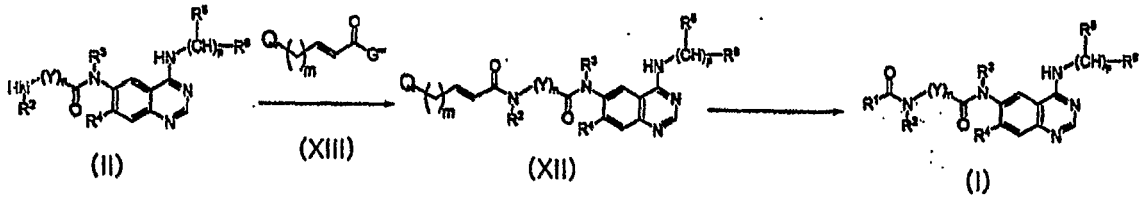
wherein,

R^1, R^2, R^3, R^4, R^5, R^6, Y, n, p, W, G' and m have same meanings as defined above.

In Reaction Scheme (V), when the R^1 is C_{1-6}alkylsulfinyl or C_{1-6}alkylsulfonyl, the compound of formula (XIV) may be prepared by subjecting the compounds of formula (II) and (XV) to condensation reaction, and then the compound of formula (I) may be prepared by oxidizing the compound of

formula (XIV) in the presence of an oxidizing agent such as *m*-chloroperoxybenzoic acid (CPBA) or OXONE (Koichiro Matsumoto) in an amount of 1 to 5 equivalents based on the compound of formula (XIV), and as occasion demands, an inorganic base such as sodium carbonate or an aqueous solution thereof can be used. The reaction can be carried out at a temperature ranging from -20℃ to 50℃.

Reaction Scheme (VI)



wherein,

R^1, R^2, R^3, R^4, R^5, R^6, Y, n, p, Q, G''' and m have same meanings as defined above.

In Reaction Scheme (VI), when the R^1 is C_{1-6}alkenyl, the compound of formula (XII) may be prepared by subjecting the compounds of formula (II) and (XIII) to condensation reaction, and then the compound of formula (I) may be prepared by adding amine, alcohol or thiol corresponding to R^1.

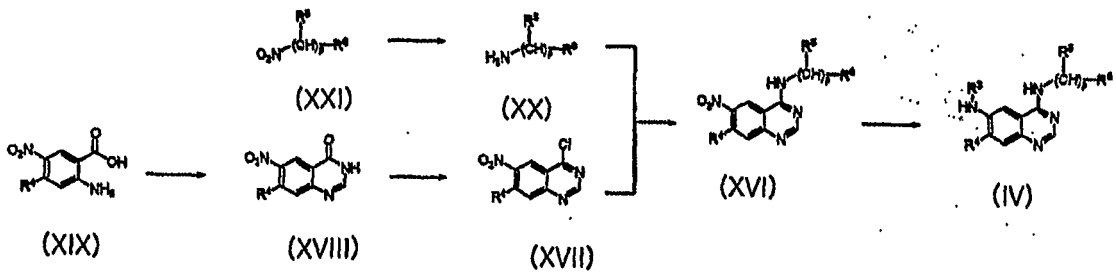
The compound of formula (XIII) is commercially available and it can be prepared in accordance with the conventional method [*Synthesis*, 1983, 745]. In case that the G''' is halogen, the compound of formula (VI) may be prepared by just adding a base, and in case that the G''' is hydroxy or trialkylsilyloxy, the compound of formula (VI) may be prepared by using the base after substituting the G''' to halogen by using thionylchloride, oxalylchloride or phosphorousoxychloride at at a temperature ranging from 0℃ to room temperature. Further, during the substitution, *N,N*-dimethylformamide can be optionally added in an catalytic amount, and the compound of formula (XIII) may be employed in an amount ranging from 1 to 3 equivalents based on the compound of formula (II). In this reaction, the base such as triethylamine, *N,N*-diisopropylethylamine, pyridine or *N*-methylmorpholine may be employed in an amount ranging from 1 to 5 equivalents. The solvent used in this

reaction may be selected from the group consisting of methylene chloride, chloroform, *N,N*-dimethylformamide, THF, 1,4-dioxane, acetonitrile and a mixture thereof, and the reaction can be carried out at a temperature ranging from -20℃ to 50℃, preferably 0 to room temperature.

The amine, alcohol or thiol added to the compound of formula (XII) is commercially available and it can be prepared in accordance with conventional methods, and the compounds may be employed in an amount of 1 to 10 equivalents, preferably 1 to 3 equivalents based on the compound of formula (XII). Further, an inorganic or organic base such as potassium carbonate, sodium carbonate, sodium hydride, triethylamine, 1,8-diazabicyclo[5.4.0]undec-7-en (DBU) and *N,N*-diisopropylethylamine may be used in an amount of 1 to 5 equivalents based on the compound of formula (XII). The solvent used in this reaction may be selected from the group consisting of THF, 1,4-dioxane, toluene, *N,N*-dimethylformamide, dimethoxyethane and a mixture thereof, and the reaction can be carried out at a temperature ranging from 0℃ to 150℃, preferably 0℃ to 60℃.

The compound of formula (IV) forementioned in Reaction Schemes (II) and (III) can be prepared by reducing the compound of formula (XVI) after reacting compounds of formula (XVII) and (XVIII) to obtain the compound of formula (XVI).

Reaction Scheme (VII)



wherein,

R^3, R^4, R^5, R^6 and p have same meanings as defined above.

In Reaction Scheme (VII), the compound of formula (XVI) can be

prepared by reacting compounds of formula (XVII) and (XVIII) to substitute a chloride of the compound of formula (XVII) to the compound of formula (XX). In this reaction, a base such as *N,N*-dimethylaniline can be added, and the reaction can be carried out in a solvent such as isopropanol and acetonitrile at a temperature ranging from 0℃ to 150℃, preferably room temperature to 100℃.

The reducing agent which used in this reaction may be selected from the group consisting of indium, palladium, platinum, iron, tartar, and oxide or chloride thereof, and employed in an amount of 1 to 5 equivalents based on the compound of formula (XVI). The reducing reaction can be carried out in the presence of hydrogen gas, and cyclohexene or cyclohexadien, or an inorganic or organic acid such as acetic acid, hydrochloric acid can be added thereto. The solvent used in this reaction may be selected from the group consisting of THF, 1,4-dioxane, ethylacetate, C_{1-6}alcohol, methylene chloride, chloroform, water, hexane, toluene and a mixture thereof.

The compound of formula (XX) is commercially available and it can be prepared in accordance with similar or identical method preparing the compound of formula (IV) from the compound of formula (XXI).

The compound of formula (XXI) is commercially available and it can be prepared in accordance with the method described by Yue-Mei Zhang *et al.*, [*Bioorganic and Medicinal Chemistry Letters*, 2004 *14*:111].

The compound of formula (XVII) can be prepared from the compound of formula (XIX) via the compound of formula (XVIII) ([Alexander J. Bridges *et al.*, *Journal of Medicinal Chemistry*, 1996 *39*:267]).

The compound of formula (I) of the present invention can also be used in the form of a pharmaceutically acceptable salt formed with an inorganic or organic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, acetic acid, glycolic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, malic acid, mandelic acid, tartaric acid, citric acid, ascorbic acid, palmitic acid, maleic acid, hydroxymaleic acid, benzoic acid, hydroxybenzoic acid, phenylacetic acid, cinnamic acid, salicylic acid, methanesulfonic acid, benzenesulfonic acid and toluenesulfonic acid.

The inventive compound or a pharmaceutically acceptable salt thereof

selectively inhibits the growth of cancer cells induced by epitelial cell growth factors, and provides enhanced anticancer effects when combined with other anticancer agents. Namely, the inventive compound or a pharmaceutically acceptable salt thereof is useful for enhancing the effects of anticancer agents selected from the group consisting of cell signal transduction inhibitors, mitosis inhibitors, alkylating agents, antimetabolites, antibiotics, growth factor inhibitors, cell cycle inhibitors, topoisomerase inhibitors, biological reaction modifiers, antihormonal agents and antiandrogen.

Therefore, the present invention provides a pharmaceutical composition for inhibiting cancer cell growth comprising the compound of formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient

The inventive compound or a pharmaceutically acceptable salt thereof may be administered orally or parenterally as an active ingredient in an effective amount ranging from about 0.01 to 100 mg/kg, preferably 0.2 to 50 mg/kg body weight per day in case of mammals including human in a single dose or in divided doses. However, the foregoing dosage should be monitored, and change in consideration of idiosyncrasy and weight of the patient, kind and seriousness of illnesses, characteristics of the drug and interval and duration of drug.

The pharmaceutical composition of the present invention may be formulated for oral and parenteral administration, including intravenous, intraperitoneal, subcutaneous, rectal and topical routes of administration in accordance with conventional methods. The composition for administration may take various forms such as tablets, powder, soft and hard gelatin capsules, aqueous solutions, suspensions, emulsions, syrups, granules, aerosol elixirs, sterilized aqueous solution, sterilized powder, non-aqueous solution and lyophilized agent, and additionally includes conventional additives such as a diluent, lubricant, filler, extender, wetting agent, absorbent, colorant, flavor, sweetener, preservative, emulsifier and the like.

The inventive pharmaceutical composition for oral administration may be prepared by mixing the active ingredient with a carrier, diluent or excipient. Examples of the carrier, excipient and diluent are a disintegrator (e.g., starch, sugar and mannitol); a filler and extender (e.g., calcium phosphate and silicate

derivatives); a binder (e.g., carboxymethylcellulose and a derivative thereof, gelatin, and polyvinylpyrrolidone); and a lubricant (e.g., talc, calcium stearate and magnesium stearate, and polyethylene glycol(s)).

Examples of the carrier employed in the injectable composition of the present invention is a water, saline solution, glucose solution, alcohol, glycol, ether (e.g., polyethylene glycol 400), oil, fatty acid, fatty acid ester, glyceride, surfactant, suspension or emulsifier.

The following Examples are intended to further illustrate the present invention without limiting its scope.

Example 1: Preparation of ({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-methyl)-carbamic acid *t*-butylester

(1-1) Preparation of 6-nitro-3*H*-quinazolin-4-one

150 g of 2-amino-5-nitro-benzoylic acid was added to 200 ml of formamide, the resulting solution was heated to 170℃ for 4 hours, and cooled to 100℃. 500 ml of ice water was added thereto, stirred for 1 hour, and the resulting mixture was filtered under a reduced pressure. The resulting residue was washed with water to obtain a solid, which was dried at 40℃ for 15 hours to obtain the title compound of formula (140 g, 90%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 8.77 (d, *J*=2.7 Hz, 1H), 8.55 (dd, *J*=6.9 Hz, 1H), 8.36 (s, 1H), 7.84 (d, *J*=9 Hz, 1H).

(1-2) Preparation of 4-chloro-6-nitro-quinazoline hydrochloride

415 ml of thionylchloride and 123 ml of phosphorousoxy chloride were added to 80 g of the compound obtained in (1-1), and the mixture was stirred at 120℃ for 10 hours after adding 3 ml of *N,N*-dimethylformamide. The reacted solution was cooled to room temperature, concentrated under a reduced pressure, 240 ml of toluene was added thereto, and the resulting solution was

concentrated under a reduced pressure again to obtain the title compound of formula (72 g, 69%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 8.80 (d, J=2.6 Hz, 1H), 8.57 (dd, J=3.9 Hz, 1H), 8.35 (s, 1H), 7.89 (d, J=9 Hz, 1H).

(1-3) Preparation of [3-chloro-4-(3-fluoro-benzyloxy)-phenyl]-(6-nitro-quinazolin-4-yl)-amine hydrochloride

72 g of the compound obtained in (1-2) and 74 g of 3-chloro-4-(3-fluoro-benzyloxy)-phenylamine were added to 1,000 ml of isopropanol, and the solution was stirred at 100℃ for 17 hours. The mixture was cooled to room temperature and concentrated under a reduced pressure. The concentrate was washed with acetone and dried at 40℃ for 15 hours to obtain the tile compound (118 g, 91%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.82 (d, J=2 Hz, 1H), 8.97 (d, J=3 Hz, 1H), 8.75 (dd, J=6,9 Hz, 1H), 8.14 (d, J=9 Hz, 1H), 7.93 (d, J=3 Hz, 1H), 7.70 (dd, J=2.6, 9 Hz, 1H), 7.45-7.48 (m, 1H), 7.29-7.36 (m, 3H), 7.18 (t, J=6 Hz, 1H), 5.29 (s, 2H).

(1-4) Preparation of N^4-[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]-quinazolin-4,6-diamine

700 ml of THF and 1,400 ml of water were added to 118 g of the compound obtained in (1-3), and 92 g of indium and 192 ml of HCl were added thereto sequentially. The reacted solution was stirred at room temperature for 10 hours, distilled under a reduced pressure to remove THF, and left at 0℃ for 30 mins. The resulting solid was filtered and stirred for 30 mins in 1,000 ml of saturated aqueous sodium bicarbonate solution. The resulting mixture was filtered under a reduced pressure, and the residue was washed with water and dried at 40℃ to obtain the title compound (80 g, 83%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.42 (s, 1H), 8.40(s, 1H), 8.03 (d, *J*=2 Hz, 1H), 7.73 (dd, *J*=2.4, 9 Hz, 1H), 7.43-7.53 (m, 2H), 7.29-7.33 (m, 3H), 7.18-7.25 (m, 3H), 5.61 (s, 2H), 5.24 (s, 2H).

(1-5) Preparation of ({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-methyl)-carbamic acid *t*-butylester

297 mg of 1-hydroxylbenzotriazole and 959 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 664 mg of *t*-buthoxycarbonylacetic acid dissolved in 10 ml of THF, and the solution was reacted at room temperature for 2 hours after adding 1 g of the compound obtained in (1-4). The reacted solution was washed with distilled water, dried over magnesium sulfate, filtered and distilled under a reduced pressure to obtain impure residue, and the resulting residue was subjected to column chromatography (column- silica gel 60 (Merck, 107719); eluent- methylene chloride : methanol = 20 : 1) to obtain the title compound (1.35 g, 97%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.40 (br s, 1H), 8.67 (s, 1H), 8.34 (br s, 1H), 8.02 (d, 1H), 7.73 (m, 3H), 7.4 8(m, 2H), 7.35 (m, 2H), 7.15 (t, 1H), 7.07 (d, 1H), 5.63 (t, 1H), 5.26 (s, 2H), 4.16 (d, 2H), 1.59 (s, 9H).

Example 2: Preparation of *N*-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-methyl)-2-methoxy-acetamide

(2-1) Preparation of (2-methoxy-acetylamino)-acetic acid ethylester

1.5 ml of triethylamine was added to 500 mg of amino-acetic acid ethylester hydrochloride dissolved in 5 ml of chloroform, and the solution was cooled to -78℃. 0.34 ml of methoxyacetylchloride diluted with 3 ml of chloroform was slowly added thereto, and the resulting solution was heated slowly to room temperature and reacted for 6 hours. The reacted solution was washed with distilled water, adjusted to pH 8 to 9 by adding saturated sodium bicarbonate solution, extracted with organic solvent, dried over magnesium sulfate, and filtered and distilled under a reduced pressure to obtain the title compound (595 mg, 75%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 7.15 (br s, 1H), 4.26 (q, 2H), 4.11 (d, 2H), 3.98 (s, 2H), 3.48 (s, 3H), 1.33 (t, 3H).

(2-2) Preparation of (2-methoxy-acetylamino)-acetic acid

229 mg of lithium hydroxide was added to 595 mg of the compound obtained in (2-1) dissolved in 6 ml of 50% aqueous THF solution, and the solution was reacted for 4 hours. The reacted solution was washed with distilled water, adjusted to pH 2 by adding 1 N HCl solution, extracted with organic solvent several times, dried over magnesium sulfate, and filtered and distilled under a reduced pressure to obtain the title compound (110 mg, 21%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 4.09 (s, 2H), 3.50 (s, 3H), 3.45 (d, 2H).

(2-3) Preparation of 2-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-acetamide

25 ml of trifluoroacetic acid was added to 1.3 g of the compound obtained in (1-5) of Example 1 dissolved in 25 ml of methylene chloride, and the solution was reacted at room temperature for 2 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was dissolved in distilled water, washed with saturated sodium bicarbonate solution. The organic layer was dried over magnesium sulfate, and filtered and distilled under a reduced pressure to obtain the title compound (394 mg, 36%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.96 (s, 1H), 8.93 (d, 1H), 8.80 (s, 1H), 7.99 (m, 2H), 7.66 (dd, 1H), 7.60 (dd, 1H), 7.44 (m, 1H), 7.35 (m, 2H), 7.08 (m, 2H), 5.27 (s, 2H), 3.6 7(s, 2H).

(2-4) Preparation of *N*-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-methyl)-2-methoxy-acetamide

110 mg of the compound obtained in (2-2) and 0.4 ml of triethylamine were dissolved in 5 ml of THF, and the solution was cooled to 0℃. 0.18 ml of isobutylchloroformate was added thereto, and the resulting solution was stirred

for 20 mins. 134 mg of the compound obtained in (1-4) of Example 1 diluted with 2 ml of THF was added thereto, and the solution was reacted at -20℃ for 8 hours. The reacted solution was adjusted to pH 9 by adding saturated sodium bicarbonate solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (10 mg, 6%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.73 (m, 2H), 8.52 (s, 1H), 7.87 (m, 2H), 7.62 (s, 1H), 7.51 (td, 2H), 7.35 (m, 1H), 7.23 (m, 1H), 7.00 (m, 2H), 5.16 (s, 2H), 4.09 (s, 2H), 3.56 (s, 3H), 3.50 (m, 2H).

Example 3: Preparation of *N*-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-methyl)-2-methanesulfonyl-acetamide

16 mg of 1-hydroxylbenzotriazole and 53 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 18 mg of methanesulfonylacetic acid dissolved in 3 ml of THF, and the solution was reacted at room temperature for 2 hours after adding 50 mg of the compound obtained in (2-1) of Example 2. The reacted solution was extracted with distilled water, and the resulting residue was filtered under a reduced pressure to obtain the title compound (44 mg, 70%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.60 (s, 1H), 8.52 (s, 1H), 7.82 (d, 1H), 7.69 (m, 2H), 7.54 (dd, 1H), 7.31 (m, 2H), 7.21 (t, 2H), 6.97 (m, 2H), 5.12 (s, 2H), 4.12 (s, 2H), 4.03 (s, 2H), 3.14 (s, 3H).

Example 4: Preparation of *N*-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-methyl)-acrylamide

22 μl of acrylic acid dissolved in 2 ml of THF was cooled to 0℃, and 30 μl of pyridine was added thereto. 70 mg of the compound (2-1) of Example 2

and 59 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added thereto, and the solution was reacted at 0℃ for 7.5 hours. The reacted solution was washed with saturated sodium bicarbonate solution, dried over sodium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent-chloroform : methanol = 15 : 1) to obtain the title compound (14.8 mg, 19%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.51 (d, 1H), 8.35 (s, 1H), 7.78 (d, 1H), 7.64 (m, 2H), 7.48 (m,1H), 7.29 (m, 2H), 7.18 (m, 2H), 7.04 (d, 1H), 6.95 (t, 1H), 6.27 (d, 1H), 6.20 (dd, 1H), 5.64 (dd, 1H), 5.11 (s, 2H), 4.07 (s, 2H).

Example 5: Preparation of (2*S*)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-(2-methoxy-acetylamino)-3-phenyl-propionamide

(5-1) Preparation of (2*S*)-2-(2-methoxy-acetylamino)-3-phenyl-propionic acid methylester

500 mg of 2-amino-3-phenyl-propionic acid methylester hydrochloride dissolved in 10 ml of chloroform was cooled to -78℃, 0.96 ml of triethylamine and 0.23 ml of methoxyacetylchloride were added thereto, and the solution was reacted at room temperature for 2 hours. The reacted solution dissolved in distilled water was adjusted to pH 9 by adding saturated sodium bicarbonate solution, extracted with organic solvent, dried over magnesium sulfate, and filtered and distilled under a reduced pressure to obtain the title compound (427 mg, 73%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 7.27 (m, 5H), 7.13 (d, 2H), 6.92 (d, 1H), 4.92 (m, 1H), 3.88 (s, 2H), 3.72 (s, 3H), 3.35 (s, 3H), 3.14 (m, 2H).

(5-2) Preparation of (2*S*)-(2-methoxy-acetylamino)-3-phenyl-propionic acid

122 mg of lithium hydroxide was added to 427 mg of the compound obtained in (5-1) dissolved in 10 ml of 50% aqueous THF solution, and the

solution was reacted for 2 hours. The reacted solution was diluted with distilled water, adjusted to pH 3 to 4 by adding 1 N HCl solution, extracted with organic solvent, dried over magnesium sulfate, and filtered and distilled under a reduced pressure to obtain the title compound (120 mg, 100%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 7.28 (m, 3H), 7.19 (d, 2H), 6.95 (d, 1H), 4.91 (q, 1H), 3.89 (s, 2H), 3.34 (s, 3H), 3.25 (dd, 1H), 3.15 (dd, 1H).

(5-3) Preparation of (2*S*)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-(2-methoxy-acetylamino)-3-phenyl-propionamide

76 mg of 1-hydroxylbenzotriazole, 244 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, and 200 mg of the compound obtained in (1-4) of Example 1 were added to 120 mg of the compound obtained in (5-2) dissolved in 8 ml of THF, and the solution was reacted at room temperature for 15 hours. The reacted solution was washed with distilled water, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (94 mg, 30%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.30 (br s, 1H), 8.58 (d, 1H), 8.08 (d, 1H), 7.86 (m, 2H), 7.63 (m, 2H), 7.48 (m, 1H), 7.29 (m, 7H), 7.00 (m, 2H), 5.15 (s, 2H), 4.93 (m, 1H), 3.93 (m, 2H), 3.37 (s, 3H), 3.30 (m, 1H), 3.16 (m, 1H).

Example 6: Preparation of (1*S*)-(1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-3-methanesulfanyl-propyl)-carbamic acid *t*-butylester

The procedure of (5-3) of Example 5 was repeated except for using 126 mg of 2-*t*-buthoxycarbonylamino-4-methanesulfanyl-butyric acid instead of the compound obtained in (5-2) of Example 5 to obtain the title compound (80 mg, 25%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.64 (br s, 1H), 8.48 (s, 1H), 7.91 (d, 1H), 7.79 (m, 2H), 7.60 (dd, 1H), 7.42 (m, 1H), 7.34 (m, 3H), 7.18 (d, 1H), 7.08 (t, 1H), 5.24 (s, 2H), 4.40 (m, 1H), 2.67 (m, 2H), 2.14 (s, 3H), 2.08 (m, 2H), 1.46 (s, 9H); MS(ESI): [M+H+] 626.

Example 7: Preparation of (2*S*)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-(2-methoxy-acetylamino)-4-methanesulfanyl-butyramide

(7-1) Preparation of (2*S*)-2-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-methanesulfanyl-butyramide

10 ml of trifluoroacetic acid was added to 527 mg of the compound obtained in Example 6 dissolved in 10 ml of methylene chloride, and the solution was reacted at room temperature for 3 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was adjusted to pH 9 by adding saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate, and filtered and distilled under a reduced pressure to obtain the title compound (370 mg, 84%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.97 (br s, 1H), 8.82 (d, 1H), 8.68 (s, 1H), 7.85 (m, 2H), 7.51 (m, 2H), 7.37 (m, 1H), 7.23 (m, 2H), 7.00 (m, 2H), 5.16 (s, 2H), 3.74 (m, 1H), 2.70 (m, 2H), 2.35 (m, 1H), 2.15 (s, 3H), 1.88 (m, 1H).

(7-2) Preparation of (2*S*)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-(2-methoxy-acetylamino)-4-methanesulfanyl-butyramide

108 mg of the compound obtained in (7-1) dissolved in 3 ml of chloroform was cooled to -78℃ after adding 70 μl of triethylamine, and 70 μl of methoxyacetylchloride dissolved in 2 ml of chloroform was added thereto. The reacted solution was washed with saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (16 mg, 16%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.27 (s, 1H), 8.62 (s, 1H), 8.32 (m, 1H), 7.86 (m, 1H), 7.75 (m, 2H), 7.60 (m, 2H), 7.34 (m, 1H), 7.15 (m, 1H), 6.89 (m, 3H), 5.16 (s, 2H), 4.85 (m, 1H), 3.98 (m, 2H), 3.47 (s, 2H), 3.45 (s, 3H), 2.65 (m, 2H), 2.14 (s, 3H); MS(ESI): [M+H+] 598.

Example 8: Preparation of (2*S*)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-(2-methanesulfonyl-acetamino)-4-methanesulfanyl-butyramide

43 mg of 1-hydroxylbenzotriazole, 103 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 150 mg of the compound obtained in (7-1) of Example 7 were added to 47.2 mg of methanesulfonylacetic acid dissolved in 6 ml of methylene chloride, and the solution was reacted at room temperature for 6 hours. The reacted solution was washed with distilled water, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (40 mg, 22%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.31 (s, 1H), 8.51 (s, 1H), 8.39 (d, 1H), 8.24 (s, 1H), 7.72 (d, 1H), 7.52 (m, 3H), 7.33 (m, 1H), 7.18 (t, 2H), 7.00 (t, 1H), 6.83 (d, 1H), 5.03 (s, 2H), 4.85 (m, 1H), 4.18 (m, 2H), 3.15 (s, 3H), 2.61 (t, 2H), 2.18 (m, 2H), 2.03 (s, 3H); MS(ESI): [M+H+] 647.

Example 9: Preparation of (2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-methanesulfanyl-butyramide

5 μl of acrylic acid dissolved in 5 ml of methylene chloride was cooled to 0℃, 20 μl of *N,N'*-diisopropylethylamine, 27 mg of *O*-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate and 30 mg of the compound obtained in (7-1) of Example 7 were added thereto, and reacted for 2 hours.

The reacted solution was washed with distilled water, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (6 mg, 19%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.13 (s, 1H), 8.49 (s, 1H), 7.79 (d, 2H), 7.69 (d, 1H), 7.54 (m, 3H), 7.34 (m, 1H), 7.20 (m, 2H), 7.01 (t, 1H), 6.88 (d, 1H), 6.30 (dd, 2H), 5.71 (dd, 1H), 5.09 (s, 2H), 5.02 (m, 1H), 2.72 (t, 2H), 2.02 (m, 2H), 2.13 (s, 3H).

Example 10: Preparation of (1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-cyclopropyl)-carbamic acid *t*-butylester

76 mg of 1-hydroxylbenzotriazole, 244 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 200 mg of the compound obtained in (1-4) of Example 1 were added to 180 mg of 1-*t*-buthoxycarbonylamino-cyclopropylcarboxylic acid dissolved in 15 ml of methylene chloride, and reacted at room temperature for 6 hours. The reacted solution was washed with distilled water, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (160 mg, 55%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.92 (br s, 1H), 8.66 (m, 2H), 7.83 (m, 2H), 7.54 (dd, 1H), 7.39 (m, 2H), 7.22 (m, 2H), 6.98 (m, 2H), 5.15 (s, 2H), 1.70 (m, 2H), 1.50 (s, 9H), 1.18 (m, 2H).

Example 11: Preparation of (2*S*)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-(2-methoxy-acetylamino)-2-phenyl-acetamide

38 mg of 1-hydroxylbenzotriazole and 121 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 68 mg of (2-methoxy-acetylamino)-phenyl-acetic acid dissolved in 5 ml of methylene chloride, and reacted at room temperature for 28 hours after adding 100 mg of the compound obtained in (1-4) of Example 1. The reacted solution was washed with distilled water, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (22 mg, 15%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.52 (s, 1H), 8.44 (s, 1H), 7.74 (m, 2H), 7.54 (m, 1H), 7.45 (m, 2H), 7.30 (m, 3H), 7.13 (m, 3H), 6.94 (m, 2H), 6.81 (m, 1H), 5.03 (s, 2H), 3.91 (s, 1H), 3.83 (s, 2H), 3.34 (s, 3H); MS(ESI): [M+H+] 602.

Example 12: Preparation of (4*S*)-4-*t*-buthoxycarbonylamino-4-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-butyric acid methylester

109 mg of 1-hydroxylbenzotriazole and 350 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 230 mg of 2-*t*-buthoxycarbonylamino-pentanedionic acid-5-methylester dissolved in 10 ml of methylene chloride, and reacted at room temperature for 13 hours after adding 289 mg of the compound obtained in (1-4) of Example 1. The reacted solution was washed with distilled water, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (87 mg, 19%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.57 (s, 1H), 8.38 (s, 1H), 7.80 (d, 1H), 7.71 (d, 1H), 7.56 (m, 1H), 7.46 (m ,2H), 7.26 (m, 2H), 7.12 (m, 1H), 6.92 (m ,2H), 5.08 (s, 2H), 4.27 (m, 1H), 3.65 (s, 3H), 2.18 (m, 2H), 1.98 (m, 2H), 1.38 (s, 9H).

Example 13: Preparation of 4-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-4-(2-methoxy-acetylamino)-butyric acid methylester

(13-1) Preparation of (4*S*)-4-amino-4-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-butyric acid methylester

4.6 ml of trifluoroacetic acid was added to 80 mg of the compound obtained in Example 12 dissolved in 4.6 ml of methylene chloride, and reacted at room temperature for 4 hours. The reacted solution was distilled under a reduced pressure to obtain residue, and the residue was washed with saturated sodium bicarbonate, dried over magnesium sulfate, and filtered and distilled under a reduced pressure to obtain the title compound (76 mg, 99%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.83 (s, 1H), 8.70 (s, 1H), 7.89 (m, 2H), 7.59 (m, 2H), 7.37 (m, 2H), 7.25 (m, 1H), 6.98 (m, 2H), 5.18 (s, 2H), 3.73 (s, 3H), 2.60 (t, 1H), 2.32 (m, 2H), 2.06 (m, 2H).

(13-2) Preparation of 4-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-4-(2-methoxy-acetylamino)-butyric acid methylester

17 mg of 1-hydroxylbenzotriazole and 53 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 20 μl of methoxyacetic acid dissolved in 5 ml of methylene chloride, and the solution was reacted at room temperature for 8 hours after adding 60 mg of the compound obtained in (13-1). The reacted solution was washed with distilled water, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (20 mg, 29%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.67 (s, 1H), 8.50 (s, 1H), 8.07 (s, 1H), 7.80 (d, 1H), 7.57 (d, 3H), 7.43 (d, 1H), 7.29 (m, 1H), 7.16 (t, 2H), 6.88 (m, 2H),

5.08 (s, 2H), 4.56 (m, 1H), 3.92 (d, 2H), 3.65 (s, 3H), 3.40 (s, 3H), 2.50 (m, 2H), 2.25 (m, 2H).

Example 14: Preparation of 4-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-4-(2-methoxy-acetylamino)-butyric acid

8 mg of the compound obtained in (13-2) of Example 13 dissolved in 2.4 ml of 50% aqueous THF solution was reacted for 13 hours after adding 1 mg of lithium hydroxide. The reacted solution was diluted with distilled water, adjusted to pH 4.8 by adding 1 N HCl aqueous solution, and filtered under a reduced pressure to obtain the title compound (6.2 mg, 80%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.53 (d, 1H), 8.37 (s, 1H), 7.81 (d, 1H), 7.75 (d, 1H), 7.67 (d, 1H), 7.50 (dd, 1H), 7.32 (m, 1H), 7.19 (m, 2H), 7.07 (d, 1H), 6.96 (t, 1H), 5.13 (s, 2H), 4.52 (m, 1H), 4.47 (s, 2H), 3.37 (s, 3H), 2.34 (t, 2H), 2.14 (m, 2H); MS(ESI): [M+H+] 596.

Example 15: Preparation of 2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-pyrrolidine-1-carboxylic acid *t*-butylester

187 mg of 1-hydroxylbenzotriazole and 604 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 299 mg of proline-1,2-dicarboxylic acid-1-*t*-butylester dissolved in 5 ml of THF, and reacted at room temperature for 5 hours after adding 500 mg of the compound obtained in (1-4) of Example 1. The reacted solution was washed with distilled water, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (459 mg, 61%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.24 (s, 1H), 8.47 (s, 1H), 7.93 (s, 1H), 7.73 (m, 4H), 7.35 (m, 2H), 7.24 (m, 1H), 7.00 (m, 2H), 5.15 (s, 2H), 4.66 (m, 1H), 3.68 (m, 1H), 3.53 (m, 1H), 2.25 (m, 4H), 1.46 (s, 9H).

Example 16: Preparation of 1-(2-methoxy-acetyl)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide

(16-1) Preparation of pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of (13-1) of Example 13 was repeated except for using 448 mg of the compound obtained in Example 15 instead of the compound obtained in Example 12 to obtain the title compound (297 mg, 82%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.39 (br s, 1H), 8.93 (s, 1H), 8.83 (s, 1H), 8.06 (d, 1H), 7.79 (d, 1H), 7.69 (m, 2H), 7.54 (m, 1H), 7.40 (m, 2H), 7.18 (m, 2H), 5.33 (s, 2H), 4.20 (m, 1H), 3.31 (m, 2H), 2.46 (m, 1H), 2.28 (m, 1H), 2.02 (m, 2H).

(16-2) Preparation of 1-(2-methoxy-acetyl)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide

21 mg of 1-hydroxylbenzotriazole and 68 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 19 mg of methoxyacetic acid dissolved in 5 ml of THF, and reacted at room temperature for 9 hours after adding 70 mg of the compound obtained in (16-1). The reacted solution was washed with distilled water, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (73 mg, 91%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.51 (s, 1H), 7.96 (s, 1H), 7.83 (d, 1H), 7.67 (m, 2H), 7.56 (d, 1H), 7.26 (m, 1H), 7.17 (m, 1H), 6.93 (m, 2H), 5.09 (s,

2H), 4.84 (m, 1H), 4.11 (d, 2H), 3.68 (m, 2H), 3.51 (m, 2H), 3.40 (s, 3H), 2.19 (m, 2H).

Example 17: Preparation of 1-(2-methanesulfonyl-acetyl)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide

21 mg of 1-hydroxylbenzotriazole and 67 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 30 mg of methanesulfonylacetic acid dissolved in 5 ml of THF, and reacted at room temperature for 9 hours after adding 70 mg of the compound obtained in (16-1) of Example 16. The reacted solution was washed with distilled water, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (66 mg, 76%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.59 (s, 1H), 8.57 (s, 1H), 7.82 (d, 1H), 7.75 (d, 1H), 7.54 (m, 2H), 7.29 (m, 1H), 7.19 (m, 2H), 6.91 (m, 2H), 5.09 (s, 2H), 4.79 (m, 1H), 4.10 (dd, 2H), 3.92 (m, 1H), 3.69 (m, 1H), 3.13 (s, 3H), 2.41 (m, 1H), 2.12 (m, 3H).

Example 18: Preparation of 1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide

40 μl of pyridine and 100 mg of the compound obtained in (16-1) of Example 16 dissolved in 4 ml of THF were added to 30 μl of acrylic acid dissolved in 1 ml of THF at 0℃, and reacted with 82 mg of the compound obtained in (16-1) of Example 16 for 6 hours. The reacted solution was washed with distilled water, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (30 mg, 27%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.56 (s, 1H), 8.49 (s, 1H), 7.90 (d, 1H), 7.75 (m, 3H), 7.44 (d, 1H), 7.37 (m, 1H), 7.25 (m, 2H), 7.05 (t, 1H), 7.10 (d, 1H), 6.60 (dd, 1H), 6.45 (dd, 1H), 5.81 (dd, 1H), 5.15 (s, 2H), 5.00 (m, 1H), 3.93 (m, 1H), 3.76 (m, 1H), 2.26 (m, 4H).

Example 19: Preparation of (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid *t*-butylester

0.29 g of 3-*t*-buthoxycarbonylamino-propionic acid, 0.6 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride 0.6 g and 0.2 g of hydroxylbenzotriazole dissolved in 20 ml of methylene chloride were stirred at room temperature for 13 hours after adding 0.5 g of the compound obtained in (1-4) of Example 1 at room temperature for 13 hours. The reacted solution was extracted with methylene chloride 2 times after adding saturated sodium bicarbonate solution, washed with distilled saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent-chloroform : methanol = 15 : 1) to obtain the title compound (0.3 g, 42%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.20 (s, 1H), 9.73 (s, 1H), 8.64 (s, 1H), 8.48 (s, 1H), 7.92 (d, 1H), 7.74 (m, 2H), 7.45 (d, 2H), 7.18 (m, 4H), 6.84 (t, 1H), 5.20 (s, 2H), 3.40 (t, 2H), 2.42 (t, 2H), 1.33 (s, 9H); MS(ESI): [M+H+] 566.

Example 20: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-propionamide

(20-1) Preparation of 3-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide

0.42 g of the compound obtained in Example 19 dissolved in 13 ml of methylene chloride and 13 ml of trifluoroacetic acid was stirred at room temperature for 2 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was melted in 10 ml of methylene chloride

while adding 20 ml of saturated sodium bicarbonate slowly, and filtered under a reduced pressure to obtain the title compound as solid (0.34 g, 98%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.67 (s, 1H), 8.47 (s, 1H), 7.90 (d, 1H), 7.76 (m, 2H), 7.60 (dd, 1H), 7.42 (m, 1H), 7.30 (m, 2H), 7.16 (d, 1H), 7.06 (t, 1H), 5.22 (s, 2H), 3.08 (m, 2H), 2.68 (t, 2H).

(20-2) Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-propionamide

0.07 ml of triethylamine was added to 0.08 g of the compound obtained in (20-1) dissolved in 3 ml of methylene chloride, and reacted with 0.03 ml of methoxyacetylchloride at -70 ℃ for 30 mins and at room temperature for 4 hours. The reacted solution was extracted with methylene chloride 2 times after adding saturated sodium bicarbonate solution, washed with distilled saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.04 g, 44%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.64 (s, 1H), 8.47 (s, 1H), 7.87 (d, 1H), 7.80 (s, 1H), 7.73 (s, 2H), 7.58 (dd, 1H), 7.36 (m, 1H), 7.30 (m, 2H), 7.13 (d, 1H), 7.04 (t, 1H), 5.21 (s, 2H), 3.90 (s, 2H), 3.66 (t, 2H), 3.42 (s, 3H), 2.72 (t, 2H).

Example 21: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-propionamide

0.12 g of methanesulfonylacetic acid, 0.34 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.12 g of methylene chloride dissolved in 2 ml of methylene chloride was stirred at room temperature for 2 hours after adding 0.2 g of the compound obtained in (20-1) of Example 20. The reacted solution was filtered under a reduced pressure

after adding saturated sodium bicarbonate to obtain the title compound as solid (0.2 g, 80%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.35 (s, 1H), 9.83 (s, 1H), 8.66 (s, 1H), 8.50 (m, 2H), 7.95 (s, 1H), 7.86 (d, 1H), 7.65 (m, 2H), 7.48 (m, 1H), 7.32 (m, 2H), 7.18 (m, 2H), 5.23 (s, 2H), 4.08 (s, 2H), 3.44 (m, 2H), 3.11 (s, 3H), 2.58 (t, 2H).

Example 22: Preparation of *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

0.03 ml of acrylic acid, 0.1 ml of diisopropylethylamine and 0.15 g of *O*-(1*H*-benzotriazolyl-1-yl)-*N,N,N'N'*-tetramethyluronium tetrafluoroborate dissolved in 10 ml of methylene chloride at 0 ℃ was reacted with 0.14 g of the compound obtained in (20-1) of Example 20 for 10 mins and at room temperature for 15 hours. The reacted solution was extracted with methylene chloride 2 times after adding saturated sodium bicarbonate solution, washed with distilled saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.05 g, 37%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.59 (s, 1H), 8.37 (s, 1H), 7.84 (d, 1H), 7.70 (s, 1H), 7.60 (d, 1H), 7.51 (m, 1H), 7.37 (m, 1H), 7.21 (m, 2H), 7.04 (m, 2H), 6.23 (d, 2H), 5.65 (t, 1H), 5.17 (s, 2H), 3.66 (t, 2H), 2.72 (t, 2H); MS(ESI): [M+H+] 520.2.

Example 23: Preparation of 3-phenyl-propionylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

32.2 mg of phenylpropagylic acid dissolved in 1 ml of THF was cooled to 0℃, and reacted with 22 μl of pyridine, 50 mg of the compound obtained (20-1) of Example 20 and 41 mg of 1-(3-dimethylaminopropyl)-3-

ethylcarbodiimide hydrochloride for 15 hours. The reacted solution was diluted with distilled water, washed with saturated sodium bicarbonate solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent-chloroform : methanol = 15 : 1) to obtain the title compound (16.9 mg, 26%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.46 (s, 1H), 8.24 (s, 1H), 7.67 (d, 1H), 7.53 (s, 2H), 7.34 (dd, 1H), 7.30 (m, 2H), 7.20 (m, 4H), 7.05 (m, 2H), 6.94 (d, 1H), 6.83 (t, 1H), 5.00 (s, 2H), 3.45 (t, 2H), 2.52 (t, 2H); MS(ESI): [M+H+] 594.

Example 24: Preparation of hexa-2,4-dienonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

The procedure of Example 23 was repeated except for using 25 mg of 2,4-hexadienonylic acid instead of phenylpropagylic acid. The resulting solution was poured into ice water after adding 4 droplets of saturated sodium bicarbonate solution to obtain solid. The solid was dissolved in a mixture of methylene chloride and methanol, and the solution was recrystallized with hexane to obtain the title compound (36.1 mg, 58.2%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.77 (s, 1H), 8.58 (s, 1H), 8.01 (d, 1H), 7.87 (d, 2H), 7.72 (dd, 1H), 7.53 (m, 1H), 7.43 (m, 2H), 7.26 (m, 2H), 7.18 (m, 1H), 6.25 (m, 3H), 6.01 (d, 1H), 5.34 (s, 2H), 3.77 (t, 2H), 2.83 (t, 2H), 1.94 (d, 3H); MS(ESI): [M+H+] 560.

Example 25: Preparation of cyclopent-1-en carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

The procedure of Example 23 was repeated except for using 25 mg of 1-cyclopentene carboxylic acid instead of phenylpropagylic acid. 2 ml of distilled water was added to the resulting solution to obtain solid. The solid was dissolved in a mixture of methylene chloride and methanol, and the

solution was recrystallized with hexane to obtain the title compound (29.3 mg, 47.3%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.55 (s, 1H), 8.30 (s, 1H), 7.80 (d, 1H), 7.66 (s, 2H), 7.51 (dd, 1H), 7.31 (m, 1H), 7.19 (m, 2H), 7.08 (d, 1H), 6.96 (m, 1H), 6.47 (s, 1H), 5.13 (s, 2H), 3.55 (t, 2H), 2.63 (t, 2H), 2.41 (m, 4H), 1.87 (t, 2H); MS(ESI) : [M+H+] 560.

Example 26: Preparation of *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-3-phenyl-acrylamide

The procedure of Example 23 was repeated except for using 32.3 mg of cinnamic acid instead of phenylpropagylic acid. The resulting solution was poured into ice water after adding 4 droplets of saturated sodium bicarbonate solution to obtain solid. The solid was dissolved in a mixture of methylene chloride and methanol, and the solution was recrystallized with hexane to obtain the title compound (35.6 mg, 56%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.87 (s, 1H), 8.66 (s, 1H), 8.09 (d, 1H), 7.94 (m, 2H), 7.77 (m, 4H), 7.56 (m, 5H), 7.37 (d, 1H), 7.26 (m, 1H), 6.82 (d, 2H), 5.43 (s, 2H), 3.91 (t, 2H), 2.96 (t, 2H); MS(ESI): [M+H+] 596.

Example 27: Preparation of but-2-ynoylic acid(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

The procedure of Example 23 was repeated except for using 19 mg of 2-butenoylic acid instead of phenylpropagylic acid to obtain the title compound (11.8 mg, 20%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.54 (s, 1H), 8.34 (s, 1H), 7.77 (s, 1H), 7.62 (s, 2H), 7.46 (dd, 1H), 7.28 (m, 1H), 7.17 (m, 2H), 7.04 (d, 1H), 6.93 (t, 1H), 5.10 (s, 2H), 3.47 (t, 2H), 2.57 (t, 2H), 1.82 (s, 3H); MS(ESI): [M+H+] 532.

Example 28: Preparation of but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

0.64 ml of pyridine was added to 50 mg of the compound obtained (20-1) of Example 20, cooled to 0℃, and reacted with 12.5 μl of crotonylchloride dissolved in 0.26 ml of diethylether for 4 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was dissolved in distilled water, washed with saturated sodium bicarbonate solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent-chloroform : methanol = 15 : 1) to obtain the title compound (12.6 mg, 22%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.56 (s, 1H), 8.37 (s, 1H), 7.80 (d, 1H), 7.65 (d, 2H), 7.51 (dd, 1H), 7.31 (m, 1H), 7.21 (m, 2H), 7.07 (d, 1H), 6.96 (td, 1H), 6.70 (dd, 1H), 5.84 (dd, 1H), 5.13 (s, 2H), 3.54 (t, 2H), 2.61 (t, 2H), 1.74 (dd, 2H); MS(ESI): [M+H] 534.

Example 29: Preparation of 3-methyl-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

The procedure of Example 28 was repeated except for using 14.3 μl of 3,3-dimethylacryloylchloride instead of crotonylchloride. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred after adding distilled water, and filtered under a reduced pressure to obtain the title compound (47.9 mg, 81.2%).

^{1}H-NMR (CD_3OD, 300MHz)): δ 8.87 (s, 1H), 8.66 (s, 1H), 7.98 (d, 1H), 7.95 (dd, 1H), 7.86 (d, 1H), 7.69 (dd, 1H), 7.50 (m, 1H), 7.36 (m, 2H), 7.29 (d, 1H), 7.13 (t, 1H), 5.77 (s, 1H), 5.34 (d, 2H), 3.69 (t, 2H), 2.79 (t, 2H), 2.19 (d, 3H), 1.92 (d, 3H); MS(ESI): [M+H+] 548.

Example 30: Preparation of *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-2-methyl-acrylamide

The procedure of Example 28 was repeated except for using 13 μl of metacryloy chloride instead of crotonylchloride to obtain the title compound (14.6 mg, 25.5%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.86 (s, 1H), 8.66 (s, 1H), 8.09 (d, 1H), 7.95 (s, 2H), 7.80 (dd, 1H), 7.59 (m, 1H), 7.49 (m, 2H), 7.37 (d, 1H), 7.26 (t, 1H), 5.90 (s, 1H), 5.57 (s, 1H), 5.41 (s, 2H), 3.84 (t, 2H), 2.92 (t, 2H), 2.14 (s, 3H); MS(ESI): [M+H] 534.

Example 31: Preparation of *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-2-cyano-acetamide

The procedure of Example 21 was repeated except for using cyano acetic acid instead of methanesulfonylacetic acid and 0.09 g of the compound obtained in (20-1) of Example 20 to obtain the title compound (0.09 g, 88%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.28 (s, 1H), 9.76 (s, 1H), 8.66 (s, 1H), 8.49 (s, 1H), 8.35 (t, 1H), 7.97 (d, 1H), 7.83 (dd, 1H), 7.73 (d, 1H), 7.68 (dd, 1H), 7.45 (m, 1H), 7.29 (m, 2H), 7.23 (d, 1H), 7.17 (t, 1H), 5.24 (s, 2H), 3.61 (s, 2H), 3.41 (q, 2H), 2.59 (t, 2H).

Example 32: Preparation of 3-methyl-isoxazol-5-carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

The procedure of Example 21 was repeated except for using 3-methyl-isoxazol-5-carboxylic acid instead of methanesulfonylacetic acid and 0.09 g of the compound obtained in (20-1) of Example 20 to obtain the title compound (0.04 g, 58%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.67 (s, 1H), 8.46 (s, 1H), 7.90 (d, 1H), 7.40 (d, 2H), 7.60 (dd, 1H), 7.40 (m, 1H), 7.29 (m, 2H), 7.17 (d, 1H), 7.05 (t, 1H), 6.81 (s, 1H), 5.23 (s, 2H), 3.77 (t, 2H), 2.80 (t, 2H), 2.32 (s, 3H).

Example 33: Preparation of furan-3-carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

The procedure of Example 21 was repeated except for using furan-3-carboxylic acid instead of methanesulfonylacetic acid and 0.09 g of the compound obtained in (20-1) of Example 20 to obtain the title compound (0.06 g, 56%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.30 (s, 1H), 9.77 (s, 1H), 8.67 (d, 1H), 8.50 (s, 1H), 8.33 (t, 1H), 8.17 (t, 1H), 7.98 (d, 1H), 7.83 (dd, 1H), 7.72 (m, 3H), 7.47 (m, 1H), 7.31 (m, 2H), 7.24 (d, 1H), 7.18 (t, 1H), 6.85 (t, 1H), 5.25 (s, 2H), 3.55 (q, 2H), 2.68 (t, 2H).

Example 34: Preparation of 1*H*-pyrazol-4-carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

The procedure of Example 21 was repeated except for using 1*H*-pyrazol-4-carboxylic acid and 0.09 g of the compound obtained in (20-1) of Example 20 instead of methanesulfonylacetic acid to obtain the title compound (0.07 g, 65%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.89 (d, 1H), 8.69 (s, 1H), 8.03 (m, 3H), 7.86 (d, 1H), 7.81 (d, 1H), 7.60 (dd, 1H), 7.38 (m, 1H), 7.25 (m, 2H), 7.17 (d, 1H), 7.04 (t, 1H), 5.22 (s, 2H), 3.76 (t, 2H), 2.81 (t, 2H).

Example 35: Preparation of *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-benzamide

The procedure of (20-2) of Example 20 was repeated except for using benzoic acid and 0.05 g of the compound obtained in (20-1) of Example 20 instead of methoxyacetic acid to obtain the title compound (0.03 g, 49%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.82(d, 1H), 8.61 (s, 1H), 7.88 (dd, 1H), 7.75 (d, 1H), 7.68 (m, 3H), 7.48 (dd, 1H), 7.38 (m, 1H), 7.30 (m, 3H), 7.13 (m, 3H), 6.95 (t, 1H), 5.12 (s, 2H), 3.70 (t, 2H), 2.73 (t, 2H); MS(ESI): [M+H+] 569.

Example 36: Preparation of *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-oxalamic acid ethylester

The procedure of (20-2) of Example 20 was repeated except for using oxalic acid monoethylester and 0.09 g of the compound obtained in (20-1) of Example 20 instead of methoxyacetic acid, and subjecting column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.04 g, 37%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.93 (s, 1H), 8.47 (d, 1H), 7.88 (m, 2H), 7.38 (d, 1H), 7.28 (m, 1H), 7.13 (m, 3H), 7.06 (d, 1H), 6.95 (t, 1H), 5.09 (s, 2H), 4.19 (q, 2H), 3.53 (t, 2H), 2.61 (t, 2H), 1.22 (t, 3H)

Example 37: Preparation of cyclopropylcarboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

The procedure of (20-2) of Example 20 was repeated except for using cyclopropylcarboxylic acid and 0.09 g of the compound obtained in (20-1) of Example 20 instead of methoxyacetic acid, and subjecting column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.05 g, 49%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.59 (s, 1H), 8.39 (s, 1H), 7.83 (d, 1H), 7.68 (s, 2H), 7.53 (dd, 1H), 7.33 (m, 1H), 7.23 (m, 2H), 7.10 (d, 1H), 6.99 (t,

1H), 5.16 (s, 2H), 3.52 (t, 2H), 2.61 (t, 2H), 1.49 (m, 1H), 0.77 (m, 2H), 0.68 (m, 2H).

Example 38: Preparation of acetic acid 2-*t*-buthoxycarbonylamino-1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethylester

1.83 g of 2-acetoxy-3-*t*-buthoxycarbonylamino-propionic acid, 2.83 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1 g of 1-hydroxylbenzotriazole dissolved in 30 ml of methylene chloride was reacted with 1.46 g of the compound obtained in (1-4) of Example 1 at room temperature for 22 hours. The reacted solution was extracted with methylene chloride 2 times after adding saturated sodium bicarbonate solution, washed with distilled saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (1.08 g, 47%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.37 (s, 1H), 8.55 (s, 1H), 8.15 (s, 2H), 7.76 (d, 1H), 7.50 (m, 3H), 7.32 (m, 1H), 7.22 (m, 2H), 6.99 (t, 1H), 6.86 (d, 1H), 5.53 (t, 1H), 5.29 (t, 1H), 5.07 (s, 2H), 3.72 (m, 2H), 2.19 (s, 3H), 1.40 (s, 9H).

Example 39: Preparation of acetic acid 1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-2-(2-methoxy-acetylamino)-ethylester

(39-1) Preparation of acetic acid 2-amino-1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethylester

0.12 g of the compound obtained in Example 38 dissolved in 3 ml of methylene chloride and 3 ml of trifluoroacetic acid was stirred at room temperature for 1.5 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred in 3 ml of methylene

chloride while adding 10 ml of saturated sodium bicarbonate slowly and filtered under a reduced pressure to obtain the title compound (0.08 g, 84%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.53 (m, 2H), 7.81 (d, 1H), 7.76 (d, 1H), 7.63 (dd, 1H), 7.56 (dd, 1H), 7.30 (m, 1H), 7.15 (m, 2H), 6.96 (m, 2H), 5.08 (s, 2H), 4.28 (m, 1H), 3.65 (m, 2H), 2.02 (s, 3H).

(39-2) Preparation of acetic acid 1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-2-(2-methoxy-acetylamino)-ethylester

0.4 g of metonym acetic acid, 1.69 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.6 g of 1-hydroxylbenzotriazole dissolved in 20 ml of methylene chloride were reacted with 1.14 g of the compound obtained in (39-1) at room temperature for 6.5 hours. The reacted solution was filtered under a reduced pressure after adding saturated sodium bicarbonate solution to obtain the title compound as solid (0.7 g, 54%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.62 (s, 1H), 9.93 (s, 1H), 8.74 (s, 1H), 8.58 (s, 1H), 8.17 (t, 1H), 8.07 (d, 1H), 7.98 (d, 1H), 7.77 (m, 2H), 7.52 (m, 1H), 7.40 (m, 2H), 7.31 (d, 1H), 7.24 (t, 1H), 5.31 (s, 2H), 4.26 (m, 2H), 3.72 (m, 2H), 3.56 (m, 1H), 3.42 (s, 3H), 1.90 (s, 3H),

Example 40: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-hydroxyl-3-(2-methoxy-acetylamino)-propionamide

0.5 ml of ammonia water was added to 0.1 g of the compound obtained in (39-2) of Example 39 dissolved in 10 ml of methanol, and the solution was stirred at room temperature for 1.5 hours. The reacted solution was filtered under a reduced pressure after adding distilled water to obtain the title compound as solid (0.08 g, 86%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.00 (s, 1H), 9.80 (s, 1H), 8.72 (d, 1H), 8.58 (s, 1H), 8.14 (dd, 1H), 8.05 (m, 2H), 7.79 (m, 2H), 7.54 (m, 1H), 7.39

(m, 2H), 7.34 (d, 1H), 7.23 (t, 1H), 6.22 (d, 1H), 5.31 (s, 2H), 4.26 (m, 1H), 3.61 (m, 1H), 3.36 (s, 3H), 3.28 (m, 1H), 1.90 (s, 2H).

Example 41: Preparation of (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-carbamic acid *t*-butylester

0.44 g of 3-*t*-buthoxycarbonylamino-2-methyl-propionic acid, 0.83 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.29 g of 1-hydroxylbenzotriazole dissolved in 20 ml of methylene chloride were reacted with 0.43 g of the compound obtained in (1-4) of Example 1 at room temperature for 18 hours. The reacted solution was extracted with methylene chloride 3 times after adding saturated sodium bicarbonate solution, washed with saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.32 g, 52%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.17 (s, 1H), 9.70 (s, 1H), 8.64 (s, 1H), 8.41 (s, 1H), 7.88 (d, 1H), 7.73 (t, 1H), 7.59 (m, 2H), 7.38 (m, 1H), 7.24 (m, 2H), 7.17 (d, 1H), 7.10 (t, 1H), 6.83 (t, 1H), 5.17 (s, 2H), 2.93 (m, 1H), 1.30 (s, 9H), 1.04 (d, 2H), 0.95 (d, 2H).

Example 42: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-2-methyl-propionamide

(42-1) Preparation of 3-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-methyl-propionamide

0.24 g of the compound obtained in Example 41 dissolved in 7 ml of methylene chloride and 7 ml of trifluoroacetic acid was stirred at room temperature for 8 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred in 4 ml of methylene chloride

while adding 20 ml of saturated sodium bicarbonate slowly and filtered under a reduced pressure to obtain the title compound as solid (0.19 g, 96%).

^{1}H-NMR (CD_3OD, 300MHz): δ 9.84 (s, 1H), 8.71 (s, 1H), 8.49 (s, 1H), 7.99 (d, 1H), 7.88 (dd, 1H), 7.72 (m, 2H), 7.46 (m, 1H), 7.32 (m, 2H), 7.26 (d, 1H), 7.15 (t, 1H), 5.25 (s, 2H), 2.75 (m, 2H), 2.40 (m, 1H), 1.12 (d, 3H); MS(ESI): [M+H+] 480.2.

(42-2) Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-2-methyl-propionamide

0.02 g of methoxy acetic acid, 0.08 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.03 g of 1-hydroxylbenzotriazole dissolved in 3 ml of methylene chloride were reacted with 0.05 g of the compound obtained in (42-1) at room temperature for 46 hours. The reacted solution was filtered under a reduced pressure after adding saturated sodium bicarbonate solution to obtain the title compound as solid (0.4 g, 70%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.29 (s, 1H), 9.82 (s, 1H), 8.74 (d, 1H), 8.52 (s, 1H), 8.00 (d, 1H), 7.84 (m, 2H), 7.75 (m, 2H), 7.50 (m, 1H), 7.35 (m, 2H), 7.27 (d, 1H), 7.21 (t, 1H), 5.28 (s, 2H), 3.83 (s, 2H), 3.40 (m, 2H), 3.31 (s, 3H), 2.85 (m, 1H), 1.17 (d, 3H).

Example 43: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-2-methyl-propionamide

0.03 g of methanesulfonylacetic acid, 0.08 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.03 g of 1-hydroxylbenzotriazole dissolved in 3 ml of methylene chloride were reacted with 0.05 g of the compound obtained in (42-1) of Example 42 at room temperature for 46 hours. The reacted solution was filtered under a reduced pressure after adding saturated sodium bicarbonate solution to obtain the title compound as solid (0.4 g, 64%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.29 (s, 1H), 9.79 (s, 1H), 8.71 (d, 1H), 8.49 (m, 2H), 7.98 (d, 1H), 7.85 (d, 1H), 7.73 (m, 2H), 7.46 (m, 1H), 7.25 (m,4H), 5.25 (s, 1H), 4.10 (s, 2H), 3.11 (s, 3H), 2.75 (m, 2H), 2.20 (m, 1H), 1.18 (d, 3H).

Example 44: Preparation of *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-acrylamide

0.02 g of acrylic acid, 0.1 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.04 g of 1-hydroxylbenzotriazole dissolved in 5 ml of methylene chloride were reacted with 0.06 g of the compound obtained in (42-1) of Example 42 at room temperature for 24 hours. The reacted solution was extracted with methylene chloride 2 times after adding saturated sodium bicarbonate solution, washed with saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent-chloroform : methanol = 15 : 1) to obtain the title compound (0.01 g, 15%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.50 (s, 1H), 8.31 (s, 1H), 7.74 (d, 1H), 7.60 (m, 2H), 7.44 (dd, 1H), 7.24 (m, 1H), 7.15 (m, 2H), 7.01 (d, 1H), 6.90 (t, 1H), 6.09 (m, 2H), 5.49 (m, 1H), 5.07 (s, 2H), 3.50 (m, 2H), 2.75 (m, 1H), 1.13 (d, 3H).

Example 45: Preparation of (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-1-phenyl-ethyl)-carbamic acid *t*-butylester

1.35 g of 3-*t*-buthoxycarbonylamino-3-phenyl-propionic acid, 1.95 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.69 g of 1-hydroxylbenzotriazole dissolved in 30 ml of methylene chloride were reacted with 1 g of the compound obtained in (1-4) of Example 1 at room temperature for 12 hours. The reacted solution was extracted with methylene chloride 2

times after adding saturated sodium bicarbonate solution, washed with saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.7 g, 43%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.18 (s, 1H), 8.77 (s, 1H), 7.62 (s, 1H), 7.45 (s, 1H), 6.92 (d, 1H), 6.70 (m, 3H), 6.40 (m, 2H), 6.25 (m, 8H), 4.22 (s, 2H), 4.04 (m, 1H), 1.79 (d, 2H), 0.30 (s, 9H).

Example 46: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-3-phenyl-propionamide

(46-1) Preparation of 3-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-phenyl-propionamide

0.64 g of the compound obtained in Example 45 dissolved in 20 ml of methylene chloride and 20 ml of trifluoroacetic acid was stirred at room temperature for 4 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred in 5 ml of methylene chloride while adding 20 ml of saturated sodium bicarbonate slowly and filtered under a reduced pressure to obtain the title compound as solid (0.53 g, 98%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.46 (s, 1H), 9.77 (s, 1H), 8.55 (s, 1H), 8.50 (s, 1H), 8.10 (bs, 2H), 7.95 (d, 1H), 7.79 (dd, 1H), 7.72 (d, 1H), 7.70 (dd, 1H), 7.53 (d, 2H), 7.40 (m, 3H), 7.31 (m, 2H), 7.26 (d, 1H), 7.21 (t, 1H), 5.25 (s, 2H), 4.73 (t, 1H), 3.08 (d, 2H).

(46-2) Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-3-phenyl-propionamide

0.03 g of methoxyacetic acid, 0.14 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.05 g of 1-hydroxylbenzotriazole dissolved in 5 ml of methylene chloride were reacted with 0.1 g of the

compound obtained in (46-1) at room temperature for 23 hours. The reacted solution was extracted with methylene chloride 2 times after adding saturated sodium bicarbonate solution, washed with saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent-chloroform : methanol = 15 : 1) to obtain the title compound (0.05 g, 45%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.25 (s, 1H), 9.78 (s, 1H), 8.61 (s, 1H), 8.46 (s, 1H), 8.42 (d, 1H), 7.93 (d, 1H), 7.70 (m, 3H), 7.43 (m, 3H), 7.29 (m, 3H), 7.20 (m, 2H), 5.40 (m, 1H), 5.23 (s, 2H), 3.80 (s, 2H), 3.28 (s, 3H), 2.94 (m, 2H).

Example 47: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-3-phenyl-propionamide

0.08 g of methanesulfonylacetic acid, 0.21 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.08 g of 1-hydroxylbenzotriazole dissolved in 10 ml of methylene chloride were reacted with 0.15 g of the compound obtained in (46-1) of Example 46 at room temperature for 24 hours. The reacted solution was extracted with methylene chloride 2 times after adding saturated sodium bicarbonate solution, washed with saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.1 g, 55%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.29(s, 1H), 9.76 (s, 1H), 8.94 (d, 1H), 8.59 (s, 1H), 8.47 (s, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.30 (m, 8H), 5.36 (m, 1H), 5.23 (s, 2H), 4.10 (m, 2H), 3.36 (m, 2H), 3.04 (s, 3H); MS(ESI): [M+H+] 662.17.

Example 48: Preparation of 3-(2-methoxy-acetylamino)-thiophene-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide

0.11 g of 3-(2-methoxy-acetylamino)-thiophene-2-carboxylic acid, 0.19 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.1 g of 1-hydroxylbenzotriazole dissolved in 10 ml of methylene chloride were reacted with 0.1 g of the compound obtained in (1-4) of Example 1 at room temperature for 3 hours. The reacted solution was extracted with methylene chloride 2 times after adding saturated sodium bicarbonate solution, washed with saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.02 g, 14%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.58 (d, 1H), 8.46 (d, 1H), 8.15 (d, 1H), 7.83 (m, 2H), 7.73 (m, 2H), 7.57 (d, 1H), 7.33 (m, 1H), 7.22 (m, 2H), 7.01 (m, 2H), 5.16 (s, 2H), 4.05 (s, 2H), 3.53 (s, 3H).

Example 49: Preparation of (2-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid *t*-butylester

(49-1) Preparation of N^4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenyl]-quinazolin-4,6-diamine

The procedures of (1-1) to (1-4) of Example 1 were repeated except for using 3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamine instead of 3-chloro-4-(3-fluoro-benzyloxy)-phenylamine to obtain the title compound (0.38 g, 56%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.62 (s, 1H), 8.28 (d, 1H), 7.77 (d, 1H), 7.64 (d, 1H), 7.53 (dd, 1H), 7.24 (dd, 1H), 7.12 (m, 3H), 6.94 (m, 2H), 4.06(bs, 2H), 2.55 (s, 3H), 2.30 (s, 3H).

(49-2) Preparation of (2-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid *t*-butylester

The procedure of Example 19 was repeated except for using 0.36 g of the compound obtained in (49-1) instead of the compound obtained in (1-4) of Example 1 to obtain the title compound (0.28 g, 53%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.92 (bs, 1H), 8.77 (s, 1H), 8.68 (s, 1H), 8.26 (s, 1H), 7.82 (d, 1H), 7.61 (s, 1H), 7.53 (m, 2H), 7.12 (m, 2H), 6.90 (d, 1H), 5.23 (m, 1H), 3.57 (m, 2H), 2.70 (m, 2H), 2.51 (s, 3H), 2.24 (s, 3H), 1.37 (s, 9H).

Example 50: Preparation of 3-(2-methanesulfonyl-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-propionamide

(50-1) Preparation of 3-amino-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-propionamide

The procedure of (20-1) of Example 20 was repeated except for using 1 g of the compound obtained in Example 49 instead of the compound obtained in (1-4) of Example 1 to obtain the title compound (0.79 g, 98%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.63 (s, 2H), 8.81 (s, 1H), 8.70 (s, 1H), 8.21 (s, 1H), 8.01 (d, 1H), 7.82 (m, 3H), 7.70 (s, 1H), 7.59 (d, 1H), 7.29 (s, 2H), 6.98 (d, 1H), 3.14 (m, 2H), 2.81 (t, 2H), 2.46 (s, 3H), 2.24 (s, 3H).

(50-2) Preparation of 3-(2-methanesulfonyl-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-propionamide

The procedure of Example 21 was repeated except for using 0.03 g of the compound obtained in (50-1) instead of the compound obtained in (1-4) of Example 1 to obtain the title compound (0.02 g, 52%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.20 (s, 1H), 9.73 (s, 1H), 8.66 (s, 1H), 8.48 (s, 1H), 8.15 (bt, 1H), 8.14 (d, 1H), 7.72 (m, 4H), 7.20 (m, 2H), 6.90

(d, 1H), 4.02 (s, 2H), 3.20 (m, 2H), 3.05 (s, 3H), 2.39 (s, 3H), 2.18 (s, 3H), 1.98 (m, 2H); MS(ESI): [M+H+] 549.25.

Example 51: Preparation of *N*-(2-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

The procedure of Example 22 was repeated except for using 0.08 g of the compound obtained in (50-1) of Example 50 instead of the compound obtained in (1-4) of Example 1 to obtain the title compound (0.03 g, 34%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 8.74 (s, 1H), 8.68 (s, 1H), 8.26 (s, 1H), 7.82 (m, 1H), 7.60 (m, 2H), 7.53 (dd, 1H), 7.40 (d, 1H), 7.09 (m, 2H), 6.91 (d, 1H), 6.30 (m, 3H), 2.52 (s, 3H), 2.27 (m, 5H), 1.80 (m, 2H); MS(ESI): [M+H+] 483.22.

Example 52: Preparation of {2-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-carbamic acid *t*-butylester

(52-1) Preparation of N^4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenyl]-quinazolin-4,6-diamine

The procedures of (1-1) to (1-4) of Example 1 were repeated except for using 3-chloro-4-fluoro-phenylamine instead of 3-chloro-4-(3-fluoro-benzyloxy)-phenylamine to obtain the title compound (1.1 g, 48%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.49 (s, 1H), 8.36 (s, 1H), 8.21 (dd, 1H), 7.80 (m, 1H), 7.55 (d, 1H), 7.41 (t, 1H), 7.31 (s, 1H), 7.25 (dd, 1H), 5.65 (bs, 2H).

(52-2) Preparation of {2-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-carbamic acid *t*-butylester

The procedure of Example 19 was repeated except for using 1 g of the compound obtained in (52-1) instead of the compound obtained in (1-4) of Example 1 to obtain the title compound (0.7 g, 44%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.27 (s, 1H), 9.90 (s, 1H), 8.70 (s, 1H), 8.52 (s, 1H), 8.10 (dd, 1H), 7.78 (m, 3H), 7.44 (t, 1H), 6.87 (bt, 1H), 3.24 (m, 2H), 2.54 (t, 2H), 1.36 (s, 9H); MS(ESI): [M+H+] 460.02.

Example 53: Preparation of *N*-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-3-(2-methanesulfonyl-acetylamino)-propionamide

(53-1) Preparation of 3-amino-*N*-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-propionamide

The procedure of (20-1) of Example 20 was repeated except for using 0.55 g of the compound obtained in Example 52 instead of the compound obtained in (1-4) of Example 1 to obtain the title compound (0.4 g, 93%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 8.69 (s, 1H), 8.51 (s, 1H), 8.11 (d, 1H), 7.79 (m, 3H), 7.40 (t, 1H), 2.88 (m, 2H), 2.55 (m, 2H).

(53-2) Preparation of *N*-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-3-(2-methanesulfonyl-acetylamino)-propionamide

The procedure of Example 21 was repeated except for using 0.08 g of the compound obtained in (53-1) instead of the compound obtained in (20-1) of Example 20 to obtain the title compound (0.06 g, 57%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.36 (s, 1H), 9.92 (s, 1H), 8.70 (s, 1H), 8.52 (s, 1H), 8.47 (bt, 1H), 8.11 (d, 1H), 7.80 (m, 3H), 7.40 (t, 1H), 4.05 (s, 2H), 3.41 (m, 2H), 3.09 (s, 3H), 2.53 (m, 2H); MS(ESI): [M+H+] 480.04.

Example 54: Preparation of *N*-{2-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide

The procedure of Example 22 was repeated except for using 0.1 g of the compound obtained in (53-1) of Example 53 instead of the compound obtained in (20-1) of Example 20 to obtain the title compound (0.09 g, 79%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.96 (s, 1H), 10.19 (s, 1H), 9.01 (s, 1H), 8.50 (s, 1H), 8.34 (m, 2H), 8.05 (m, 3H), 7.39 (t, 1H), 6.03 (m, 1H), 6.04 (m, 1H), 5.52 (dd, 1H), 3.19 (m, 2H), 2.60 (t, 2H); MS(ESI): [M+H+] 414.05.

Example 55: Preparation of 4-bromo-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

293 mg of 4-bromo-2-butenoylic acid trimethylsilylester dissolved in 3 ml of methylene chloride was stirred for 2 hours after adding 0.12 ml of oxalylchloride and 1 droplet of *N,N*-dimethylformamide, and the solution was distilled under a reduced pressure. The resulting residue dissolved in 5 ml of THF was reacted with 500 mg of the compound obtained (20-1) of Example 20 and 0.21 ml of *N,N'*-diisopropylethylamine dissolved in 10 ml of THF at 0℃ for 4 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was dissolved in distilled water, washed with saturated sodium bicarbonate solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (393 mg, 60%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.57 (s, 1H), 8.37 (s, 1H), 7.80 (d, 1H), 7.66 (s, 2H), 7.51 (dd, 1H), 7.31 (m, 1H), 7.19 (m, 2H), 7.08 (d, 1H), 6.95 (t, 1H), 6.74 (m, 1H), 6.12 (d, 1H), 5.13 (s, 2H), 4.13 (dd, 1H), 3.56 (t, 2H), 2.63 (t, 2H).

Example 56: Preparation of 4-dimethylamino-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

1.6 ml of 2 M dimethylamine dissolved in 1 ml of THF was cooled to 0℃, and reacted for 19 hours after adding 100 mg of the compound obtained in

Example 55 dissolved in 3 ml of THF. The reacted solution was washed with saturated sodium bicarbonate solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (20.5 mg, 22%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.67 (s, 1H), 8.48 (s, 1H), 7.91 (d, 1H), 7.77 (s, 2H), 7.62 (dd, 1H), 7.43 (m, 1H), 7.31 (m, 2H), 7.19 (d, 1H), 7.08 (t, 1H), 6.76 (m, 1H), 5.25 (s, 2H), 3.67 (t, 2H), 3.11 (d, 2H), 2.74 (t, 2H), 2.28 (s, 6H).

Example 57: Preparation of 4-morpholin-4-yl-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

100 mg of the compound obtained in Example 55 dissolved in 3 ml of THF was cooled to 0℃, and reacted at room temperature for 16 hours after adding 0.3 ml of morpholine. The reacted solution was washed with saturated sodium bicarbonate solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (41 mg, 41%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.55 (s, 1H), 8.36 (s, 1H), 7.79 (d, 1H), 7.64 (s, 2H), 7.50 (dd, 1H), 7.30 (m, 1H), 7.18 (m, 2H), 7.06 (d, 1H), 6.95 (t, 1H), 6.65 (m, 1H), 6.01 (d, 1H), 3.55 (m, 6H), 2.99 (d, 2H), 2.61 (t, 2H), 2.34 (br s, 4H).

Example 58: Preparation of 4-(4-methyl-piperazin-1-yl)-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

The procedure of Example 57 was repeated except for using 0.18 ml of 1-methylpiperazine instead of morpholine to obtain the title compound (20 mg, 38%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.55 (s, 1H), 8.37 (s, 1H), 7.80 (d, 1H), 7.65 (s, 2H), 7.51 (dd, 1H), 7.30 (m, 1H), 7.19 (m, 2H), 7.08 (d, 1H), 6.96 (t, 1H), 6.65 (m, 1H), 6.01 (d, 1H), 3.56 (t, 2H), 3.04 (d, 2H), 2.62 (t, 2H), 2.39 (br s, 4H), 2.17 (s, 3H).

Example 59: Preparation of 4-[(2-hydroxyl-ethyl)-methyl-amino]-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

The procedure of Example 57 was repeated except for using 0.13 ml of 2-(methylamino) ethanol instead of morpholine to obtain the title compound (10 mg, 20%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.56 (s, 1H), 8.37 (s, 1H), 7.80 (d, 1H), 7.66 (s, 2H), 7.51 (dd, 1H), 7.31 (m, 1H), 7.19 (m, 2H), 7.08 (d, 1H), 6.96 (t, 1H), 6.67 (m, 1H), 6.01 (d, 1H), 5.13 (s, 2H), 3.50 (m, 4H), 3.13 (d, 2H), 2.62 (t, 2H), 2.46 (t, 2H), 2.18 (s, 3H).

Example 60: Preparation of 4-(2-methanesulfonyl-ethylamino)-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

The procedure of Example 57 was repeated except for using 12 mg of 2-methanesulfonyl-ethylamine instead of morpholine to obtain the title compound (11 mg, 21%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.82 (s, 1H), 8.48 (s, 1H), 7.92 (d, 1H), 7.77 (s, 2H), 7.60 (dd, 1H), 7.42 (m, 1H), 7.33 (m, 2H), 7.20 (d, 1H), 7.07 (m,

1H), 6.79 (m, 1H), 6.11 (d, 1H), 5.24 (s, 2H), 3.67 (t, 2H), 3.39 (m, 2H), 3.32 (m, 2H), 3.07 (d, 2H), 3.02 (s, 3H), 2.73 (t, 2H).

Example 61: Preparation of 3-(2-chloro-acetylamide)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide

0.7 g of the compound obtained in (20-1) of Example 20 dissolved in 10 ml of THF was cooled to 0℃, and the solution was reacted at room temperature for 2 hours after adding 0.25 ml of pyridine and 0.18 ml of chloroacetylchloride. The reacted solution was extracted with ethylacetate, washed with saturated sodium bicarbonate solution, dried over magnesium sulfate, removed solvent under a reduced pressure, and vacuum dried to obtain the title compound (0.68 g, 84%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.64 (s, 1H), 8.45 (s, 1H), 7.88 (d, 1H), 7.73 (s, 2H), 7.58 (dd, 1H), 7.38 (m, 1H), 7.27 (m, 2H), 7.15 (d, 1H), 7.04 (t, 1H), 5.21 (s, 2H), 4.05 (s, 2H), 3.62 (t, 2H), 2.70 (t, 2H).

Example 62: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-morpholin-4-yl-acetylamino)-propionamide

0.07 g of the compound obtained in Example 61 dissolved in 5 ml of *N,N'*-dimethylformamide was reacted with 0.04 ml of morpholine and 0.04 g of potassium carbonate for 2 hours while heating to 100℃. The reacted solution was diluted with distilled water, extracted with ethylacetate, washed with saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.07 mg, 92%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.51 (s, 1H), 8.36 (s, 1H), 7.78 (d, 1H), 7.63 (s, 2H), 7.49 (dd, 1H), 7.30 (m, 1H), 7.17 (m, 2H), 7.03 (d, 1H), 6.95 (t, 1H), 5.10 (s, 2H), 3.55 (m, 6H), 2.92 (s, 2H), 2.61 (t, 2H), 2.38 (m, 4H).

Example 63: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-dimethylamino-acetylamino)-propionamide

The procedure of Example 62 was repeated except for using 0.25 ml of dimethylamine 2 M THF solution instead of morpholine to obtain the title compound (0.08 g, 88%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.49 (s, 1H), 8.47 (d, 1H), 7.79 (d, 1H), 7.68 (d, 1H), 7.53 (m, 2H), 7.25 (m, 1H), 7.12 (m, 2H), 6.87 (m, 2H), 5.06 (s, 2H), 3.53 (t, 2H), 2.85 (s, 2H), 2.58 (t, 2H), 2.15 (s, 6H).

Example 64: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(4-methyl-piperazin-1-yl)-acetylamino]-propionamide

The procedure of Example 62 was repeated except for using 0.06 ml of 1-methylpiperazine instead of morpholine to obtain the title compound (0.07 g, 70%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.48 (d, 1H), 8.33 (s, 1H), 7.76 (d, 1H), 7.59 (m, 2H), 7.47 (dd, 1H), 7.28 (m, 1H), 7.13 (m, 2H), 6.94 (m, 2H), 5.04 (s, 2H), 3.55 (t, 2H), 2.92 (s, 2H), 2.60 (t, 2H), 2.38 (bd, 8H), 2.06 (s, 3H)

Example 65: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(2-methoxy-ethylamino)-acetylamino]-propionamide

The procedure of Example 62 was repeated except for using 0.07 ml of 2-methoxyethylamine instead of morpholine to obtain the title compound (0.08 g, 83%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.57 (s, 1H), 8.40 (s, 1H), 7.83 (d, 1H), 7.66 (s, 2H), 7.54 (dd, 1H), 7.36 (m, 1H), 7.23 (m, 2H), 7.07 (d, 1H), 7.03 (t, 1H), 5.14 (s, 2H), 3.59 (t, 2H), 3.38 (t, 2H), 3.24 (s, 3H), 3.21 (s, 2H), 2.66 (m, 4H).

Example 66: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(2-methanesulfonyl-ethylamino)-acetylamino]-propionamide

The procedure of Example 62 was repeated except for using 0.1 g of 2-methanesulfonyl-ethylamine instead of morpholine to obtain the title compound (0.1 g, 96%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.56 (s, 1H), 8.36 (s, 1H), 7.80 (m, 1H), 7.65 (s, 2H), 7.49 (dd, 1H), 7.32 (m, 1H), 7.18 (m, 2H), 7.07 (d, 1H), 6.96 (t, 1H), 5.13 (s, 2H), 3.54 (t, 2H), 3.25 (m, 5H), 2.96 (t, 2H), 2.86 (s, 2H), 2.62 (t, 2H); MS(ESI): [M+H+] 629.11.

Example 67: Preparation of 3-(2-chloro-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-propionamide

The procedure of Example 61 was repeated except for using 0.88 g of the compound obtained in (50-1) of Example 50 and 0.3 ml of chloroacetylchloride instead of the compound obtained in (20-1) of Example 20 to obtain the title compound (0.6 g, 58%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.71 (s, 1H), 8.68 (s, 1H), 8.46 (s, 1H), 8.26 (s, 1H), 7.86 (d, 1H), 7.58 (m, 3H), 7.14 (m, 2H), 6.92 (d, 1H), 4.08 (s, 2H), 3.74 (q, 2H), 2.80 (t, 2H), 2.54 (s, 3H), 2.29 (s, 3H), 2.17 (s, 2H).

Example 68: Preparation of *N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-3-(2-morpholin-4-yl-acetylamino)-propionamide

The procedure of Example 62 was repeated except for using 0.09 g of the compound obtained in Example 67 and 0.05 ml of morpholine instead of the compound obtained in Example 61 to obtain the title compound (0.08 g, 81%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.94 (s, 1H), 8.60 (m, 2H), 8.38 (bs, 1H), 8.19 (s, 1H), 7.78 (t, 1H), 7.67 (m, 2H), 7.57 (s, 1H), 7.50 (d, 1H), 7.08 (m, 2H), 6.82 (d, 1H), 3.63 (m, 6H), 2.98 (s, 2H), 2.68 (t, 2H), 2.49 (s, 3H), 2.44 (m, 4H), 2.20 (s, 3H); MS(ESI): [M+H+] 556.24.

Example 69: Preparation of 3-(2-dimethylamino-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-propionamide

The procedure of Example 62 was repeated except for using 0.08 g of the compound obtained in Example 67 and 0.24 ml of dimethylamine 2 M THF instead of the compound obtained in Example 61 to obtain the title compound (0.04 g, 50%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.85 (s, 1H), 8.65 (s, 1H), 8.62 (s, 1H), 8.22 (d, 1H), 7.80 (t, 1H), 7.70 (m, 2H), 7.61 (s, 1H), 7.51 (d, 1H), 7.12 (m, 2H), 6.86 (d, 1H), 3.68 (m, 2H), 2.99 (s, 2H), 2.72 (t, 2H), 2.44 (s, 3H), 2.26 (s, 6H), 2.23 (s, 3H).

Example 70: Preparation of *N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(4-methyl-piperazin-1-yl)-acetylamino]-propionamide

The procedure of Example 62 was repeated except for using 0.07 g of the compound obtained in Example 67 and 0.05 ml of 1-methylpiperazine instead of the compound obtained in Example 61 to obtain the title compound (0.04 g, 51%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.83 (s, 1H), 8.64 (s, 2H), 8.21 (s, 1H), 7.75 (m, 2H), 7.58 (m, 3H), 7.10 (m, 2H), 6.87 (d, 1H), 3.66 (m, 2H), 3.01 (s, 2H), 2.72 (m, 2H), 2.51 (bs, 8H), 2.38 (s, 3H), 2.24 (s, 3H), 2.18 (s, 3H).

Example 71: Preparation of 3-[2-(2-methoxy-ethylamino)-acetylamino]-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-methylamino]-quinazolin-6-yl}-propionamide

The procedure of Example 62 was repeated except for using 0.07 g of the compound obtained in Example 67 and 0.06 ml of 2-methoxyethylamine instead of the compound obtained in Example 61 to obtain the title compound (0.04 g, 54%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.87 (s, 1H), 8.61 (s, 2H), 8.21 (d, 1H), 8.01 (t, 1H), 7.71 (s, 2H), 7.61 (m, 1H), 7.50 (d, 1H), 7.12 (m, 2H), 6.86 (d, 1H), 3.66 (q, 2H), 3.40 (m, 2H), 3.37 (s, 2H), 3.30 (s, 3H), 2.72 (m, 4H), 2.52 (s, 3H), 2.20 (s, 3H); MS(ESI): [M+H+] 544.23.

Example 72: Preparation of 3-[2-(2-methanesulfonyl-ethylamino)-acetylamino]-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-propionamide

The procedure of Example 62 was repeated except for using 0.09 g of the compound obtained in Example 67 and 0.11 g of 2-methanesulfonyl-ethylamine instead of the compound obtained in Example 61 to obtain the title compound (0.03 g, 29%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.50 (m, 2H), 8.10 (m, 1H), 7.97 (s, 1H), 7.59 (s, 1H), 7.53 (m, 1H), 7.41 (d, 1H), 7.05 (m, 2H), 6.76 (m, 1H), 3.56 (m, 2H), 3.10 (m, 2H), 2.98 (m, 2H), 2.91 (s, 3H), 2.84 (s, 3H), 2.59 (m, 2H), 2.45 (s, 3H), 2.12 (s, 2H).

Example 73: Preparation of *N*-{2-[4-(2-methyl-1*H*-indol-5-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide

(73-1) Preparation of 3-amino-*N*-[4-(2-methyl-1*H*-indol-5-ylamino)-quinazolin-6-yl]-propionamide

150 mg of 2-[4-(2-methyl-1*H*-indol-5-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl-carbamic acid *t*-butylester dissolved in 5 ml of methylene chloride was reacted with 5 ml of trifluoroacetic acid at room temperature for 4 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred in 50 ml of saturated aqueous sodium bicarbonate solution for 30 mins, filtered under a reduced pressure, and dried to obtain the title compound (100 mg, 82%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.66 (s, 1H), 8.32 (s, 1H), 7.82 (dd, *J*=2,9 Hz, 1H) 7.79(d, *J*=9 Hz, 1H), 7.63 (s, 1H), 7.34 (d, *J*=8Hz, 1H), 7.21 (dd, *J*=2,9 Hz, 1H), 6.16 (s, 1H), 3.32 (m, 2H), 2.72 (m, 2H), 2.44 (s,3H).

(73-2) Preparation of *N*-{2-[4-(2-methyl-1*H*-indol-5-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide

106 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 58 μl of pyridine were added to 40 μl of acrylic acid dissolved in 3 ml of THF at 0℃, reacted with 50 mg of the compound obtained in (73-1) for 30 mins while heating to room temperature, and the resulting solution was stirred at room temperature for 2 hours. The reacted solution was extracted with 9 ml of ethylacetate 3 times after adding 4 ml of water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography

(eluent- chloroform : methanol = 15 : 1) to obtain the title compound (5.2 mg, 9%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.66 (s, 1H), 8.32 (s, 1H), 7.81 (dd, *J*=2,9 Hz, 1H), 7.73 (d, *J*=9 Hz, 1H), 7.63 (s, 1H), 7.34 (d, *J*=8 Hz, 1H), 7.21 (dd, *J*=2,9 Hz, 1H), 6.24-6.60 (m, 2H), 6.16 (s, 1H), 5.64-5,68 (m, 1H), 3.69 (t, *J*=7 Hz, 2H), 2.75 (t, *J*=7 Hz, 2H), 2.44 (s, 3H).

Example 74: Preparation of 3-(2-methanesulfonyl-acetylamino)-*N*-[4-(1-phenyl-ethylamino)-quinazolin-6-yl]-propionamide

(74-1) Preparation of 3-amino-*N*-[4-(1-phenyl-ethylamino)-quinazolin-6-yl]-propionamide

250 mg of 2-[4-(1-phenyl-ethylamino)-quinazolin-6-ylcarbamoyl]-ethyl-carbamic acid *t*-butylester dissolved in 5 ml of methylene chloride was reacted with 5 ml of trifluoroacetic acid at room temperature for 4 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred in 50 ml of saturated aqueous sodium bicarbonate solution for 30 mins, filtered under a reduced pressure, and dried to obtain the title compound (90 mg, 52%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.54 (s, 1H), 8.37 (s, 1H), 7.79 (dd, *J*=2,9 Hz, 1H), 7.70 (d, *J*=9 Hz, 1H), 7.47 (d, *J*=7 Hz, 2H), 7.35 (t, *J*=7 Hz, 2H), 7.25 (t, *J*=7 Hz, 1H), 3.26 (m, 3H), 2.90 (t, *J*=6 Hz, 2H), 1.7 (d, *J*=7 Hz, 3H).

(74-2) Preparation of 3-(2-methanesulfonyl-acetylamino)-*N*-[4-(1-phenyl-ethylamino)-quinazolin-6-yl]-propionamide

40 mg of 1-hydroxylbenzotriazole and 114 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 41 mg of methanesulfonylacetic acid dissolved in 2 ml of THF, and reacted with 50 mg of the compound obtained in (74-1) at room temperature for 12 hours. The reacted solution was extracted with 6 ml of ethylacetate 3 times after adding 4 ml of water, dried over anhydrous magnesium sulfate, and filtered and distilled

under a reduced pressure. 5 ml of diethylether was added to the resulting residue dissolved in 0.5 ml of methanol to obtain solid, and the solid was filtered under a reduced pressure and dried to obtain the title compound (3 mg, 6%).

^{1}H-NMR(CD_3OD, 300MHz): δ 8.59 (s, 1H), 8.39 (s, 1H), 7.79-7.68 (m, 2H), 7.22-7.46 (m, 5H), 4.04 (s, 2H), 3.65 (m, 3H), 2.73 (t, *J*=6 Hz, 2H), 1.70 (d, *J*=7 Hz, 3H).

Example 75: Preparation of *N*-{2-[4-(1-phenyl-ethylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide

62 μl of pyridine and 114 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 41 μl of acrylic acid dissolved in 3 ml of THF at 0℃, reacted with 50 mg of the compound obtained in (74-2) of Example 74 for 30 mins while heating to room temperature, and the resulting solution was stirred at room temperature for 2 hours. The reacted solution was extracted with 9 ml of ethylacetate 3 times after adding 4 ml of water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (4.8 mg, 10%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.54 (s, 1H), 8.37 (s, 1H), 7.69 (s, 2H), 7.47 (d, *J*=7.5 Hz, 2H), 7.32 (t, *J*=7 Hz, 2H), 7.23 (t, *J*=7 Hz, 1H), 6.29 (m, 2H), 5.67 (m, 1H), 3.66 (m, 2H), 2.66-2.76 (m, 3H), 1.7 (d, *J*=7 Hz, 3H).

Example 76: Preparation of *N*-[2-(4-{4-[2-(6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-phenylamino}-quinazolin-6-ylcarbamoyl)-ethyl]-acrylamide

(76-1) Preparation of 3-amino-*N*-(4-{4-[2-(6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-phenylamino}-quinazolin-6-yl)-propionamide

800 mg of [2-(4-{4-[2-(6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2yl)-ethyl]phenylamino}-quinazolin-6-ylcarbamoyl)-ethyl]-carbamic acid *t*-butylester dissolved in 16 ml of methylene chloride was reacted with 16 ml of trifluoroacetic acid at room temperature for 4 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred in 200 ml of saturated aqueous sodium bicarbonate solution for 30 mins, filtered under a reduced pressure and dried to obtain the title compound (310 mg, 46%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.64 (s, 1H), 8.46 (s, 1H), 7.8 (d, *J*=9 Hz, 1H), 7.69-7.75 (m, 3H), 7.33 (d, *J*=7.5 Hz, 2H), 6.71 (d, *J*=9 Hz, 2H), 3.8 (s, 2H), 3.67 (s, 2H), 3.37 (m, 2H), 2.72-2.92 (m, 10H).

(76-2) Preparation of *N*-[2-(4-{4-[2-(6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-phenylamino}-quinazolin-6-ylcarbamoyl)-ethyl]-acrylamide

59 μl of pyridine and 109 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 39 μl of acrylic acid dissolved in 3 ml of THF, and the solution was reacted with 150 mg of the compound obtained in (76-1) at 0℃ for 30 mins and for 2 hours while heating to room temperature. The reacted solution was extracted with 6 ml of ethylacetate 3 times after adding 4 ml of water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (22 mg, 20%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.66 (s, 1H), 8.43 (s, 1H), 7.74 (s, 2H), 7.68 (d, *J*=9 Hz, 2H), 7.33 (d, *J*=9 Hz, 2H), 6.70 (d, *J*=9 Hz, 2H), 6.71 (d, *J*=9 Hz, 2H), 6.22-6.24 (m, 2H), 5.67 (m, 1H), 3.79 (s, 6H), 3.78 (s, 2H), 3.67 (t, *J*=7 Hz, 2H), 2.81-2.93 (m, 8H), 2.71 (t, *J*=7 Hz, 2H).

Example 77: Preparation of {2-[4-(1-benzyl-1*H*-indazol-5-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-carbamic acid *t*-butylester

1.1 g of 2-[3-cyano-4-(dimethylamino-methylene amino)-phenylcarbamoyl]-ethyl-carbamic acid *t*-butylester (see, *Journal of Medicinal Chemistry* 2004, 44:2719) dissolved in 6 ml of acetic acid was reacted with 1.05 g of 1-benzyl-1*H*-indazol-5-ylamine at 60℃ for 3 hours, and the resulting residue was stirred in 100 ml of saturated aqueous sodium bicarbonate solution at room temperature for 30 mins. The reacted solution was extracted with 30 ml of ethylacetate 3 times after adding 4 ml of water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent-chloroform : methanol = 15 : 1) to obtain the title compound (810 mg, 66%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.70 (s, 1H), 8.39 (s, 1H), 8.07-8.11 (m, 2H), 7.73 (s, 2H), 7.55-7.64 (m, 2H), 7.21-7.32 (m, 5H), 5.66 (s, 2H), 3.47 (t, *J*=7 Hz, 2H), 2.67 (t, *J*=7 Hz, 2H), 1.4 (s, 9H).

Example 78: Preparation of *N*-[4-(1-benzyl-1*H*-indazol-5-ylamino)-quinazolin-6-yl]-3-(2-methanesulfonyl-acetylamino)-propionamide

(78-1) Preparation of 3-amino-*N*-[4-(1-benzyl-1*H*-indazol-5-ylamino)-quinazolin-6-yl]-propionamide

815 mg of the compound obtained in Example 77 dissolved in 16 ml of methylene chloride was reacted with 16 ml of trifluoroacetic acid at room temperature for 4 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred in 100 ml of saturated aqueous sodium bicarbonate for 30 mins, filtered under a reduced pressure, and dried to obtain the title compound (490 mg, 53%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.70 (s, 1H), 8.40 (s, 1H), 8.11 (d, *J*=8 Hz, 2H), 7.76-7.79 (m, 2H), 7.56-7.63 (m, 2H), 7.22-7.33 (m, 5H), 5.67 (s, 2H), 3.32 (m, 2H), 2.73 (m, 2H).

(78-2) Preparation of *N*-[4-(1-benzyl-1*H*-indazol-5-ylamino)-quinazolin-6-yl]-3-(2-methanesulfonyl-acetylamino)-propionamide

50 μl of pyridine and 87 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 63 mg of methanesulfonylacetic acid dissolved in 3 ml of THF at 0℃, reacted with 50 mg of the compound obtained in (78-1) at for 30 mins while heating to room temperature and the resulting solution was stirred at room temperature for 2 hours. The reacted solution was extracted with 6 ml of ethylacetate 3 times after adding 4 ml of water, dried over anhydrous magnesium sulfate, and filtered and distilled under a reduced pressure. 5 ml of diethylether was added to the resulting residue dissolved in 0.5 ml of methanol to obtain solid, and the solid was filtered under a reduced pressure and dried to obtain the title compound (11 mg, 17%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.76 (s, 1H), 8.46 (s, 1H), 8.09-8.12 (m, 3H), 7.76-7.79 (m, 2H), 7.59-7.65 (m, 2H), 7.25-7.32 (m, 5H), 5.69 (s, 2H), 4.05 (s, 2H), 3.58 (m, 2H), 3.24 (s, 3H), 2.90 (m, 2H).

Example 79: Preparation of *N*-{2-[4-(1-benzyl-1*H*-imidazol-5-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide

71 μl of pyridine and 132 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 47 μl of acrylic acid dissolved in 3 ml of THF at 0℃, reacted with 150 mg of the compound obtained in (78-1) of Example 78 for 30 mins while heating to room temperature, and the resulting solution was stirred at room temperature for 2 hours. The reacted solution was extracted with 6 ml of ethylacetate 3 times after adding 4 ml of water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (13 mg, 8%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.63 (s, 1H), 8.32 (s, 1H), 7.99-8.02 (m, 3H), 7.68-7.70 (m, 2H), 7.56-7.52 (m, 2H), 7.14-7.123 (m, 5H), 6.08-6.18 (m, 2H), 5.56-5.60 (m, 3H), 3.61 (t, *J*=7 Hz, 2H), 2.68 (t, *J*=7 Hz, 2H).

Example 80: Preparation of {2-[4-(4-phenylcarbamoyl-phenylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-carbamic acid *t*-butylester

1 g of 2-[3-cyano-4-(dimethylamino-methylene amino)-phenylcarbamoyl]-ethyl-carbamic acid *t*-butylester (see, *Journal of Medicinal Chemistry* 2004, 44:2719) dissolved in 6 ml of acetic acid was reacted with 650 mg of 4-amino-*N*-phenyl-benzamide at 60℃ for 3 hours, and the resulting residue was stirred in 100 ml of saturated aqueous sodium bicarbonate solution at room temperature for 30 mins. The reacted solution was extracted with 30 ml of ethylacetate 3 times, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (350 mg, 25%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.64 (s, 1H), 8.51 (s, 1H), 7.92-8.01 (m, 3H), 7.87 (s, 1H), 7.67-7.69 (m, 4H), 7.36 (t, *J*=7.5 Hz, 2H), 7.14 (t, *J*=7.5 Hz, 1H), 3.47 (t, *J*=4 Hz, 2H), 2.65 (t, *J*=7 Hz, 2H), 1.4 (s, 9H).

Example 81: Preparation of 4-{6-[3-(2-methanesulfonyl-acetylamino)-propionylamino]-quinazolin-4-ylamino}-*N*-phenyl-benzamide

(81-1) Preparation of 4-[6-(3-amino-propionylamino)-quinazolin-4-ylamino]-*N*-phenyl-benzamide

350 mg of the compound obtained in Example 80 dissolved in 7 ml of methylene chloride was reacted with 7 ml of trifluoroacetic acid at room temperature for 4 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred in 50 ml of saturated aqueous sodium bicarbonate for 30 mins, filtered under a reduced pressure, and dried to obtain the title compound (250 mg, 89%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.75 (s, 1H), 8.59 (s, 1H), 8.00-8.07 (m, 4H), 7.80 (s, 2H), 7.73 (d, *J*=9 Hz, 2H), 7.40 (t, *J*=7.5 Hz, 2H), 7.18 (t, *J*=7.5 Hz, 1H), 3.31 (m, 2H), 2.71 (t, *J*=7 Hz, 2H).

(81-2) Preparation of 4-{6-[3-(2-methanesulfonyl-acetylamino)-propionylamino]-quinazolin-4-ylamino}-*N*-phenyl-benzamide

32 mg of hydroxyl-benzotriazole and 90 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 32 mg of methanesulfonylacetic acid dissolved in 2 ml of THF, and reacted with 50 mg of the compound obtained in (81-1) at room temperature for 2 hours. The reacted solution was extracted with 6 ml of ethylacetate 3 times after adding 4 ml of water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (10 mg, 16%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.77 (s, 1H), 8.62 (s, 1H), 8.00-8.07 (m, 4H), 7.82 (s, 2H), 7.73 (d, *J*=9 Hz, 2H), 7.41 (t, *J*=7.5 Hz, 2H), 7.17 (t, *J*=7.5 Hz, 1H), 4.08 (s, 2H), 3.67 (t, *J*=7 Hz, 2H), 3.14 (s, 3H) 2.77 (t, *J*=7 Hz, 2H).

Example 82: Preparation of 4-[6-(3-acryloylamino-propionylamino)-quinazolin-4-ylamino]-*N*-phenyl-benzamide

124 μl of pyridine and 228 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 82 μl of acrylic acid dissolved in 6 ml of THF at 0℃, reacted with 127 mg of the compound obtained in (81-1) of Example 81 for 30 mins while heating to room temperature, and the resulting solution was stirred at room temperature for 2 hours. The reacted solution was extracted with 6 ml of ethylacetate 3 times after adding 5 ml of water, dried over anhydrous magnesium sulfate, and filtered and distilled under a reduced pressure. 10 ml of diethylether was added to the resulting residue dissolved in 0.5 ml of methanol to obtain solid, and the solid was filtered under a reduced pressure and dried to obtain the title compound (15 mg, 10%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.74 (s, 1H), 8.59 (s, 1H), 8.00-8.07 (m, 4H), 7.82 (s, 2H), 7.72 (d, *J*=9 Hz, 2H), 7.40 (t, *J*=7.5 Hz, 2H), 7.16 (t, *J*=7.5

Hz, 1H), 6.25-6.27 (m, 2H), 5.61-5.69 (m, 1H), 3.68 (t, *J*=7 Hz, 2H), 2.73 (t, *J*=7 Hz, 2H).

Example 83: Preparation of *N*-[4-(biphenyl-4-ylamino)-quinazolin-6-yl]-3-(2-methanesulfonyl-acetylamino)-propionamide

(83-1) Preparation of 3-amino-*N*-[4-(biphenyl-4-ylamino)-quinazolin-6-yl]-propionamide

480 mg of 2-[4-(biphenyl-4-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl-carbamic acid *t*-butylester (prepared in accordance with the procedure of Example 80) dissolved in 10 ml of methylene chloride was reacted with 10 ml of trifluoroacetic acid at room temperature for 4 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred in 50 ml of saturated aqueous sodium bicarbonate for 30 mins, filtered under a reduced pressure, and dried to obtain the title compound (400 mg, 99%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.71 (s, 1H), 8.50 (s, 1H), 7.89 (d, *J*=9 Hz, 2H), 7.78-7.80 (m, 2H), 7.65-7.75 (m, 4H), 7.43 (t, *J*=7.5 Hz, 2H), 7.34 (t, *J*=7.5 Hz, 1H) 3.32 (t, *J*=7 Hz, 2H), 2.71 (t, *J*=7 Hz, 2H).

(83-2) Preparation of *N*-[4-(biphenyl-4-ylamino)-quinazolin-6-yl]-3-(2-methanesulfonyl-acetylamino)-propionamide

56 mg of hydroxyl-benzotriazole and 160 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 58 mg of methanesulfonylacetic acid dissolved in 5 ml of THF, and reacted with 80 mg of the compound obtained in (83-1) at room temperature for 12 hours. The reacted solution was extracted with 10 ml of ethylacetate 3 times after adding 5 ml of water, dried over anhydrous magnesium sulfate, and filtered and distilled under a reduced pressure. 5 ml of diethylether was added to the resulting residue dissolved in 0.5 ml of methanol to obtain solid, and the solid was filtered under a reduced pressure and dried to obtain the title compound (30 mg, 76%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.76 (s, 1H). 8.56 (s, 1H), 7.84-7.89 (m, 3H), 7.63-7.73 (m, 5H), 7.42 (t, *J*=7.5 Hz, 2H), 7.34 (t, *J*=7.5 Hz, 1H), 4.1 (s, 2H), 3.68 (t, *J*=7 Hz, 2H), 3.16(s, 3H), 2.77 (t, *J*=7 Hz, 2H).

Example 84: Preparation of *N*-{2-[4-(biphenyl-4-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide

54 μl of pyridine and 100 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 36 μl of acrylic acid dissolved in 3 ml of THF at 0℃, reacted with 100 mg of the compound obtained in (83-1) of Example 83 for 30 mins while heating to room temperature, and the resulting solution was stirred at room temperature for 2 hours. The reacted solution was extracted with 6 ml of ethylacetate 3 times after adding 4 ml of water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (11 mg, 10%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.64 (s, 1H), 8.42 (s, 1H), 7.78 (d, *J*=8Hz, 2H), 7.69-7.71 (m, 2H), 7.57-7.62 (m, 4H), 7.39 (t, *J*=7.5 Hz, 2H), 7.25 (t, *J*=7.5 Hz, 1H), 6.16-6.18 (m, 2H), 5.66-5.71 (m, 1H), 3.60 (t, *J*=7 Hz, 2H), 2.69 (t, *J*=7 Hz, 2H).

Example 85: Preparation of *N*-{2-[4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide

(85-1) Preparation of N^4-[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]-7-(3-morpholin-4-yl-propoxy)-quinazolin-4,6-diamine

353 mg of iron dissolved in aqueous 5% acetic acid solution was activated at 100℃. 450 mg of [3-chloro-4-(3-fluoro-benzyloxy)-phenyl]-[7-(3-morpholin-4-yl-propoxy)-6-nitro-quinazolin-4-yl]-amine (see, *Journal of Medicinal Chemistry* 2000, *43*, 1380) dissolved in a mixture of ethylacetate and

acetic acid (1 : 1) was added thereto dropwise, and refluxed. The hot reacted solution was filtered under a reduced pressure through celite pad, and the pad was washed with ethylacetate. The washed solvent was washed with saturated sodium bicarbonate solution several times. The organic layer was dried over magnesium sulfate, and filtered and distilled under a reduced pressure to obtain the title compound (353 mg, 83%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.22 (s, 1H), 8.32 (s, 1H), 8.03 (d, 1H), 7.71 (dd, 1H), 7.46 (m, 1H), 7.39 (s, 1H), 7.32 (m, 2H), 7.19 (m, 2H), 7.06 (s, 1H), 5.28 (br s, 2H), 5.23 (s, 2H), 4.19 (t, 2H), 3.59 (t, 4H), 2.50 (t, 2H), 2.40 (br s, 4H), 1.99 (m, 2H); MS(ESI): [M+H+] 537.

(85-2) Preparation of *N*-{2-[4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide

The procedure of Example 4 was repeated except for using 250 mg of the compound obtained in Example (85-1) and 60 μl of acrylic acid instead of the compound obtained in (2-3) of Example 2 to obtain the title compound (10 mg, 4%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.73 (s, 1H), 8.40 (s, 1H), 7.82 (d, 1H), 7.53 (dd, 1H), 7.39 (m, 1H), 7.29 (m, 2H), 7.09 (m, 3H), 6.25 (m, 2H), 5.66 (dd, 1H), 5.19 (s, 2H), 4.24 (t, 2H), 3.71 (t, 4H), 3.67 (t, 2H), 2.80 (t, 2H), 2.60 (t, 2H), 2.53 (br s, 4H), 2.12 (m, 2H); MS(ESI): [M+H+] 662.

Example 86: Preparation of (3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-carbamic acid *t*-butylester

1.54 g of 4-*t*-buthoxycarbonylamino-butyric acid, 2.9 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1.03 g of 1-hydroxylbenzotriazole dissolved in 25 ml of methylene chloride was reacted with 1.5 g of the compound obtained in (1-4) of Example 1 at room temperature for 14 hours. Saturated sodium bicarbonate solution was added to the reacted

solution, and the resulting solution was filtered under a reduced pressure to obtain the title compound as solid (0.9 g, 41%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.20 (s, 1H), 9.76 (s, 1H), 8.68 (d, 1H), 8.48 (s, 1H), 7.96 (d, 1H), 7.70 (m, 3H), 7.45 (m, 1H), 7.31 (m, 4H), 6.86 (m, 1H), 5.24 (s, 2H), 2.99 (q, 2H), 2.37 (t, 2H), 1.73 (m, 2H), 1.37 (s, 9H).

Example 87: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-methoxy-acetylamino)-butyramide

(87-1) Preparation of 4-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-butyramide

0.76 g of the compound obtained in Example 86 dissolved in 22 ml of methylene chloride and 22 ml of trifluoroacetic acid was stirred at room temperature for 4 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred in 5 ml of methylene chloride while adding 50 ml of saturated aqueous sodium bicarbonate slowly, and filtered under a reduced pressure to obtain the title compound as solid (0.62 g, 99%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 8.58 (s, 1H), 8.38 (s, 1H), 7.87 (s, 1H), 7.73 (d, 1H), 7.62 (m, 2H), 7.35 (m, 1H), 7.20 (m, 2H), 7.15 (d, 1H), 7.08 (t, 1H), 5.15 (s, 2H), 2.56 (m, 2H), 2.33 (t, 2H), 1.65 (m, 2H).

(87-2) Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-methoxy-acetylamino)-butyramide

The procedure of (20-2) of Example 20 was repeated except for using 0.1 g of the compound obtained in (87-1) instead of 4-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide, and the resultant was filtered under a reduced pressure to obtain the title compound as solid (0.06 g, 53%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.28 (s, 1H), 9.78 (bs, 1H), 8.67 (d, 1H), 8.44 (s, 1H), 7.95 (d, 1H), 7.84 (m, 2H), 7.67 (m, 2H), 7.43 (m, 1H), 7.26 (m, 2H), 7.20 (d, 1H), 7.12 (t, 1H), 5.21 (s, 2H), 3.76 (s, 2H), 3.26 (s, 3H), 3.15 (q, 2H), 2.38 (t, 2H), 1.77 (m, 2H).

Example 88: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-methanesulfonyl-acetylamino)-butyramide

The procedure of Example 21 was repeated except for using 0.1 g of the compound obtained in (87-1) of Example 87 instead of 4-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide, and the resultant was filtered under a reduced pressure to obtain the title compound as solid (0.05 g, 40%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.41 (s, 1H), 9.85 (bs, 1H), 8.72 (s, 1H), 8.48 (m, 1H), 7.99 (s, 1H), 7.87 (d, 1H), 7.68 (m, 2H), 7.46 (m, 1H), 7.33 (m, 2H), 7.24 (d, 1H), 7.17 (t, 1H), 5.23 (s, 2H), 4.06 (s, 2H), 3.18 (m, 2H), 3.11 (s, 3H), 2.43 (t, 2H), 1.79 (m, 2H).

Example 89: Preparation of 4-acryloylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-butyramide

36 μl of pyridine, 100 mg of the compound obtained in (87-1) of Example 87 and 80 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 30 μl of acrylic acid dissolved in 2 ml of THF, and reacted at 0℃ for 5 hours. The reacted solution was washed with saturated sodium bicarbonate, dried over sodium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (14 mg, 13%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.61 (s, 1H), 8.45 (s, 1H), 7.87 (d, 1H), 7.73 (m, 2H), 7.58 (dd, 1H), 7.39 (m, 1H), 7.28 (m, 2H), 7.11 (m, 2H), 6.22 (m, 2H), 5.65 (dd, 1H), 5.19 (s, 2H), 3.39 (t, 2H), 2.50 (t, 2H), 1.94 (m, 2H).

Example 90: Preparation of *N*-(3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-benzamide

The procedure of Example 35 was repeated except for using 0.06 g of the compound obtained in (87-1) of Example 87 instead of 4-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide to obtain the title compound (0.05 g, 69%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.95 (d, 1H), 8.84 (s, 1H), 8.12 (dd, 1H), 8.04 (d, 1H), 7.98 (dd, 2H), 7.93 (d, 1H), 7.78 (dd, 1H), 7.58 (m, 4H), 7.42 (m, 2H), 7.34 (d, 1H), 7.21 (t, 1H), 5.37 (s, 2H), 3.72 (t, 2H), 2.75 (t, 2H), 2.26 (m, 2H); MS(ESI): [M+H+] 583.

Example 91: Preparation of *N*-(3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-oxalamic acid ethylester

The procedure of Example 36 was repeated except for using 0.09 g of the compound obtained in (87-1) of Example 87 instead of 4-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide, and the resultant was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.07 g, 65%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.21 (s, 1H), 9.76 (s, 1H), 8.66 (s, 1H), 8.47 (s, 1H), 7.95 (d, 1H), 7.69 (m, 3H), 7.45 (m, 2H), 7.30 (m, 2H), 7.22 (d, 1H), 7.16 (t, 1H), 5.23 (s, 2H), 4.20 (q, 2H), 3.20 (q, 2H), 2.37 (t, 2H), 1.82 (m, 2H), 1.24 (t, 3H).

Example 92: Preparation of cyclopropylcarboxylic acid (3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-amide

The procedure of Example 37 was repeated except for using 0.09 g of the compound obtained in (87-1) of Example 87 instead of 4-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide, and the resultant was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.03 g, 30%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.22 (s, 1H), 9.76 (s, 1H), 8.66 (s, 1H), 8.47 (s, 1H), 7.95 (d, 1H), 7.73 (m, 3H), 7.46 (m, 2H), 7.28 (m, 2H), 7.21 (d, 1H), 7.15 (t, 1H), 5.23 (s, 2H), 3.13 (q, 2H), 2.39 (t, 2H), 1.76 (m, 2H), 1.50 (m, 1H), 0.76 (m, 2H), 0.62 (m, 2H).

Example 93: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-cyano-acetylamino)-butyramide

The procedure of Example 31 was repeated except for using 0.06 g of the compound obtained in (87-1) of Example 87 instead of 4-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide, and the resultant was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.03 g, 44%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.48 (s, 1H), 8.33 (s, 1H), 7.76 (d, 1H), 7.59 (s, 2H), 7.46 (dd, 1H), 7.28 (m, 1H), 7.17 (m, 2H), 6.99 (d, 1H), 6.92 (t, 1H), 5.06 (s, 2H), 3.22 (m, 4H), 2.40 (t, 2H), 1.84 (m, 2H).

Example 94: Preparation of furan-3-carboxylic acid (3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-amide

The procedure of Example 33 was repeated except for using 0.06 g of the compound obtained in (87-1) of Example 87 instead of 4-amino-*N*-{4-[3-

chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide, and the resultant was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.04 g, 56%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.57 (d, 1H), 8.44 (s, 1H), 8.05 (dd, 1H), 7.88 (d, 1H), 7.71 (m, 2H), 7.57 (dd, 1H), 7.53 (t, 1H), 7.39 (m, 1H), 7.27 (m, 2H), 7.10 (d, 1H), 7.04 (t, 1H), 6.79 (t, 1H), 5.17 (s, 2H), 3.48 (t, 2H), 2.54 (t, 2H), 2.04 (m, 2H).

Example 95: Preparation of 1*H*-pyrazol-4-carboxylic acid (3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-amide

The procedure of Example 34 was repeated except for using 0.09 g of the compound obtained in (87-1) of Example 87 instead of 4-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide, and the resultant was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.04 g, 37%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.80 (d, 1H), 8.67 (s, 1H), 8.01 (s, 2H), 7.96 (dd, 1H), 7.86 (d, 1H), 7.76 (d, 1H), 7.59 (dd, 1H), 7.38 (m, 1H), 7.26 (m, 2H), 7.17 (d, 1H), 7.03 (t, 1H), 5.20 (s, 2H), 3.45 (t, 2H), 2.55 (t, 2H), 2.03 (m, 2H).

Example 96: Preparation of {3-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-ylcarbamoyl]-propyl}-carbamic acid *t*-butylester

The procedure of Example 86 was repeated except for using 0.5 g of N^4-(3-chloro-4-fluoro-phenyl)-quinazolin-4,6-diamine instead of the compound obtained in (1-4) of Example 1, and the resultant was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.39 g, 57%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.21 (s, 1H), 9.89 (s, 1H), 8.70 (s, 1H), 8.52 (s, 1H), 8.10 (dd, 1H), 7.78 (m, 3H), 7.40 (t, 1H), 6.84 (bt, 1H), 2.98 (q, 2H), 2.36 (t, 2H), 1.72 (m, 2H), 1.35 (s, 9H).

Example 97: Preparation of *N*-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-4-(2-methanesulfonyl-acetylamino)-butyramide

(97-1) Preparation of 4-amino-*N*-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-butyramide

The procedure of (87-1) of Example 87 was repeated except for using 0.08 g of the compound obtained in Example 96 instead of the compound obtained in Example 86 to obtain the title compound (0.06 g, 96%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 8.75 (d, 1H), 8.51 (s, 1H), 8.12 (bt, 1H), 7.82 (m, 3H), 7.40 (t, 1H), 2.80 (m, 2H), 2.43 (m, 2H), 1.72 (m, 2H).

(97-2) Preparation of *N*-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-4-(2-methanesulfonyl-acetylamino)-butyramide

The procedure of Example 21 was repeated except for using 0.05 g of the compound obtained in (97-1) instead of 4-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide, and the resultant was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.03 g, 44%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.69 (s, 2H), 7.98 (dd, 1H), 7.85 (d, 1H), 7.61 (m, 2H), 7.16 (t, 1H), 6.92 (m, 1H), 3.48 (m, 2H), 3.15 (s, 2H), 2.52 (t, 2H), 2.17 (s, 3H), 1.60 (m, 2H); MS(ESI): [M+H+] 494.09.

Example 98: Preparation of 4-acryloylamino-*N*-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-butyramide

The procedure of Example 22 was repeated except for using 0.1 g of the compound obtained in (97-1) of Example 97 instead of 4-amino-*N*-{4-[3-

chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide to obtain the title compound (0.04 g, 35%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.26 (s, 1H), 9.90 (s, 1H), 8.70 (s, 1H), 8.52 (s, 1H), 8.11 (m, 2H), 7.78 (m, 3H), 7.40 (t, 1H), 6.20 (m, 1H), 6.04 (m, 1H), 5.55 (dd, 1H), 3.19 (q, 2H), 2.40 (t, 2H), 1.79 (m, 2H); MS(ESI): [M+H+] 428.07.

Example 99: Preparation of (3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-ylcarbonyl}-propyl)-carbamic acid *t*-butylester

The procedure of Example 86 was repeated except for using 1.2 g of N^4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenyl]-quinazolin-4,6-diamine instead of the compound obtained in (1-4) of Example 1, and the resultant was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (1.58 g, 87%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.17 (s, 1H), 9.74 (s, 1H), 8.67 (d, 1H), 8.47 (s, 1H), 8.15 (d, 1H), 7.78 (dd, 1H), 7.70 (m, 2H), 7.63 (dd, 1H), 7.18 (m, 2H), 6.92 (d, 1H), 6.84 (bt, 1H), 2.98 (q, 2H), 2.41 (s, 3H), 2.36 (t, 2H), 2.18 (s, 3H), 1.72 (m, 2H), 1.35 (s, 9H).

Example 100: Preparation of 4-(2-methanesulfonyl-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide

(100-1) Preparation of 4-amino-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide

The procedure of (87-1) of Example 87 was repeated except for using 1.51 g of the compound obtained in Example 99 instead of the compound obtained in example 86 to obtain the title compound (1.21 g, 98%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 12.60 (bs, 1H), 10.64 (s, 1H), 9.55 (s, 1H), 8.61 (d, 1H), 8.47 (s, 1H), 8.26 (m, 2H), 8.17 (d, 1H), 7.63 (d, 1H), 7.20 (m, 2H), 6.92 (d, 2H), 3.12 (m, 2H), 2.40 (m, 5H), 2.17 (s, 3H), 1.75 (m, 2H).

(100-2) Preparation of 4-(2-methanesulfonyl-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide

The procedure of Example 88 was repeated except for using 0.1 g of the compound obtained in (100-1) instead of the compound obtained in (87-1) of Example 87 to obtain the title compound (0.04 g, 32%).

^{1}H-NMR(DMSO-d_6, 300MHz): δ 10.22 (s, 1H), 9.75 (s, 1H), 8.68 (s, 1H), 8.47 (s, 1H), 8.39 (bt, 1H), 8.15 (d, 1H), 7.70 (m, 4H), 7.17 (m, 2H), 6.91 (d, 1H), 4.03 (s, 2H), 3.19 (q, 2H), 3.09 (s, 3H), 2.39 (m, 5H), 2.18 (s, 3H), 1.78 (m, 2H); MS(ESI [M+H+] 563.19.

Example 101: Preparation of 4-acryloylamino-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide

The procedure of Example 89 was repeated except for using 0.15 g of the compound obtained in (100-1) of Example 100 instead of the compound obtained in (87-1) of Example 87 to obtain the title compound (0.03 g, 18%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.64 (d, 1H), 8.44 (s, 1H), 8.11 (d, 1H), 7.75 (m, 2H), 7.66 (d, 1H), 7.58 (dd, 1H), 7.28 (m, 2H), 6.97 (d, 1H), 6.23 (d, 1H), 6.20 (s, 1H), 5.63 (dd, 1H), 3.38 (t, 2H), 2.52 (m, 5H), 2.24 (s, 3H), 1.96 (m, 2H); MS(ESI): [M+H+] 497.19.

Example 102: Preparation of 4-(2-chloro-acetylamino)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-butyramide

The procedure of Example 61 was repeated except for using 0.3 g of the compound obtained in (87-1) of Example 87 instead of the compound obtained in (20-1) of Example 20 to obtain the title compound (0.33 g, 95%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.63 (d, 1H), 8.46 (s, 1H), 7.87 (d, 1H), 7.74 (m, 2H), 7.58 (dd, 1H), 7.39 (m, 1H), 7.27 (m, 2H), 7.14 (d, 1H), 7.04 (t, 1H), 5.20 (s, 2H), 4.05 (s, 2H), 3.36 (t, 2H), 2.50 (t, 2H), 1.98 (m, 2H).

Example 103: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-morpholin-4-yl-acetylamino)-butyramide

The procedure of Example 62 was repeated except for using 0.04 g of the compound obtained in Example 102 instead of the compound obtained in Example 61 to obtain the title compound (0.02 g, 42%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.61 (d, 1H), 8.45 (s, 1H), 7.88 (d, 1H), 7.75 (m, 2H), 7.58 (dd, 1H), 7.40 (m, 1H), 7.27 (m, 2H), 7.14 (d, 1H), 7.05 (t, 1H), 5.20 (s, 2H), 3.68 (m, 4H), 3.35 (t, 2H), 3.00 (s, 2H), 2.50 (m, 6H), 1.95 (m, 2H).

Example 104: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-dimethylamino-acetylamino)-butyramide

The procedure of Example 63 was repeated except for using 0.04 g of the compound obtained in Example 102 instead of the compound obtained in Example 61 to obtain the title compound (0.02 g, 45%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.63 (s, 1H), 8.46 (s, 1H), 7.90 (d, 1H), 7.76 (m, 2H), 7.60 (dd, 1H), 7.40 (m, 1H), 7.28 (m, 2H), 7.15 (d, 1H), 7.07 (t, 1H), 5.22 (s, 2H), 3.37 (t, 2H), 3.02 (s, 2H), 2.51 (t, 2H), 2.32 (s, 6H), 1.97 (m, 2H).

Example 105: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-[2-(4-methyl-piperazin-1-yl)-acetylamino]-butyramide

The procedure of Example 64 was repeated except for using 0.02 g of the compound obtained in Example 102 instead of the compound obtained in Example 61 to obtain the title compound (0.01 g, 10%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.57 (s, 1H), 8.52 (s, 1H), 7.88 (d, 1H), 7.80 (m, 2H), 7.66 (dd, 1H), 7.37 (m, 1H), 7.24 (m, 2H), 7.04 (m, 2H), 5.18 (s, 2H), 3.41 (t, 2H), 3.07 (s, 2H), 2.63 (bs, 4H), 2.46 (t, 2H), 2.03 (m, 6H), 1.43 (s, 3H).

Example 106: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-[2-(2-methoxy-ethylamino)-acetylamino]-butyramide

The procedure of Example 65 was repeated except for using 0.07 g of the compound obtained in Example 102 instead of the compound obtained in Example 61 to obtain the title compound (0.02 g, 28%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.61 (d, 1H), 8.45 (s, 1H), 7.88 (d, 1H), 7.73 (m, 2H), 7.58 (dd, 1H), 7.39 (m, 1H), 7.28 (m, 2H), 7.13 (d, 1H), 7.05 (t, 1H), 5.19 (s, 2H), 3.47 (t, 2H), 3.35 (t, 2H), 3.30 (s, 3H), 3.28 (s, 2H), 2.75 (t, 2H), 2.50 (t, 2H), 1.98 (m, 2H).

Example 107: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-[2-(2-methanesulfonyl-ethylamino)-acetylamino]-butyramide

The procedure of Example 66 was repeated except for using 0.09 g of the compound obtained in Example 102 instead of the compound obtained in Example 61 to obtain the title compound (0.02 g, 20%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.60 (d, 1H), 8.45 (s, 1H), 7.88 (d, 1H), 7.75 (m, 2H), 7.58 (dd, 1H), 7.40 (m, 1H), 7.27 (m, 2H), 7.14 (d, 1H), 7.05 (t, 1H), 5.20 (s, 2H), 3.37 (m, 4H), 3.27 (s, 2H), 3.05 (m, 5H), 2.50 (t, 2H), 1.98 (m, 2H).

Example 108: Preparation of 4-(2-chloro-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide

1 g of the compound obtained in (100-1) of Example 100 dissolved in 20 ml of THF was cooled to 0℃, and reacted with 0.4 ml of pyridine and 0.3 ml of chloroacetylchloride at room temperature for 5 hours. Saturated sodium bicarbonate solution was added to the reacted solution, and the resulting solution was extracted with chloroform, washed with saturate saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure. The resulting residue was vacuum dried to obtain the title compound (0.4 g, 35%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.89 (s, 1H), 9.01 (s, 1H), 8.71 (s, 1H), 8.50 (s, 1H), 8.14 (m, 2H), 7.75 (m, 4H), 7.21 (m, 2H), 6.92 (d, 1H), 4.04 (s, 2H), 3.18 (m, 2H), 2.42 (m, 5H), 2.18 (s, 3H), 1.75 (m, 2H); MS(ESI): [M+H+] 519.08.

Example 109: Preparation of *N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-4-(2-morpholin-4-yl-acetylamino)-butyramide

0.07 g of the compound obtained in Example 108 dissolved in 5 ml of *N,N'*-dimethylformamide was reacted with 0.02 ml of morpholine and 0.04 g of potassium carbonate for 10 hours while heating to 100℃. The reacted solution was diluted with distilled water, extracted with ethylacetate, washed with saturated saline solution, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected

to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.03 g, 38%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.62 (s, 1H), 8.42 (s, 1H), 8.10 (d, 1H), 7.72 (m, 2H), 7.63 (d, 1H), 7.57 (d, 1H), 7.24 (m, 2H), 6.94 (d, 1H), 3.67 (m, 4H), 3.35 (t, 2H), 2.99 (s, 2H), 2.48 (m, 9H), 2.22 (s, 3H), 1.94 (m, 2H); MS(ESI): [M+H+] 570.28.

Example 110: Preparation of 4-(2-dimethylamino-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide

The procedure of Example 109 was repeated except for using dimethylamine 2 M THF instead of morpholine to obtain the title compound (0.03 g, 37%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.27 (s, 1H), 8.76 (s, 1H), 8.66 (s, 1H), 8.25 (d, 1H), 8.12 (bs, 1H), 7.80 (s, 2H), 7.58 (m, 3H), 7.11 (m, 2H), 6.87 (d, 1H), 3.44 (q, 2H), 2.88 (s, 2H), 2.52 (s, 3H), 2.40 (m, 2H), 2.32 (s, 6H), 2.24 (s, 3H), 1.94 (m, 2H).

Example 111: Preparation of *N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-4-[2-(4-methyl-piperazin-1-yl)-acetylamino]-butyramide

The procedure of Example 109 was repeated except for using 1-methyl-piperazine instead of morpholine to obtain the title compound (0.05 g, 56%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.22 (s, 1H), 8.65 (s, 1H), 8.53 (s, 1H), 8.24 (s, 2H), 7.79 (s, 2H), 7.53 (m, 3H), 7.10 (m, 2H), 6.87 (d, 1H), 3.44 (m, 2H), 3.07 (s, 2H), 2.57 (bs, 4H), 2.51 (s, 3H), 2.40 (m, 6H), 2.29 (s, 3H), 2.23 (s, 3H), 1.92 (m, 2H).

Example 112: Preparation of 4-[2-(2-methanesulfonyl-ethylamino)-acetylamino]-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide

The procedure of Example 109 was repeated except for using 2-methanesulfonylethylamine instead of morpholine to obtain the title compound (0.04 g, 33%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.83 (s, 1H), 8.64 (s, 2H), 8.23 (d, 1H), 7.80 (m, 3H), 7.64 (s, 1H), 7.54 (d, 1H), 7.12 (m, 2H), 6.88 (d, 1H), 3.42 (m, 2H), 3.34 (s, 2H), 3.20 (m, 4H), 3.02 (s, 3H), 2.52 (s, 3H), 2.42 (m, 2H), 2.25 (s, 3H), 1.96 (m, 2H).

Example 113: Preparation of 4-[2-(2-methoxy-ethylamino)-acetylamino]-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide

The procedure of Example 109 was repeated except for using 2-methoxyethylamine instead of morpholine to obtain the title compound (0.05 g, 60%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.27 (s, 1H), 8.71 (s, 1H), 8.64 (s, 1H), 8.23 (d, 1H), 7.82 (m, 3H), 7.61 (d, 1H), 7.53 (dd, 1H), 7.08 (m, 2H), 6.86 (d, 1H), 3.44 (m, 4H), 3.35 (s, 5H), 2.78 (m, 2H), 2.51 (s, 3H), 2.39 (m, 2H), 2.23 (s, 3H), 1.91 (m, 2H).

Example 114: Preparation of (4-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-butyl)-carbamic acid *t*-butylester

The procedure of Example 19 was repeated except for using 0.4 g of 5-*t*-buthoxycarbonylamino-pentanoic acid instead of 3-*t*-buthoxycarbonylamino-propionic acid to obtain the title compound (0.6 g, 40%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.19 (s, 1H), 9.77 (s, 1H), 8.69 (s, 1H), 8.48 (s, 1H), 7.97 (d, 1H), 7.71 (m, 2H), 7.45 (m, 1H), 7.33 (m, 2H), 7.24 (d, 1H), 7.16 (t, 1H), 6.81 (s, 1H), 5.25 (s, 2H), 2.94 (m, 2H), 2.38 (t, 2H), 1.61 (m, 2H), 1.44 (m, 2H), 1.36 (s, 9H).

Example 115: Preparation of 5-(2-methoxy-acetylamino)-pentanoic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide

(115-1) Preparation of 5-amino-pentanoic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of (20-1) of Example 20 was repeated except for using 0.42 g of the compound obtained in Example 114 instead of the compound obtained in Example 19 to obtain the title compound (0.34 g, 98%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.25 (s, 1H), 8.68 (s, 1H), 8.47 (s, 1H), 7.96 (s, 1H), 7.83 (m, 1H), 7.68 (m, 2H), 7.44 (m, 1H), 7.25 (m, 4H), 5.24 (s, 2H), 3.35 (m, 2H), 2.37 (t, 2H), 1.65 (m, 2H), 1.42 (m, 2H).

(115-2) Preparation of 5-(2-methoxy-acetylamino)-pentanoic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of (20-2) of Example 20 was repeated except for using 0.09 g of the compound obtained in (115-1) instead of the compound obtained in (20-1) of Example 20 to obtain the title compound (0.06 g, 59%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.20 (s, 1H), 9.77 (s, 1H), 8.69 (s, 1H), 8.49 (s, 1H), 7.96 (d, 1H), 7.71 (m, 4H), 7.46 (m, 1H), 7.32 (m, 2H), 7.24 (d, 1H), 7.18 (t, 1H), 5.25 (s, 2H), 3.77 (s, 2H), 3.29 (s, 3H), 3.13 (q, 2H), 2.39 (t, 2H), 1.62 (m, 2H), 1.50 (m, 2H).

Example 116: Preparation of 5-(2-methanesulfonyl-acetylamino)-pentanoic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-pentylamino]-quinazolin-6-yl}-amide

The procedure of Example 21 was repeated except for using 0.09 g of the compound obtained in (115-1) of Example 115 instead of the compound obtained in (20-1) of Example 20 to obtain the title compound (0.05 g, 45%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.19 (s, 1H), 9.76 (s, 1H), 8.67 (s, 1H), 8.48 (s, 1H), 8.34 (d, 1H), 7.96 (s, 1H), 7.70 (m, 3H), 7.45 (m, 1H), 7.25 (m, 4H), 5.24 (s, 2H), 4.02 (s, 2H), 3.13 (m, 2H), 3.05 (s, 3H), 2.40 (m, 2H), 1.65 (m, 2H), 1.39 (m, 2H).

Example 117: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfanyl-acetylamino)-propionamide

The procedure of Example 21 was repeated except for using 0.19 ml of methylthioacetic acid instead of methanesulfonylacetic acid to obtain the title compound (520 mg, 87%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.31 (s, 1H), 9.80 (s, 1H), 8.69 (s, 1H), 8.51 (s, 1H), 8.13 (t, 1H), 7.99 (d, 1H), 7.83 (dd, 1H), 7.72 (m, 2H), 7.47 (m, 1H), 7.31 (m, 2H), 7.26 (d, 1H), 7.20 (t, 1H), 5.26 (s, 2H), 3.42 (q, 2H), 3.33 (s, 3H), 3.08 (s, 2H), 2.61 (t, 2H).

Example 118: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfinyl-acetylamino)-propionamide

100 mg of the compound obtained in (20-1) of Example 20 dissolved in 5 ml of THF and 5 ml of saturated aqueous sodium bicarbonate solution was reacted with 40 mg of *m*-CPBA at room temperature for 27 hours, and the reacted solution was diluted with distilled water and chloroform, and filtered under a reduced pressure to obtain the title compound as solid (80 mg, 78%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.23 (s, 1H), 9.75 (s, 1H), 8.66 (s, 1H), 8.48 (s, 1H), 8.34 (t, 1H), 7.92 (s, 1H), 7.79 (dd, 1H), 7.65 (m, 2H), 7.43 (m, 1H), 7.29 (m, 2H), 7.19 (m, 2H), 5.21 (s, 2H), 3.60 (dd, 2H), 3.39 (q, 2H), 2.56 (s, 3H), 2.52 (t, 2H); MS(ESI): [M+H+] 569.99.

Example 119: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2,2,2-trifluoro-acetylamino)-propionamide

80 mg of the compound obtained in (20-1) of Example 20 dissolved in 3 ml of THF at 0℃ was reacted with 0.03 mg of pyridine and 0.03 ml of anhydrous trifluoroacetic acid for 4 hours while heating to room temperature. The reacted solution was diluted with saturated sodium bicarbonate solution, extracted with ethylacetate, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (40 mg, 42%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.58 (s, 1H), 8.42 (s, 1H), 7.84 (d, 1H), 7.66 (m, 2H), 7.54 (dd, 1H), 7.35 (m, 1H), 7.21 (m, 2H), 7.05 (m, 2H), 5.15 (s, 2H), 3.67 (t, 2H), 2.74 (t, 2H).

Example 120: Preparation of 3-acetylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide

The procedure of Example 119 was repeated except for using 0.03 ml of anhydrous acetic acid instead of trifluoroacetic acid to obtain the title compound (60 mg, 69%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.25 (s, 1H), 9.76 (s, 1H), 8.65 (s, 1H), 8.46 (s, 1H), 7.94 (m, 2H), 7.79 (dd, 1H), 7.66 (m, 2H), 7.43 (m, 1H), 7.30 (m, 2H), 7.21 (d, 1H), 7.13 (t, 1H), 5.22 (s, 2H), 3.38 (t, 2H), 2.52 (t, 2H), 1.77 (s, 3H).

Example 121: Preparation of acetic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethylcarbamoyl)-methylester

The procedure of Example 119 was repeated except for using 0.03 ml of acetoxyacetylchloride instead of trifluoroacetic acid to obtain the title compound (80 mg, 74%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.35 (s, 1H), 9.81 (s, 1H), 8.70 (s, 1H), 8.50 (s, 1H), 8.16 (t, 1H), 7.99 (d, 1H), 7.83 (dd, 1H), 7.74 (m, 2H), 7.46 (m, 1H), 7.32 (m, 2H), 7.25 (d, 1H), 7.16 (t, 1H), 5.25 (s, 2H), 4.44 (s, 2H), 3.43 (t, 2H), 2.60 (t, 2H), 2.10 (s, 3H).

Example 122: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(2-dimethylamino-ethoxy)-acetylamino]-propionamide

44 mg of sodium hydride (60%, oil suspension) dissolved in 2 ml of THF was reacted with 0.03 ml of dimethylethanol for 30 mins, 100 mg of the compound obtained (20-1) of Example 20 dissolved in 5 ml of THF was added thereto at 0℃, and the resulting solution was reacted for 3 hours while heating to room temperature. The reacted solution was diluted with saturated sodium bicarbonate solution, extracted with chloroform, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent-chloroform : methanol = 15 : 1) to obtain the title compound (70 mg, 64%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.53 (d, 1H), 8.37 (s, 1H), 7.81 (d, 1H), 7.67 (m, 2H), 7.51 (dd, 1H), 7.36 (m, 1H), 7.21 (m, 2H), 7.02 (m, 2H), 5.09 (s, 2H), 3.91 (s, 2H), 3.62 (t, 2H), 3.56 (t, 2H), 2.66 (t, 2H), 2.48 (t, 2H), 2.20 (s, 6H).

Example 123: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(3-ethyl-ureido)-propionamide

80 mg of the compound obtained in (20-1) of Example 20 dissolved in 5 ml of chloroform was reacted with 0.02 ml of ethylisocyanate at room temperature for 2 hours. The reacted mixture was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (70 mg, 77%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.26 (s, 1H), 9.77 (s, 1H), 8.66 (s, 1H), 8.47 (s, 1H), 7.95 (d, 1H), 7.79 (dd, 1H), 7.72 (d, 1H), 7.68 (dd, 1H), 7.45 (m, 1H), 7.30 (m, 2H), 7.22 (d, 1H), 7.16 (t, 1H), 5.88 (q, 2H), 5.23 (s, 2H), 2.97 (m, 2H), 2.51 (m, 2H), 0.94 (t, 3H).

Example 124: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(3-phenyl-ureido)-propionamide

The procedure of Example 123 was repeated except for using 0.02 ml of phenylisocyanate instead of ethylisocyanate to obtain the title compound (73 mg, 73%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.40 (s, 1H), 9.82 (s, 1H), 8.71 (s, 1H), 8.68 (s, 1H), 8.51 (s, 1H), 8.00 (d, 1H), 7.89 (dd, 1H), 7.72 (m, 2H), 7.30 (m, 8H), 6.92 (m, 2H), 6.39 (t, 1H), 5.23 (s, 2H), 3.42 (q, 2H), 2.60 (t, 2H).

Example 125: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(3-furan-2-ylmethyl-ureido)-propionamide

The procedure of Example 123 was repeated except for using 0.02 ml of furfurylisocyanate instead of ethylisocyanate to obtain the title compound (80 mg, 80%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.34 (s, 1H), 9.80 (s, 1H), 8.70 (s, 1H), 8.48 (s, 1H), 7.98 (d, 1H), 7.83 (dd, 1H), 7.69 (m, 2H), 7.51 (s, 1H), 7.44 (m, 1H), 7.30 (m, 2H), 7.22 (d, 1H), 7.16 (t, 1H), 6.38 (t, 1H), 6.16 (d, 1H), 6.05 (t, 1H), 5.23 (s, 2H), 4.16 (d, 2H), 3.38 (m, 2H), 2.56 (m, 2H).

Example 126: Preparation of (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid methylester

The procedure of Example 119 was repeated except for using 0.02 ml of methylchloroformate instead of ethylisocyanate to obtain the title compound (60 mg, 67%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.64 (s, 1H), 8.45 (s, 1H), 7.87 (d, 1H), 7.81 (s, 2H), 7.57 (dd, 1H), 7.38 (m, 1H), 7.29 (m, 2H), 7.12 (d, 1H), 7.04 (t, 1H), 5.20 (s, 2H), 3.64 (s, 3H), 3.51 (t, 2H), 2.66 (t, 2H).

Example 127: Preparation of (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid phenylester

The procedure of Example 119 was repeated except for using 0.03 ml of phenylchloroformate instead of ethylisocyanate to obtain the title compound (20 mg, 20%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.54 (s, 1H), 8.07 (s, 1H), 7.80 (d, 1H), 7.69 (d, 1H), 7.57 (m, 2H), 7.30 (m, 3H), 7.13 (m, 2H), 6.98 (m, 5H), 5.08 (s, 2H), 3.56 (t, 2H), 2.68 (t, 2H).

Example 128: Preparation of (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid benzylester

The procedure of Example 119 was repeated except for using 0.04 ml of benzylchloroformate instead of ethylisocyanate to obtain the title compound (50 mg, 49%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.27 (s, 1H), 9.77 (s, 1H), 8.68 (s, 1H), 8.49 (s, 1H), 7.96 (d, 1H), 7.83 (dd, 1H), 7.75 (d, 1H), 7.70 (dd, 1H), 7.49 (m, 1H), 7.37 (m, 6H), 7.28 (d, 1H), 7.20 (t, 1H), 5.14 (s, 2H), 5.00 (s, 2H), 3.38 (q, 2H), 2.60 (t, 2H).

Example 129: Preparation of *N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-propionamide

(129-1) Preparation of 3-amino-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-propionamide

350 mg of 2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid *t*-butylester dissolved in 7 ml of methylene chloride was reacted with 7 ml of trifluoroacetic acid at room temperature for 4 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred with 50 ml of saturated aqueous sodium bicarbonate solution for 30 mins, filtered under a reduced pressure and dried to obtain the title compound (280 mg, 97%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.65 (s, 1H) 8.57 (s, 1H), 8.50 (s, 1H), 7.92-7.94 (m, 2H), 7.72-7.78 (m, 3H), 7.59-7.62 (m, 1H), 7.40 (t, *J*=5 Hz, 1H), 7.19 (d, *J*=9 Hz, 1H), 5.29 (s, 2H), 3.53 (bs, 2H), 2.65 (bs, 2H).

(129-2) Preparation of *N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-propionamide

30 mg of 1-hydroxylbenzotriazole and 85 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 17 μl of methoxyacetic acid dissolved in 3 ml of THF, and reacted at room temperature for 12 hours after adding 50 mg of the compound obtained in (129-1). The reacted solution was extracted with ethylacetate 3 times after adding 5 ml of water, dried over anhydrous magnesium sulfate, distilled under a reduced pressure, and the resulting residue was subjected to column chromatography

(eluent- chloroform : methanol = 15 : 1) to obtain the title compound (15 mg, 26%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.90 (s, 1H), 8.71-8.75 (m, 2H), 8.08-8.11 (m, 2H), 7.92-7.95 (m, 3H), 7.79 (m, 1H), 7.63 (t, *J*=5 Hz, 1H), 7.39 (d, *J*=9 Hz, 1H), 5.47 (s, 2H), 4.08 (s, 2H), 3.85 (t, *J*=6 Hz, 2H) 3.53 (s, 3H), 2.93 (bs, 2H).

Example 130: Preparation of *N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-propionamide

56 mg of 1-hydroxylbenzotriazole and 85 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 31 mg of methanesulfonylacetic acid dissolved in 2 ml of THF, and the solution was reacted at room temperature for 12 hours after adding 50 mg of the compound obtained in (129-1) of Example 129. The reacted solution was extracted with 10 ml of ethylacetate 3 times after adding 5 ml of water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent-chloroform : methanol = 15 : 1) to obtain the title compound (5.2 mg, 8%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.66 (s, 1H), 8.54 (bs, 1H), 8.47 (s, 1H), 7.93 (m, 2H), 7.70 - 7.75 (m, 3H), 7.58 (m, 1H), 7.39 (t, *J* = 5 Hz, 1H), 7.17 (d, *J* = 9 Hz, 1H), 5.29 (s, 2H), 4.03 (s, 2H), 3.64 (t, *J* = 6 Hz, 2H), 3.29 (s, 3H), 2.72 (t, *J* = 6 Hz, 2H).

Example 131: Preparation of *N*-(2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

85 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 46 μl of pyridine were added to 31 μl of acrylic acid dissolved in 3 ml of THF, and reacted with 100 mg of the compound obtained

in (129-1) of Example 129 at 0℃ for 30 mins. The reacted solution was extracted with 6 ml of ethylacetate 3 times after adding 4 ml of water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (7 mg, 6%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.67 (s, 1H), 8.56 (bs, 1H), 8.48 (s, 1H), 7.89-7.94 (m, 2H), 7.72-7.76 (m, 3H), 7.64 (dd, *J*=6,9 Hz, 1H), 7.42 (t, *J*=5 Hz, 1H), 7.17 (d, *J*=9 Hz, 1H), 6.24-6.26 (m, 2H), 5.66-5.68 (m, 1H), 5.29 (s, 2H), 3.69 (t, *J*=6 Hz, 2H), 2.76 (t, *J*=6 Hz, 2H).

Example 132: Preparation of *N*-{4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-propionamide

(132-1) Preparation of 3-amino-*N*-{4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-yl}-propionamide

280 mg of 2-{4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid *t*-butylester dissolved in 6 ml of methylene chloride was reacted with 6 ml of trifluoroacetic acid at room temperature for 4 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred with 50 ml of saturated aqueous sodium bicarbonate solution for 30 mins, filtered under a reduced pressure and dried to obtain the title compound (220 mg, 96%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.69 (bs, 1H), 8.63 (s, 1H), 8.50 (bs, 1H), 8.44 (s, 1H), 8.00 (d, *J*=8 Hz, 1H), 7.90 (d, *J*=2.5 Hz, 1H), 7.72-7.77 (m, 2H), 7.63 (dd, *J*=9, 2.5 Hz, 1H), 7.46-7.50 (m, 1H), 7.19 (d, *J*=9 Hz, 1H), 5.24 (s, 2H), 3.30 (bs, 2H), 2.63 (bs, 2H).

(132-2) Preparation of *N*-{4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-propionamide

30 mg of 1-hydroxylbenzotriazole and 85 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 17 μl of methoxyacetic acid dissolved in 3 ml of THF, and reacted at room temperature for 12 hours after adding 50 mg of the compound obtained in (132-1). The reacted solution was extracted with 10 ml of ethylacetate 3 times after adding 5 ml of water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (5 mg, 9%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.69 (bs, 1H), 8.63 (s, 1H), 8.50 (bs, 1H), 8.44 (s, 1H), 8.00 (d, *J*=8 Hz, 1H), 7.90 (d, *J*=2.5 Hz, 1H), 7.72-7.77 (m, 2H), 7.63 (dd, *J*=9, 2.5 Hz, 1H), 7.46-7.50 (m, 1H), 7.19 (d, *J*=9 Hz, 1H), 5.24 (s, 2H), 3.30 (bs, 2H), 2.63 (bs, 2H).

Example 133: Preparation of *N*-{4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-propionamide

56 mg of 1-hydroxylbenzotriazole and 85 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 31 mg of methansulfonylacetic acid dissolved in 2 ml of THF, and reacted at room temperature for 12 hours after adding 50 mg of the compound obtained in (132-1) of Example 132. The reacted solution was extracted with 10 ml of ethylacetate 3 times after adding 5 ml of water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent-chloroform : methanol = 15 : 1) to obtain the title compound (16 mg, 25%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 8.74 (s, 1H), 8.70 (s, 1H), 8.66 (d, *J*=2 Hz, 1H), 8.50 (s, 1H), 8.21 (d, *J*=8 Hz, 1H), 8.11 (d, *J*=2.5 Hz, 1H), 7.93-7.98 (m, 2H), 7.85 (dd, *J*=9, 2.5 Hz, 1H), 7.69 (bs, 1H), 7.43 (d, *J*=9 Hz, 1H),

5.29 (s, 2H), 4.11 (s, 2H), 3.71 (t, *J*=6 Hz, 2H), 3.16 (s, 3H), 2.79 (t, *J*=6 Hz, 2H).

Example 134: Preparation of *N*-(2-{4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

46 μl of pyridine and 85 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 31 μl of acrylic acid dissolved in 3 ml of THF at 0℃, reacted with 100 mg of the compound (132-1) of Example 132 for 30 mins, and stirred for 2 hours while heating to room temperature. The reacted solution was extracted with 6 ml of ethylacetate 3 times after adding 4 ml of water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (20 mg, 18%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.86 (bs, 1H), 8.85 (s, 1H), 8.73 (bs, 1H), 8.72 (s, 1H), 8.21 (d, *J*=8 Hz, 1H), 8.11 (d, *J*=2.5 Hz, 1H), 7.93-7.98 (m, 2H), 7.85 (dd, *J*=9, 2.5 Hz, 1H), 7.69 (bs, 1H), 7.43 (d, *J*=9 Hz,1H), 6.37-6.44 (m, 2H), 5.82-5.86 (m, 1H), 5.46 (s, 2H), 3.87 (t, *J*=6 Hz, 2H), 2.94 (t, *J*=6 Hz, 2H).

Example 135: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(2-methoxy-ethoxy)-acetylamino]-propionamide

0.04 ml of 2-(2-methoxyethoxy) acetic acid, 0.05 g of 1-hydroxylbenzotriazole and 0.13 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride dissolved in 5 ml of dichloromethane were reacted at room temperature for 21 hours after adding 0.08 g of the compound obtained in (20-1) of Example 20. The reacted solution was extracted with chloroform 2 times after adding saturated sodium bicarbonate, washed with saturated saline solution, dried over anhydrous magnesium sulfate, filtered and

distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.07 g, 71%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.50 (s, 1H), 8.35 (s, 1H), 7.78 (d, 1H), 7.59 (d, 2H), 7.48 (dd, 1H), 7.28 (m, 1H), 7.15 (m, 2H), 6.94 (m, 2H), 5.07 (s, 2H), 3.90 (s, 2H), 3.53 (m, 4H), 3.42 (m, 2H), 3.20 (s, 3H), 2.62 (t, 2H).

Example 136: Preparation of 5-methyl-isoxazol-4-carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

The procedure of Example 140 was repeated except for using 0.05 g of 5-methylisoxazol-4-carboxylic acid instead of 2-(2-methoxyethoxy)acetic acid to obtain the title compound (0.05 g, 51%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.56 (s, 1H), 8.53 (s, 1H), 8.38 (s, 1H), 7.80 (m, 1H), 7.65 (m, 2H), 7.50 (dd, 1H), 7.32 (m, 1H), 7.19 (m, 2H), 7.07 (d, 1H), 6.98 (t, 1H), 5.13 (s, 2H), 3.65 (t, 2H), 2.70 (t, 2H), 2.57 (s, 3H).

Example 137: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-methanesulfanyl-acetylamino)-butyramide

The procedure of Example 135 was repeated except for using 0.3 g of the compound obtained in (20-1) of Example 20 and 0.11 ml of methylthioacetic acid 0.11 ml to obtain the title compound (0.3 g, 85%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.65 (s, 1H), 8.47 (s, 1H), 7.89 (d, 1H), 7.73 (m, 2H), 7.59 (dd, 1H), 7.40 (m, 1H), 7.27 (m, 2H), 7.17 (d. 1H), 7.02 (t, 1H), 5.23 (s, 2H), 3.15 (s, 2H), 2.51 (t, 2H), 2.15 (s, 3H), 1.96 (t, 2H).

Example 138: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-methanesulfinyl-acetylamino)-butyramide

The procedure of Example 118 was repeated except for using 0.11 g of the compound obtained in Example 137 instead of the compound obtained in Example 117 to obtain the title compound (70 mg, 61%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.57 (d, 1H), 8.43 (s, 1H), 7.88 (d, 1H), 7.69 (m, 2H), 7.57 (dd, 1H), 7.38 (m, 1H), 7.25 (m, 2H), 7.08 (d, 1H), 7.02 (t, 1H), 5.16 (s, 2H), 3.82 (d, 1H), 3.63 (d, 1H), 3.38 (m, 2H), 2.75 (s, 3H), 2.51 (t, 2H), 1.95 (m, 2H).

Example 139: Preparation of *N*-[2-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-methyl-carbamoyl)-ethyl]-acrylamide

(139-1) Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-formamide

2 g of the compound obtained in (1-4) of Example 1 and 0.78 ml of formic acid dissolved in 20 ml of dichloromethane was reacted with 1.64 ml of pyridine and 3.88 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride at room temperature for 3 hours. The reacted solution was filtered under a reduced pressure after adding saturated sodium bicarbonate to obtain the title compound as solid (1.8 g, 84%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.64 (d, 1H), 8.46 (d, 1H), 8.30 (d, 1H), 7.88 (d, 1H), 7.76 (d, 1H), 7.72 (d, 1H), 7.58 (dd, 1H), 7.39 (m, 1H), 7.27 (m, 2H), 7.12 (d, 1H), 7.03 (t, 1H), 5.21 (s, 2H).

(139-2) Preparation of N^4-[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]-*N*6-methyl-quinazolin-4,6-diamine

1 g of the compound obtained in (139-1) dissolved in 20 ml of THF was added to 0.45 g of lithium aluminum hydride dissolved in 5 ml of THF at 0℃,

and reacted for 4 hour while heating the solution slowly to 60℃. The reacted solution was dried over magnesium sulfate after adding 0.5 ml of distilled water, 2.8 ml of 1 N aqueous sodium hydroxide solution and 1 ml of distilled water sequentially, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.6 g, 62%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.57 (s, 1H), 7.79 (s, 1H), 7.71 (d, 1H), 7.52 (dd, 1H), 7.32 (m, 1H), 7.15 (m, 3H), 6.98 (m, 3H), 6.52 (s, 1H), 5.14 (s, 2H), 2.96 (s, 3H).

(139-3) Preparation of [2-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-methyl-carbamoyl)-ethyl]-carbamic acid *t*-butylester

0.55 g of the compound obtained in (139-2) and 1.02 g of 3-*t*-buthoxycarbonylamino-propionic acid dissolved in 15 ml of pyridine were reacted with 1.29 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride at room temperature for 2 hours. The reacted solution was distilled under a reduced pressure to remove solvent, and saturated sodium bicarbonate was added thereto. The resultant was extracted with chloroform 2 times, washed with saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.62 g, 80%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.78 (s, 1H), 8.38 (s, 1H), 7.91 (m, 2H), 7.70 (d, 1H), 7.59 (m, 1H), 7.34 (m, 1H), 7.23 (m, 2H), 6.97 (m, 2H), 5.17 (s, 2H), 3.42 (m, 2H), 3.35 (s, 3H), 2.55 (m, 2H), 1.2 5(s, 9H).

(139-4) Preparation of 3-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-*N*-methyl-propionamide

0.58 g of the compound obtained in (139-3) dissolved in 10 ml of dichloromethane and 10 ml of trifluoroacetic acid was stirred at room temperature for 1 hour. The residue obtained from distillation of the reacted

solution under a reduced pressure was dissolved in small amount of dichloromethane and stirred while adding saturated sodium bicarbonate. The resulting solution was extracted with chloroform, washed with saturated saline solution, dried over magnesium sulfate, and filtered and distilled under a reduced pressure to obtain the title compound (0.4 g, 83%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.75 (s, 1H), 8.38 (s, 1H), 7.97 (m, 3H), 7.59 (m, 2H), 7.33 (m, 1H), 7.20 (m, 2H), 6.98 (m, 2H), 5.15 (s, 2H), 3.36 (s, 3H), 2.98 (m, 2H), 2.37 (m, 2H); MS(ESI): [M+H+] 480.

(139-5) Preparation of *N*-[2-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-methyl-carbamoyl)-ethyl]-acrylamide

The procedure of Example 22 was repeated except for using 0.5 g of the compound obtained in (139-4) instead of the compound obtained in (20-1) of Example 20 to obtain the title compound (0.25 g, 45%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.30 (s, 1H), 8.74 (s, 1H), 8.13 (s, 1H), 7.93 (m, 2H), 7.71 (d, 1H), 7.57 (dd, 1H), 7.35 (m, 1H), 7.23 (m, 2H), 6.98 (m, 3H), 6.15 (m, 2H), 5.63(dd, 1H), 5.15 (s, 2H), 3.55 (m, 2H), 3.34 (s, 3H), 2.55 (t, 2H).

Example 140: Preparation of *N*-[2-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-ethyl-carbamoyl)-ethyl]-acrylamide

The procedure of (139-5) of Example 139 was repeated except for using 3-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-*N*-ethyl-propionamide instead of the compound obtained in (139-4) of Example 139 to obtain the title compound (15 mg, 5%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.21 (s, 1H), 8.77 (s, 1H), 7.95 (s, 2H), 7.88 (d, 1H), 7.72 (dd, 1H), 7.56 (dd, 1H), 7.33 (m, 1H), 7.22 (m, 2H), 7.00 (m, 2H), 6.71 (bt, 1H), 6.18 (m, 2H), 5.67 (dd, 1H), 5.17 (s, 2H), 3.84 (m, 2H), 3.57 (m, 2H), 2.50 (m, 2H), 1.09 (t, 3H).

Example 141: Preparation of *N*-{2-[{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-(3-dimethylamino-propyl)-carbamoyl]-ethyl}-acrylamide

(141-1) Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-acrylamide

The procedure of Example 22 was repeated except for using 8.8 g of the compound obtained in (1-4) of Example 1 instead of the compound obtained in (139-4) of Example 139 to obtain the title compound (5 g, 50%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.77 (s, 1H), 10.01 (s, 1H), 8.95 (s, 1H), 8.66 (s, 1H), 8.15 (s, 1H), 8.09 (d, 1H), 7.86-7.92 (m, 2H), 7.58-7.63 (m, 1H), 7.32-7.46 (m, 4H), 6.61-6.65 (m, 1H), 6.50 (d, 1H), 5.99 (d, 1H), 5.39 (s, 2H).

(141-2) Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-dimethylamino-propionamide

6 ml of dimethylamine 2 M THF was added to 534 mg of the compound obtained in (141-1) and 113 mg of *p*-toluene sulfonic acid dissolved in 15 ml of THF, and reacted for 5 hour while heating the solution slowly to 50℃. The reacted solution was cooled to room temperature, extracted with ethylacetate 3 times after adding saturated sodium bicarbonate, washed with saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.4 g, 68%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.50 (s, 1H), 8.40 (s, 1H), 7.83 (d, 1H), 7.63 (s, 2H), 7.52 (dd, 1H), 7.3 (m, 1H), 7.19 (m, 2H), 6.97 (m, 2H), 5.08 (s, 2H), 2.76 (t, 2H), 2.61 (t, 2H), 2.33 (s, 6H).

(141-3) Preparation of N^4-[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]-N^6-(3-dimethylamino-propyl)-quinazolin-4,6-diamine

The procedure of (139-2) of Example 139 was repeated except for using 0.13 g of the compound obtained in (141-2) instead of the compound obtained in (139-1) of Example 139 to obtain the title compound (0.12 g, 93%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.22 (s, 1H), 7.80 (s, 1H), 7.48 (m, 3H), 7.31 (m, 1H), 7.22 (m, 3H), 7.04 (m, 2H), 5.06 (s, 2H), 3.19 (bt, 2H), 2.41 (t, 2H), 2.25 (s, 6H), 1.83 (m, 2H).

(141-4) Preparation of *N*-{2-[{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-(3-dimethylamino-propyl)-carbamoyl]-ethyl}-acrylamide

The procedure of Example 139 was repeated except for using 335 mg of the compound obtained in (141-3) instead of the compound obtained in (139-2) of Example 139 to obtain the title compound (80 mg, 23%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.55 (s, 1H), 8.30 (s, 1H), 7.91 (s, 1H), 7.85 (d, 1H), 7.74 (d, 1H), 7.6 1(d, 1H), 7.37 (m, 1H), 7.25 (m, 2H), 7.14 (d, 1H), 7.03 (t, 1H), 6.14 (m, 2H), 5.57 (m, 1H), 5.19 (s, 2H), 3.84 (t, 2H), 3.46 (t, 2H), 2.37 (m, 4H), 2.24 (s, 6H), 1.77 (m, 2H).

Example 142: Preparation of *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-*N*-methyl-acrylamide

(142-1) Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-methylamino-propionamide

The procedure of (141-2) of Example 141 was repeated except for using methylamine instead of dimethylamine to obtain the title compound (0.41 g, 96%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.56 (d, 1H), 8.35 (s, 1H), 7.78 (d, 1H), 7.66 (m, 2H), 7.49 (dd, 1H), 7.32 (m, 1H), 7.16 (m, 2H), 7.08 (d, 1H), 6.96 (t, 1H), 5.13 (s, 2H), 2.85 (t, 2H), 2.57 (t, 2H), 2.34 (s, 3H).

(142-2) Preparation of *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-*N*-methyl-acrylamide

The procedure of Example 22 was repeated except for using 0.38 g of the compound obtained in (142-1) instead of the compound obtained in (20-1) of Example 20 to obtain the title compound (0.04 g, 10%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.06 (s, 1H), 8.61 (s, 1H), 8.47 (s, 1H), 8.08 (bs, 1H), 7.81 (d, 1H), 7.71 (m, 2H), 7.53 (dd, 1H), 7.36 (m, 1H), 7.22 (m, 2H), 7.02 (t, 1H), 6.92 (d, 1H), 6.59 (m, 1H), 6.36 (d, 1H), 5.77 (d, 1H), 5.12 (s, 2H), 3.87 (t, 2H), 3.12 (s, 3H), 2.79 (t, 2H).

Example 143: Preparation of *N*-(2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-*N*-methyl-acrylamide

The procedure of Example 22 was repeated except for using *N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-methylamino-propionamide instead of the compound obtained in (20-1) of Example 20 to obtain the title compound (80 mg, 14%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.80 (s, 1H), 8.38 (m, 3H), 7.64 (d, 1H), 7.52 (m, 3H), 7.43 (d, 1H), 7.28 (d, 1H), 7.02 (t, 1H), 6.77 (d, 1H), 6.39 (m, 1H), 6.18 (d, 1H), 5.57 (d, 1H), 5.06 (s, 2H), 3.66 (t, 2H), 2.96 (s, 3H), 2.61 (t, 2H).

Example 144: Preparation of *N*-(2-{4-[3-chloro-4-(6-methyl-pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

The procedure of Example 22 was repeated except for using 3-amino-*N*-{4-[3-chloro-4-(6-methyl-pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-

yl}-propionamide instead of the compound obtained in (20-1) of Example 20 to obtain the title compound (47 mg, 12%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.61 (s, 1H), 8.42 (s, 1H), 7.88 (d, 1H), 7.70 (m, 3H), 7.55 (dd, 1H), 7.47 (d, 1H), 7.21 (d, 1H), 7.10 (d, 1H), 6.19 (m, 2H), 5.62 (dd, 1H), 5.18 (s, 2H), 3.60 (t, 2H), 2.70 (t, 2H), 2.51 (s, 3H).

Example 145: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

(145-1) Preparation of [3-chloro-4-(pyridin-2-ylmethoxy)-phenyl]-(6-nitro-quinazolin-4-yl)-amine hydrochloride salt

The procedure of (1-3) of Example 1 was repeated except for using 3.13 g of the compound obtained in (1-2) of Example 1 and 2.99 g of 3-chloro-4-(pyridin-2-ylmethoxy)-phenylamine instead of 3-chloro-4-(3-fluorobenzyloxy)-phenylamine to obtain the title compound (5 g, 88%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.80 (s, 1H), 8.95 (s, 1H), 8.75 (dd, 1H), 8.69 (d, 1H), 8.11 (d, 1H), 8.05 (t, 1H), 7.97 (d, 1H), 7.72 (m, 2H), 7.68 (t, 1H), 7.36 (d, 1H), 5.41 (s, 2H).

(145-2) Preparation of N^4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenyl]-quinazolin-4,6-diamine

The procedure of (1-4) of Example 1 was repeated except for using 4.5 g of the compound obtained in (145-1) instead of the compound obtained in (1-3) of Example 3 to obtain the title compound (2 g, 47%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.33 (s, 1H), 8.60 (d, 1H), 8.30 (s, 1H), 8.06 (d, 1H), 7.88 (t, 1H), 7.74 (dd, 1H), 7.59 (d, 1H), 7.50 (d, 1H), 7.38 (m, 2H), 7.22 (d, 2H), 5.41 (s, 2H), 5.56 (bs, 2H), 5.27 (s, 2H).

(145-3) Preparation of (2*S*)-2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-pyrrolidine-1-carboxylic acid *t*-butylester

The procedure of (1-5) of Example 1 was repeated except for using 414 mg of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester instead of 2-*t*-butoxycarbonylamino-ethanoic acid and 368 mg of the compound obtained in (145-2) to obtain the title compound (200 mg, 35%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.69 (s, 1H), 8.58 (d, 1H), 8.49 (s, 1H), 7.90-7.93 (m, 2H), 7.72-7.79 (m, 2H), 7.63 (dd, 1H), 7.42 (t, 1H), 7.20 (d, 1H), 5.29 (s, 2H), 4.35 (m, 1H), 3.59 (m, 2H), 2.04 (m, 4H), 1.43 (m, 9H).

(145-4) Preparation of (2*S*)-pyrrolidine-2-carboxylic acid{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of (2-3) of Example 2 was repeated except for using 200 mg of the compound obtained in (145-3) instead of the compound obtained in (1-5) of Example 1 to obtain the title compound (130 mg, 79%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.57 (s, 2H), 8.49 (s, 1H), 7.93 (m, 3H), 7.75 (t, 1H), 7.60 (d, 1H), 7.39 (t, 1H), 7.10 (d, 1H), 5.26 (s, 2H), 4.85 (m, 1H), 3.85 (m, 1H), 3.75 (m, 1H), 1.80 - 2.20 (m, 4H).

(145-5) Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 18 was repeated except for using the compound obtained in (145-4) instead of the compound obtained in (16-1) of Example 16 to obtain the title compound (32 mg, 22%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.65 (d, 1H), 8.65 (d, 1H), 8.58 (s, 1H), 7.88-7.93 (m, 3H), 7.70-7.80 (m, 2H), 7.65 (t, 1H), 7.40 (t, 1H), 7.20 (d, 1H), 6.55-6.79 (m, 1H), 6.30 (dd, 1H), 5.80 (dd, 1H), 5.27 (s, 2H), 4.60-4.70 (m, 1H), 3.80 (m, 2H), 2.26 (m, 4H).

Example 146: Preparation of (2*S*)-1-(1-oxo-butyn-2-yl)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 18 was repeated except for using 2-butynoic acid instead of acrylic acid to obtain the title compound (43 mg, 13%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.70 (s, 1H), 8.92 (s, 1H), 8.61 (s, 2H), 7.85 (s, 1H), 7.75 (t, 1H), 7.67 (d, 2H), 7.51 (dd, 1H), 7.43 (s, 1H), 6.92 (d, 1H), 7.26 (m, 2H), 5.77 (t, 1H), 5.29 (s, 2H), 4.82 (d, 1H), 4.05 (s, 3H), 3.77 (m, 2H), 2.60 (m, 1H), 1.92 - 2.13 (m, 3H), 2.02 (s ,3H).

Example 147: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(6-methyl-pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using N^4-[3-chloro-4-(6-methyl-pyridin-2-ylmethoxy)-phenyl]-quinazolin-4,6-diamine as a starting material to obtain the title compound (250 mg, 66%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.59 (s, 1H), 8.48 (s, 1H), 8.15 (bs, 1H), 7.95 (d, 1H), 7.79 (m, 2H), 7.62 (t, 1H), 7.51 (bs, 1H), 7.46 (d, 1H), 7.36 (d, 1H), 7.08 (d, 1H), 6.98 (d, 1H), 6.60 (m, 1H), 6.39 (dd, 1H), 5.78 (dd, 1H), 5.26 (s, 2H), 5.02 (m, 1H), 3.93 (m, 1H), 3.74 (m, 1H), 2.58 (s, 3H), 2.39 (m, 2H), 2.28 (m, 1H), 2.15 (m, 1H).

Example 148: Preparation of (3*R*,5*S*)-acetic acid 1-acryloyl-5-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-pyrrolidin-3-ylester

The procedure of Example 145 was repeated except for using (2*S*,4*R*)-4-acetoxy-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-

pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (300 mg, 46%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.50 (s, 1H), 8.60 (d, 1H), 8.47 (s, 1H), 8.18 (bs, 1H), 7.94 (d, 1H), 7.75 (m, 4H), 7.50 (s, 1H), 7.34 (d, 1H), 7.25 (t, 1H), 7.06 (d, 1H), 6.53 (m, 1H), 6.40 (m, 1H), 5.81 (d, 1H), 5.57 (m, 1H), 5.29 (s, 2H), 5.08 (t, 1H), 4.20 (m, 1H), 3.89 (d, 1H), 2.67 (m, 1H), 2.52 (m, 1H), 2.12 (s, 3H).

Example 149: Preparation of (2*S*,4*R*)-1-acryloyl-4-hydroxyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

0.32 ml of ammonia water was added to 130 mg of the compound obtained in Example 148 diluted with 10 ml of methanol, and the solution was refluxed with stirring at 80℃ for 26 hours. The reacted solution was cooled to room temperature, and filtered under a reduced pressure to obtain solid. The solid was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (80 mg, 66%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.48 (s, 1H), 8.59 (d, 1H), 8.52 (s, 1H), 7.97 (m, 1H), 7.88 (m, 2H), 7.76 (m, 2H), 7.66 (m, 2H), 7.45 (d, 1H), 7.01 (d, 1H), 6.52 (m, 1H), 6.40 (d, 1H), 5.79 (d, 1H), 5.29 (s, 2H), 5.12 (t, 1H), 4.78 (m, 1H), 3.92 (m, 1H), 3.75 (m, 1H), 2.60 (m, 1H), 2.17 (m, 1H).

Example 150: Preparation of (2*S*,4*R*)-1-acryloyl-4-ethylsulfanyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using (2*S*,4*R*)-4-ethylsulfanyl-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (70 mg, 36%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.35 (s, 1H), 8.60 (d, 1H), 8.50 (s, 1H), 8.04 (bs, 1H), 7.97 (d, 1H), 7.70 (m, 5H), 7.42 (d, 1H), 7.25 (t, 1H), 7.01 (d, 1H), 6.68 (m, 1H), 6.40 (dd, 1H), 5.82 (dd, 1H), 5.30 (s, 2H), 4.92 (t, 1H), 4.18 (m, 1H), 3.70 (t, 1H), 3.47 (m, 1H), 2.73 (m, 1H), 2.68 (m, 2H), 2.43 (m, 1H), 1.33 (t, 3H).

Example 151: Preparation of (2*S*,4*R*)-1-acryloyl-4-dimethylamino-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using (2*S*,4*R*)-4-dimethylamino-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (60 mg, 25%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.28 (s, 1H), 8.64 (d, 1H), 8.59 (s, 1H), 7.97 (d, 1H), 7.76 (m, 6H), 7.56 (d, 1H), 7.30 (t, 1H), 7.05 (d, 1H), 6.55 (m, 2H), 5.89 (dd, 1H), 5.40 (m, 1H), 5.34 (s, 2H), 5.10 (m, 1H), 4.14 (m, 1H), 3.95 (m, 1H), 2.95 (s, 3H), 2.87 (s, 3H), 2.80 (m, 1H), 2.58 (m, 1H).

Example 152: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using N^4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenyl]-quinazolin-4,6-diamine instead of the compound obtained in (145-2) of Example 145 to obtain the title compound (19 mg, 14%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.72 (s, 1H), 8.67 (s, 1H), 8.55 (m, 1H), 8.51 (s, 1H), 7.93 (t, 1H), 7.92 (d, 1H), 7,82 (d, 1H), 7.80 (m, 1H), 7.60 (dd, 1H), 7.50 (dd, 1H), 7.26 (d, 1H), 6.35 (dd, 1H), 5.84 (d, 1H), 5.45 (d, 1H), 5.29 (s, 2H), 4.70 (m, 1H), 3.70 (m, 2H), 2.00 - 2.20 (m, 4H).

Example 153: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-4-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using N^4-[3-chloro-4-(pyridin-4-ylmethoxy)-phenyl]-quinazolin-4,6-diamine instead of the compound obtained in (145-2) of Example 145 to obtain the title compound (8.3 mg, 10%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.77 (s, 1H), 8.60 (m, 3H), 7.94 (dd, 2H), 7.80 (d, 1H), 7.60 (m, 3H), 7.20 (d, 1H), 6.70 (dd, 1H), 6.30 (d, 1H), 5.80 (d, 1H), 5.20 (s, 2H), 4.80 (m, 1H), 3.80 (m, 2H), 2.20 (m, 4H).

Example 154: Preparation of 2-(1-acryloyl-pyrrolidin-2-yl)-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-acetamide

The procedure of Example 145 was repeated except for using 2-carboxymethyl-pyrrolidine-1-carboxylic acid *t*-butylester (see, *J. Med. Chem.* 1991, 34(2):717) instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (50 mg, 13%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.23 (br s, 1H), 8.66 (s, 1H), 8.60 (br s, 2H), 7.89 (d, 1H), 7.65 - 7.83 (m, 3H), 7.56 (m, 2H), 7.24 (t, 1H), 7.01 (d, 1H), 6.48 (m, 2H), 5.79 (m, 1H), 5.30 (s, 2H), 4.50 (m, 1H), 3.68 (m, 1H), 3.59 (m, 1H), 2.92 (dd, 1H), 2.60 (dd, 1H), 2.11 (m, 4H).

Example 155: Preparation of 1-acryloyl-pyrrolidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using pyrrolidine-1,3-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (29 mg, 10%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.59 (m, 3H), 7.61-7.76 (m, 5H), 7.45 (d, 1H), 7.23 (t, 1H), 6.93 (d, 1H), 6.32 (m, 2H), 5.68 (m, 1H), 5.24 (s, 2H), 4.88 (br s, 1H), 3.80 (m, 2H), 3.58 (m, 1H), 3.15 (m, 1H), 2.40 (m, 1H), 2.20 (m, 1H).

Example 156: Preparation of 1-acryloyl-piperidine-4-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using piperidine-1,4-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (35 mg, 11%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.76 (s, 1H), 8.69 (s, 1H), 8.60 (d, 1H), 7.85 (m, 2H), 7.75 (m, 1H), 7.66 (m, 1H), 7.50 (m, 2H), 7.42 (d, 1H), 7.01 (d, 1H), 6.58 (dd, 1H), 6.30 (dd, 1H), 5.73 (dd, 1H), 5.29 (s, 2H), 4.70 (br s, 1H), 3.20 (m, 1H), 2.80 (m, 2H), 2.50 (m, 1H), 1.82 (m, 4H).

Example 157: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using N^4-[3-methyl-4-(6-methyl-pyridin-3-ylmethoxy)-phenyl]-quinazolin-4,6-diamine instead of the compound obtained in (145-2) of Example 145 to obtain the title compound (170 mg, 29%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.79 (s, 1H), 8.70 (d, 1H), 8.49 (s, 1H), 8.17 (d, 1H), 7.84 (dd, 1H), 7.74 (m, 2H), 7.65 (dd, 1H), 7.22 (m, 2H), 6.95 (d, 1H), 6.60 (dd, 1H), 6.18 (d, 1H), 5,69 (d, 1H), 4.50 (m, 1H), 3.60 (m, 2H), 2.44 (s, 3H), 2.21 (m, 1H), 2.20 (s, 3H), 2.01 (m, 3H).

Example 158: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-(3-ethynyl-phenylamino)-quinazolin-6-yl]-amide

The procedure of Example 145 was repeated except for using N^4-(3-ethynyl-phenyl)-quinazolin-4,6-diamine instead of the compound obtained in (145-2) of Example 145 to obtain the title compound (69 mg, 10%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.32 (br s, 1H), 9.81 (s, 1H), 8.65 (s, 1H), 8.48 (s, 1H), 7.93 (s, 1H), 7.79 (m, 2H), 7.73 (m, 2H), 7.31 (t, 1H), 7.13 (d, 1H), 6.61 (m, 1H), 6.08 (dd, 1H), 5.66 (dd, 1H), 4.53 (t, 1H), 4.11 (s, 1H), 3.63 (m, 2H), 1.96 (m, 4H).

Example 159: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-amide

The procedure of Example 145 was repeated except for using N^4-(3-chloro-4-fluoro-phenyl)-quinazolin-4,6-diamine instead of the compound obtained in (145-2) of Example 145 to obtain the title compound (109 mg, 19%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.38 (br s, 1H), 9.92 (s, 1H), 8.72 (s, 1H), 8.71 (s, 1H), 8.31 (m, 1H), 7.81 (m, 3H), 6.66 (m, 1H), 6.16 (dd, 1H), 5.70 (dd, 1H), 4.60 (t, 1H), 3.69 (m, 2H), 2.09 (m, 2H), 1.98 (m, 2H).

Example 160: Preparation of (2*S*,4*R*)-1-acryloyl-4-ethanesulfonyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using (2*S*,4*R*)-4-ethanesulfonyl-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (10 mg, 9%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.42 (m, 3H), 7.79 (d, 1H), 7.65 (m, 3H), 7.46 (m, 2H), 7.16 (t, 1H), 6.90 (d, 1H), 6.32 (m, 1H), 5.98 (m, 1H), 5.68 (m,

1H), 5.15 (s, 2H), 4.69 (m, 1H), 4.28 (t, 1H), 4.0 5(m, 2H), 3.75 (m, 1H), 2.7 2(m, 1H), 2.53 (m 2H), 1.32 (t, 3H).

Example 161: Preparation of (2*S*,4*R*)-1-acryloyl-4-methoxy-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using (2*S*,4*R*)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (70 mg, 42%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.96 (s, 1H), 8.61 (d, 1H), 8.60 (s, 1H), 8.17 (s, 1H), 7.91 (dd, 1H), 7.76 (m, 2H), 7.69 (s, 1H), 7.59 (s, 1H), 7.25 (t, 1H), 7.01 (d, 1H), 6.50 (m, 2H), 5.82 (m, 1H), 5.30 (s, 2H), 5.01 (t, 1H), 4.93 (m, 1H), 4.35 (m, 1H), 4.02 (m, 1H), 3.43 (s, 3H), 2.75 (m, 1H), 2.48 (m, 1H).

Example 162: Preparation of 1-acryloyl-piperidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using piperidine-1,3-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (130 mg, 43%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.63(s, 1H), 8.76 (s, 1H), 8.68 (s, 1H), 8.60 (d, 1H), 7.84 (m, 2H), 7.76 (m, 2H), 7.66 (d, 1H), 7.55 (m, 2H), 7.02 (d, 1H), 6.59 (dd, 1H), 6.39 (d, 1H), 5.8 1(d, 1H), 5.30 (s, 2H), 4.43 (d, 1H), 6.39 (d, 1H), 5.81(d, 1H), 5.30 (s, 2H), 4.43 (d, 1H), 3.77 (m, 1H), 3.64 (m, 1H), 3.49 (m, 1H), 2.80 (m, 1H), 2.48 (m, 1H), 1.70 (m, 3H).

Example 163: Preparation of 1-acryloyl-azetidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using azetidine-1,3-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (85 mg, 34%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.76 (s, 1H), 8.67 (s, 1H), 8.63 (d, 1H), 8.30 (s, 1H), 7.8 (m, 3H), 7.67 (d, 1H), 7.49 (t, 2H), 6.99 (d, 1H), 6.31 (d, 1H), 6.23 (dd, 1H), 5.73 (d, 1H), 5.29 (s, 2H), 4.60 (m, 1H), 4.29 (m, 3H), 3.49 (m, 1H).

Example 164: Preparation of 1-acryloyl-piperidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using piperidine-1,2-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (67 mg, 19%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.27 (s, 1H), 8.65 (s, 1H), 8.60 (d, 1H), 8.45 (s, 1H), 7.90 (d, 1H), 7.76 (t, 2H), 7.67 (d, 1H), 7.54 (m, 3H), 7.30 (d, 1H), 6.65 (dd, 1H), 6.44 (dd, 1H), 5.85 (dd, 1H), 4.00 (d, 1H), 3.25 (t, 1H), 2.30 (d, 1H), 1.58 - 2.03 (m, 6H).

Example 165: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-fluoro-quinazolin-6-yl}-amide

(165-1) Preparation of 4-chloro-7-fluoro-6-nitro-quinazoline

Preparation of the compound was carried out in accordance with Examples of International patent publication WO 00/031048.

(165-2) Preparation of [3-chloro-4-(pyridin-2-ylmethoxy)-phenyl]-(7-fluoro-6-nitro-quinazolin-4-yl)-amine hydrochloride salt

72 g of the compound obtained in (165-1) and 74 g of 3-chloro-4-(pyridin-2-ylmethoxy)-phenylamine was stirred at 100℃ for 17 hours after

adding 1,000 ml of isopropanol. The reacted solution was cooled, filtered under a reduced pressure, washed with acetone and dried at 40℃ for 15 hours to obtain the title compound (118 g, 91%).

(165-3) Preparation of N^4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenyl]-7-fluoro-quinazolin-4,6-diamine

The procedure of (1-4) of Example 1 was repeated except for using 1.5 g of the compound obtained in (165-2) instead of the compound obtained in (1-3) of Example 1 to obtain the title compound (1.3 g, 91%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.23 (s, 1H), 8.59 (d, 1H), 8.32 (s, 1H), 8.03 (s, 1H), 7.91 (s, 1H), 7.71 (t, 1H), 7.58 (dd, 1H), 7.35 (m, 2H), 7.22 (t, 1H), 7.05 (m, 1H), 5.32 (s, 2H), 5.25 (s, 2H).

(165-4) Preparation of (2*S*)-2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-fluoro-quinazolin-6-ylcarbamoyl}-pyrrolidine-1-carboxylic acid *t*-butylester

The procedure of (145-3) of Example 145 was repeated except for using 1.74 g of (2*S*)-pyrrolidine-1,2-dicarboxylic acid 1-*t*-butylester and 0.8 g of the compound obtained in (165-3) instead of the compound obtained in (145-2) of Example 145 to obtain the title compound (1.1 g, 89%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.71 (s, 1H), 9.49 (d, 1H), 8.90 (d, 1H), 8.65 (d, 1H), 8.41 (s, 1H), 8.20 (s, 1H), 7.90 (s, 1H), 7.88 (t, 1H), 7.67 (dd, 1H), 7.59 (d, 1H), 7.38 (t, 1H), 7.21 (m, 2H), 5.25 (s, 2H), 4.50 (m, 1H), 1.80-2.18 (m, 6H).

(165-5) Preparation of (2*S*)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-fluoro-quinazolin-6-yl}-amide

The procedure of (145-4) of Example 145 was repeated except for using 1.1 g of the compound obtained in (165-4) instead of the compound obtained in (145-3) of Example 145 to obtain the title compound (0.8 g, 90%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.40 (s, 1H), 9.75 (s, 1H), 9.06 (s, 1H), 8.60 (d, 1H), 8.45 (s, 1H), 7.93 (s, 1H), 7.88 (t, 1H), 7.65 (dd, 1H), 7.59 (d, 1H), 7.35 (t, 1H), 7.21 (m, 2H), 5.28 (s, 2H), 4.01 (s, 3H), 2.99 (m, 1H), 2.84 (m, 1H), 1.85 (m, 1H), 1.72 (m, 1H), 1.61 (m, 2H).

(165-6) Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-fluoro-quinazolin-6-yl}-amide

The procedure of (145-5) of Example 145 was repeated except for using 474 mg of the compound obtained in (165-5) instead of the compound obtained in (145-5) of Example 145 to obtain the title compound (260 mg, 49%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.70 (s, 1H), 8,51 (d, 1H), 8.35 (s, 1H), 7.88 (m, 2H), 7.71 (d, 1H), 7.55 (dd, 1H), 7.30 (t, 1H), 7,12 (m, 2H), 6,71 (dd, 1H), 6,35 (d, 1H), 5.81 (d, 1H), 5.21 (s, 2H), 4.80 (m, 1H), 3.80 (m, 2H), 2.03 - 2.30 (m, 4H).

Example 166: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

(166-1) Preparation of [3-chloro-4-(pyridin-2-ylmethoxy)-phenyl]-(7-methoxy-6-nitro-quinazolin-4-yl)-amine

100 ml of dimethylsulfoxide and 5.84 g of sodium methoxide were added to 5 g of the compound obtained in (165-2) of Example 165, and the mixture was stirred at room temperature for 20 hours. The resultant was

stirred for 30 mins after adding water, filtered under a reduced pressure and dried 40℃ to obtain the title compound (4.7 g, 99%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.13(s,1H) 8.45(d,1H) 8.49(s,1H) 7.91(s,1H) 7.81(t,1H) 7.55(m,2H) 7.23(m,2H) 7.07(m,1H) 5.24(s,2H) 3.99(s,3H)

(166-2) Preparation of N^4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenyl]-7-methoxy-quinazolin-4,6-diamine

3 g of iron was refluxed with stirring at 100℃ for 1 hour after adding 100 ml of 50% aqueous ethanol solution and 0.358 ml of HCl, the mixture was refluxed with stirring after adding 4.7 g of the compound obtained in (166-1) for 1 hour. The resultant was filtered under a reduced pressure through celite pad, and the pad was washed with ethylacetate. The organic layer was dried over magnesium sulfate, and distilled under a reduced pressure to obtain the title compound (3.4 g, 79%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.23 (s, 1H), 8.59 (d, 1H), 8.32 (s, 1H), 8.03 (s, 1H), 7.87 (s, 1H), 7.70 (t, 1H), 7.58 (dd, 1H), 7.36 (m, 2H), 7.22 (t, 1H), 7.07 (m, 1H), 5.31 (s, 2H), 5.28 (s, 2H), 3.95 (s, 3H).

(166-3) Preparation of (2*S*)-2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-pyrrolidine-1-carboxylic acid *t*-butylester

3.75 g of (2*S*)-pyrrolidine-1,2-dicarboxylic acid 1-*t*-butylester and 30 ml of pyridine were added to 3.4 g of the compound obtained in (166-2), and the mixture was stirred for 5 hours after adding 3.53 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. The reacted solution was extracted with ethylacetate after adding water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent-chloroform : methanol = 15 : 1) to obtain the title compound (3.4 g, 68%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.71 (s, 1H), 9.49 (d, 1H), 8.95 (d, 1H), 8.60 (d, 1H), 8.46 (s, 1H), 8.30 (s, 1H), 7.93 (s, 1H), 7.88 (t, 1H), 7.67 (dd, 1H), 7.59 (d, 1H), 7.38 (t, 1H), 7.21 (m, 2H), 5.28 (s, 2H), 4.51 (m, 1H), 4.03 (s, 3H), 1.80-2.18 (m, 6H).

(166-4) Preparation of (2*S*)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

60 ml of dimethylene chloride and 60 ml of trifluoroacetic acid were added to 3.3 g of the compound obtained in (166-3). After 4 hours, the reacted solution was distilled under a reduced pressure, distilled with small amount of water, and neutralized with saturated aqueous sodium bicarbonate solution. The solution was filtered under a reduced pressure and dried at 40℃ for 15 hours to obtain the title compound (2.8 g, 99%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.46 (s, 1H), 9.71 (s, 1H), 9.06 (s, 1H), 8.60 (d, 1H), 8.45 (s, 1H), 7.93 (s, 1H), 7.88 (t, 1H), 7.67 (dd, 1H), 7.59 (d, 1H), 7.38 (t, 1H), 7.21 (m, 2H), 5.28 (s, 2H), 4.03 (s, 3H), 3.81 (s, 1H), 2.99 (m, 1H), 2.84 (m, 1H), 1.89 (m, 1H), 1.69 (m, 1H), 1.64 (m, 2H).

(166-5) Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

0.489 ml of acrylic acid dissolved in 50 ml of THF was reacted with 1.77 ml of pyridine, 1.37 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1.8 g of the compound obtained in (166-4) for 4 hours. The reacted solution was diluted with water, extracted with ethylacetate, dried over anhydrous magnesium sulfate, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (743 mg, 37%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.76 (s, 1H), 8,55 (d, 1H), 8.40 (s, 1H), 7.88 (m, 2H), 7.71 (d, 1H), 7.55 (dd, 1H), 7.33 (t, 1H), 7,12 (m, 2H), 6,71 (dd,

1H), 6,36 (d, 1H), 5.82 (d, 1H), 5.23 (s, 2H), 4.85 (m, 1H), 4.02 (s, 3H), 3.81 (m, 2H), 2.03 - 2.27 (m, 4H).

Example 167: Preparation of *N*-(2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

The procedure of Example 166 was repeated except for using 3-*t*-buthoxycarbonylamino-propionic acid instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid 1-*t*-butylester to obtain the title compound (80 mg, 21%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.85 (s, 1H), 8.57 (t, 1H), 8.45 (s, 1H), 7.93 (m, 2H), 7.75 (d, 1H), 7.60 (dd, 1H), 7.41 (t, 1H), 7.22 (s, 1H), 7.19 (d, 1H), 6.26 (m, 2H), 5.69 (dd, 1H), 5.29 (s, 2H), 4.07 (s, 3H), 3.69 (t, 2H), 2.01 (t, 2H).

Example 168: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {7-methoxy-4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenyl]-7-methoxy-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (230 mg, 23%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.85 (s, 1H), 9.02 (s, 1H), 8.67 (m, 2H), 7.79 (m, 1H), 7.64 (d, 1H), 7.50 (m, 2H), 7.41 (s, 1H), 7.28 (m, 2H), 6.96 (d, 1H), 6.60 (m, 2H), 5.89 (m, 1H), 5.31 (s, 2H), 4.98 (m, 1H), 4.09 (s, 3H), 3.80 (m, 1H), 3.71 (m, 1H), 2.60 (m, 1H), 2.44 (s, 3H), 2.20 (m, 3H).

Example 169: Preparation of 2-(1-acryloyl-pyrrolidin-2-yl)-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-acetamide

The procedure of Example 166 was repeated except for using 2-carboxymethyl-pyrrolidine-1-carboxylic acid *t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (72 mg, 14%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.56 (s, 2H), 8.00 (s, 1H), 7.79 (s, 1H), 7.72 (m, 1H), 7.61 (m, 1H), 7.48 (d, 1H), 7.29 (m, 1H), 7.19 (t, 1H), 6.91 (d, 1H), 6.43 (m, 2H), 5.69 (dd, 1H), 5.23 (s, 2H), 4.42 (br s, 1H), 3.95 (s, 3H), 3.55 (m, 2H), 3.05 (m, 1H), 2.59 (m, 1H), 2.02 (m, 4H).

Example 170: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-ethoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenyl]-7-ethoxy-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (170 mg, 28%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.8 1(s, 1H), 8.79 (s, 1H), 8.57 (m, 2H), 8.08 (s, 1H), 7.80 (d, 1H), 7.73 (td, 1H), 7.64 (d, 1H), 7.52 (dd, 1H), 7.22 (t, 1H), 6.99 (s, 1H), 6.94 (d, 1H), 6.48 (m, 2H), 5.78 (dd, 1H), 5.25 (s, 2H), 4.98 (d, 1H), 3.96 (m, 2H), 3.73 (m, 1H), 3.62 (m, 1H), 2.52 (m, 1H), 2.07 (m, 3H), 1.44 (t, 3H).

Example 171: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-ethylsulfanyl-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenyl]-7-ethylsulfanyl-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (250 mg, 32%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.95 (s, 1H), 8.58 (d, 1H), 8.46 (s, 1H), 8.17 (s, 1H), 8.00 (s, 1H), 7.74 (m, 2H), 7.63 (m, 2H), 7.35 (s, 1H), 7.23 (t, 1H), 6.94 (d, 1H), 6.54 (m, 1H), 6.37 (dd, 1H), 5.74 (dd, 1H), 5.27 (s, 2H), 5.12 (m, 1H), 3.88 (m, 1H), 3.70 (m, 1H), 2.71 (m, 2H), 2.60 (m, 1H), 2.25 (m, 3H), 1.29 (t, 3H).

Example 172: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-cyclopropylmethoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenyl]-7-ethylsulfanyl-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (250 mg, 32%).

The procedure of Example 166 was repeated except for using N^4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenyl]-7-cyclopropylmethoxy-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (19 mg, 5%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.61 (m, 1H), 7.92 (s, 1H), 7.77 (m, 2H), 7.69 (d, 2H), 7.20-7.40 (m, 3H), 7.01 (m, 1H), 6.43 (d, 1H), 6.19 (dd, 1H), 5.92 (d, 1H), 5.25 (s, 2H), 4.45 (m, 1H), 4.02 (m, 2H), 3.74 (m, 1H), 2.77 (m, 1H), 2.00 (m, 5H), 0.89 (t, 2H), 0.63 (d, 2H), 0.40 (q, 2H).

Example 173: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-cyclopentyloxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenyl]-7-cyclopentyloxy-quinazolin-4,6-

diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (300 mg, 61%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.86 (s, 1H), 8.88 (s, 1H), 8.52 (s, 2H), 7.76 (s, 1H), 7.67 (m, 1H), 7.57 (d, 2H), 7.41 (dd, 1H), 7.21 (m, 3H), 6.92 (d, 1H), 6.89 (m, 2H), 5.77 (t, 1H), 5.21 (s, 2H), 4.90 (m, 2H), 3.55 (m, 2H), 2.55 (m, 1H), 1.60-2.10 (m, 10H).

Example 174: Preparation of *N*-(2-{4-[3-chloro-4-(pyridin-4-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

The procedure of Example 22 was repeated except for using N^4-[3-chloro-4-(pyridin-4-ylmethoxy)-phenyl]-quinazolin-4,6-diamine instead of the compound obtained in (1-4) of Example 1 to obtain the title compound (10 mg, 13%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.77 (s, 1H), 8.60 (m, 3H), 7.94 (dd, 2H), 7.80 (d, 1H), 7.60 (m, 3H), 7.20 (d, 1H), 6.90 (m, 1H), 6.50 (d, 1H), 6.20 (m, 1H), 5.30 (s, 2H), 3.60 (t, 2H), 2.80 (t, 2H).

Example 175: Preparation of (2*S*)-1-(4-dimethylamino-buten-2-oyl)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using 4-dimethylamino-buten-2-oic acid instead of acrylic acid to obtain the title compound (100 mg, 22%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ :9.84 (s, 1H), 8.88 (s, 1H), 8.59 (s, 2H), 7.83 (s, 1H), 7.77 (t, 1H), 7.68 (d, 1H), 7.57 (s, 1H), 7.51 (d, 1H), 7.26 (m, 1H), 7.15 (s, 1H), 7.06 (m, 2H), 6.36 (d, 1H), 5.28 (s, 2H), 4.92 (d, 2H), 3.95 (s, 3H), 3.73 (m, 2H), 3.13 (d, 2H), 2.52 (m, 1H), 2.27 (s, 6H), 1.92-2.13 (m, 3H).

Example 176: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {7-chloro-4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenyl]-7-chloro-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (250 mg, 31%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.71 (s, 1H), 8.60 (m, 2H), 8.20 (s, 1H), 7.74 (m, 2H), 7.68 (m, 1H), 7.60 (s, 1H), 7.49 (m, 1H), 7.23 (m, 1H), 6.96 (d, 1H), 6.27 (m, 1H), 6.00 (m, 1H), 5.72 (m, 1H), 5.31 (s, 2H), 4.90 (m, 1H), 4.16 (m, 2H), 4.00 (m, 1H), 3.33 (m, 1H), 3.07 (m, 1H), 2.65 (m, 1H).

Example 177: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {7-fluoro-4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenyl]-7-fluoro-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (220 mg, 36%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.35 (s, 1H), 8.90 (d, 1H), 8.65 (m, 2H), 7.77 (m, 1H), 7.6 1(m, 2H), 7.53 (d, 1H), 7.46 (m, 2H), 7.26 (m, 1H), 6.92 (d, 1H), 6.57 (m, 2H), 5.88 (m, 1H), 5.28 (s, 2H), 5.02 (m, 1H), 3.80 (m, 1H), 3.66 (m, 1H), 2.68 (m, 1H), 2.41 (s, 3H), 2.20 (m, 1H), 2.02 (m, 2H).

Example 178: Preparation of *N*-(2-{7-fluoro-4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

The procedure of Example 22 was repeated except for using N^4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenyl]-7-fluoro-quinazolin-4,6-diamine

instead of the compound obtained in (20-1) of Example 20 to obtain the title compound (100 mg, 19%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.98 (bd, 1H), 8.82 (bs, 1H), 8.60 (m, 2H), 7.74 (m, 2H), 7.67 (bs, 1H), 7.54 (m, 2H), 7.41 (m, 2H), 7.26 (m, 1H), 6.88 (d, 1H), 6.61 (m, 1H), 6.30 (m, 1H), 5.72 (m, 1H), 5.23 (s, 2H), 3.80 (m, 2H), 2.82 (m, 2H), 2.36 (s, 3H).

Example 179: Preparation of (2*S*)-1-acryloyl-2,5-dihydro-1*H*-pyrrol-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using (2*S*)-dihydro-1*H*-pyrrol-1,2-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (15 mg, 3%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.43 (bs, 1H), 8.92 (s, 1H), 8.60 (m, 2H), 7.85 (d, 1H), 7.74 (m, 1H), 7.65 (d, 1H), 7.48 (m, 2H), 7.19 (m, 2H), 6.98 (d, 1H), 6.52 (d, 2H), 6.07 (m, 2H), 5.85 (t, 1H), 5.54 (m, 1H), 5.28 (s, 2H), 4.52 (m, 2H), 4.00 (s, 3H).

Example 180: Preparation of (4*R*)-3-acryloyl-thiazolidin-4-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using (4*R*)-thiazolidin-3,4-dicarboxylic acid-3-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (150 mg, 19%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.48 (bs, 1H), 8.9 1(s, 1H), 8.60 (m, 2H), 7.83 (d, 1H), 7.74 (t, 1H), 7.65 (d, 1H), 7.56 (bs, 1H), 7.48 (dd, 1H), 7.23 (m,

1H), 7.21 (s, 1H), 6.98 (d, 1H), 6.55 (m, 2H), 5.89 (m, 1H), 5.33 (m, 1H), 5.28 (s, 2H), 4.81 (m, 1H), 4.68 (m, 1H), 4.00 (s, 3H), 3.67 (m, 1H), 3.23 (m, 1H).

Example 181: Preparation of 1-acryloyl-azetidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using azetidine-1,2-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (153 mg, 33%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.81 (s, 1H), 8.67 (s, 1H), 8.60 (d, 1H), 8.50 (s, 1H), 7.90 (d, 1H), 7.82 (d, 1H), 7.73 (td, 1H), 7.68 (m, 2H), 7.55 (m, 2H), 7.02 (d, 1H), 6.51 (d, 1H), 6.26 (dd, 1H), 5.87 (dd, 1H), 5.30 (s, 2H), 5.22 (m, 1H), 4.27 (t, 2H), 2.90 (m, 1H), 2.59 (m, 1H).

Example 182: Preparation of 1-acryloyl-azetidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 181 was repeated except for using the compound obtained in (166-2) of Example 166 instead of the compound obtained in (145-2) of Example 145 to obtain the title compound (106 mg, 17%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.34 (s, 1H), 8.97 (s, 1H), 8.63 (s, 1H), 8.60 (d, 1H), 7.87 (d, 1H), 7.76 (td, 1H), 7.67 (d, 1H), 7.51 (dd, 1H), 7.42 (s, 1H), 7.23 (s, 1H), 7.01 (d, 1H), 6.51 (dd, 1H), 6.26 (dd, 1H), 5.83 (dd, 1H), 5.30 (s, 2H), 5.16 (m, 1H), 4.25 (t, 2H), 4.04 (s, 3H), 2.87 (m, 1H), 2.62 (m, 1H).

Example 183: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2,2,2-trifluoro-ethoxy)-quinazolin-6-yl]-amide

The procedure of Example 166 was repeated except for using N^4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenyl]-7-(2,2,2-trifluoro-ethoxy)-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (70 mg, 15%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.96 (s, 1H), 8.80 (s, 1H), 8.60 (m, 2H), 7.86 (d, 1H), 7.76 (m, 2H), 7.66 (d, 1H), 7.53 (dd, 1H), 7.12 (s, 1H), 7.00 (d, 1H), 6.52 (m, 2H), 5.82 (t, 1H), 5.30 (s, 2H), 4.98 (m, 1H), 4.43 (m, 2H), 3.77 (m, 1H), 3.65 (m, 1H), 2.53 (m, 1H), 2.09 (m, 1H).

Example 184: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-dimethylamino-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenyl]-7-dimethylamino-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (190 mg, 44%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.61 (s, 1H), 8.84 (s, 1H), 8.55 (s, 1H), 8.53 (d, 1H), 7.79 (d, 1H), 7.68 (td, 1H), 7.59 (d, 1H), 7.52 (m, 3H), 7.17 (d, 1H), 6.94 (d, 1H), 6.45 (m, 2H), 5.76 (dd, 1H), 5.23 (s, 2H), 4.86 (m, 1H), 3.69 (m, 1H), 3.60 (m, 1H), 2.70 (s, 6H), 2.47 (m, 1H), 2.06 (m, 3H).

Example 185: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [7-methoxy-4-(1-pyridin-2-ylmethyl-1*H*-indazol-5-ylamino)-quinazolin-6-yl]-amide

The procedure of Example 166 was repeated except for using 7-methoxy-N^4-(1-pyridin-2-ylmethyl-1*H*-indazol-5-yl)-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (160 mg, 29%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.74 (s, 1H), 8.97 (s, 1H), 8.58 (s, 1H), 8.05 (m, 2H), 7.88 (bs, 1H), 7.55 (dd, 1H), 7.27 (m, 2H), 7.23 (s, 1H), 6.99 (m, 2H), 6.88 (m, 1H), 6.51 (m, 2H), 5.80 (m, 1H), 5.57 (s, 2H), 4.92 (m, 1H), 3.98 (s, 3H), 3.74 (m, 1H), 3.60 (m, 1H), 3.22 (m, 2H), 2.53 (m, 1H), 2.12 (m, 1H).

Example 186: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenylamino]-7-ethoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenyl]-7-ethoxy-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (130 mg, 15%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.81 (s, 1H), 9.45 (s, 1H), 8.95 (s, 1H), 8.57 (m, 2H), 7.66 (m, 1H), 7.50 (d, 1H), 7.22 (d, 1H), 7.18 (d, 2H), 6.75 (d, 1H), 6.54 (m, 2H), 5.84 (m, 1H), 5.18 (s, 2H), 4.95 (d, 1H), 4.24 (m, 2H), 3.76 (m, 1H), 3.64 (m, 1H), 2.39 (s, 1H), 2.28 (s, 3H), 2.04 (m, 3H), 1.27 (t, 3H).

Example 187: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2-fluoro-ethoxy)-quinazolin-6-yl]-amide

The procedure of Example 166 was repeated except for using N^4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenyl]-7-(2-fluoro-ethoxy)-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (155 mg, 33%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.05 (s, 1H), 8.85 (s, 1H), 8.52 (m, 2H), 7.77 (d, 1H), 7.68 (td, 1H), 7.59 (d, 1H), 7.55 (m, 1H), 7.44 (dd, 1H), 7.18 (d, 1H), 7.12 (d, 1H), 6.94 (d, 1H), 6.48 (d, 2H), 5.76 (t, 1H), 5.22 (s, 2H), 4.92 (m, 2H), 4.80 (m, 1H), 4.34 (m, 1H), 4.25 (m, 1H), 3.70 (m, 1H), 3.56 (q, 1H), 2.55 (m, 1H), 2.05 (m, 3H).

Example 188: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[1-(3-fluoro-benzyl)-1*H*-indazol-5-ylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[1-(3-fluoro-benzyl)-1*H*-indazol-5-yl)-7-methoxy-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (150 mg, 25%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.71 (s, 1H), 8.92 (s, 1H), 8.52 (s, 1H), 7.98 (m, 2H), 7.73 (bs, 1H), 7.48 (dd, 1H), 7.19 (m, 3H), 6.91 (m, 2H), 6.82 (m, 1H), 6.46 (m, 2H), 5.74 (m, 1H), 5.51 (s, 2H), 4.84 (m, 1H), 4.01 (s, 3H), 3.73 (m, 1H), 3.55 (m, 1H), 2.98 (m, 2H), 2.47 (m, 1H), 2.05 (m, 1H).

Example 189: Preparation of (1*R*)-*N*-(1-{4-[3chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

The procedure of Example 166 was repeated except for using (2*S*)-2-*t*-buthoxycarbonylamino-propionic acid instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (49 mg, 6%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.69 (s, 1H), 8.49 (d, 1H), 8.35 (s, 1H), 7.81 (m, 2H), 7.64 (d, 1H), 7.51 (dd, 1H), 7.33 (m, 1H), 7.10 (d, 1H), 6.30 (d, 1H), 6.26 (d, 1H), 5.68 (dd, 2H), 5.20 (s, 2H), 4.67 (q, 1H), 4.01 (s, 3H), 1.44 (d, 3H).

Example 190: Preparation of (1*S*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

The procedure of Example 166 was repeated except for using (2*R*)-2-*t*-buthoxycarbonylamino-propionic acid instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (32 mg, 7%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.72 (s, 1H), 8.45 (d, 1H), 8.32 (s, 1H), 7.80 (td, 2H), 7.78 (d, 1H), 7.62 (d, 1H), 7.47 (dd, 1H), 7.30 (m, 1H), 7.10 (s, 1H), 7.05 (d, 1H), 6.25 (d, 2H), 6.23 (d, 1H), 5.66 (dd, 1H), 5.17 (s, 2H), 4.64 (m, 1H), 3.95 (s, 3H), 1.39 (d, 3H).

Example 191: Preparation of (1*S*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}ethyl)-*N*-methyl-acrylamide

The procedure of Example 166 was repeated except for using (2*R*)-2-(*t*-buthoxycarbonyl-methyl-amino)-propionic acid instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (24 mg, 6%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.56 (s, 1H), 8.43 (d, 1H), 8.26 (s, 1H), 7.79 (td, 2H), 7.72 (d, 1H), 7.58 (d, 1H), 7.41 (dd, 1H), 7.26 (m, 1H), 6.9 7(s, 1H), 6.94 (dd, 1H), 6.68 (d, 1H), 5.73 (d, 1H), 5.24 (m, 1H), 5.22 (s, 3H), 4.45 (br s, 1H), 3.87 (s, 3H), 3.20 (s, 3H), 1.41 (d, 3H).

Example 192: Preparation of *N*-(2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-fluoro-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

The procedure of Example 165 was repeated except for using (3-*t*-buthoxycarbonylamino-propionic acid instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (60 mg, 19%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.79 (m, 1H), 8.55 (m, 2H), 7.86 (s, 1H), 7.76 (t, 1H), 7.66 (m, 2H), 7.52 (m, 3H), 7.22 (m, 1H), 7.01 (d, 1H), 6.30 (m, 1H), 6.10 (m, 1H), 5.65 (m, 1H), 5.26 (s, 2H), 3.65 (m, 2H), 2.74 (m, 2H); MS(ESI): [M+Na]+ 543.

Example 193: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [7-methoxy-4-(1-penta-2,4-dienyl-1*H*-indazol-5-ylamino)-quinazolin-6-yl]-amide 의

The procedure of Example 166 was repeated except for using N^4-[1-benzyl-1*H*-indazol-5-yl)-7-methoxy-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (52 mg, 22%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.81 (s, 1H), 8.99 (s, 1H), 8.61 (s, 1H), 8.00 (s, 2H), 7.72 -7.69 (m, 2H), 7.55-7.51 (m, 2H), 7.37 (m, 5H), 6,54 (dd, 2H), 5.84 (d, 1H), 5.60 (s, 2H), 4.23 (m, 1H), 4.04 (s, 3H), 3.75-3.63 (m, 2H), 2.54 (m, 1H), 1.98 (m, 3H).

Example 194: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(6-methyl-pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[3-chloro-4-(6-methyl-pyridin-2-ylmethoxy)-phenyl]-7-methoxy-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (113 mg, 21%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.76 (s,1H), 8.89 (s,1H), 8.59 (s,1H), 7.83 (d,1H), 7,71 (s,1H), 7.50 (t,1H), 7.49 (dd,1H), 7.43 (d,1H), 7.25 (s,1H), 7.19 (s,1H), 7.09 (d,1H), 6.95 (d,1H), 6.51 (m,2H), 5.83 (dd,1H), 5.78 (s,2H), 4.92 (d, 1H), 3.99 (s, 3H) 3.75-3.62(m,2H) 2.57(s,3H) 2.55(m,1H) 2.08(m,3H).

Example 195: Preparation of 1-acryloyl-azetidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-fluoro-quinazolin-6-yl}-amide

The procedure of Example 165 was repeated except for using azetidine-1,2-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (82 mg, 20%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.97 (d, 1H), 8.57 (d, 1H), 8.49 (s, 1H), 7.92 (m, 2H), 7.73 (d, 1H), 7.60 (dd, 1H), 7.51 (d, 1H), 7.40 (m, 1H), 7.17 (d, 1H), 6.39 (m, 2H), 5.84 (dd, 1H), 5.29 (s, 2H), 5.20 (m, 1H), 4.35 (t, 2H), 2.66 (m, 2H).

Example 196: Preparation of 1-acryloyl-piperidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using piperidine-1,2-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (50 mg, 9%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.07 (bs, 1H), 8.95 (s, 1H), 8.60 (m, 2H), 7.86 (d, 1H), 7.76 (m, 2H), 7.67 (d, 1H), 7.52 (dd, 1H), 7.23 (m, 2H), 6.99 (d, 1H), 6.70 (m, 1H), 6.41 (m, 1H), 5.82 (m, 1H), 5.48 (m, 1H), 5.29 (s, 2H), 4.00 (m, 1H), 3.97 (s, 3H), 3.20 (m, 1H), 2.39 (m, 1H), 1.70 (m, 5H).

Example 197: Preparation of 1-acryloyl-piperidine-4-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using piperidine-1,4-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (210 mg, 17%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.96 (s, 1H), 8.58 (m, 2H), 8.15 (s, 1H), 7.93 (bs, 1H), 7.84 (d, 1H), 7.75 (m, 1H), 7.65 (d, 1H), 7.47 (dd, 1H), 7.28 (s, 1H), 7.22 (m, 1H), 6.97 (d, 1H), 6.59 (m, 1H), 6.29 (m, 1H), 5.71 (m, 1H), 5.27

(s, 2H), 4.70 (m, 1H), 4.04 (s, 3H), 3.24 (m, 1H), 2.85 (m, 1H), 2.34 (m, 4H), 1.82 (m, 2H).

Example 198: Preparation of 1-acryloyl-pyrrolidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using piperidine-1,3-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (110 mg, 27%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.86 (s, 1H), 8.53 (m, 2H), 8.15 (d, 1H), 7.86 (bs, 1H), 7.75 (m, 1H), 7.65 (m, 1H), 7.58 (d, 1H), 7.41 (dd, 1H), 7.17 (m, 2H), 6.88 (d, 1H), 6.35 (m, 2H), 5.64 (m, 1H), 5.19 (s, 2H), 3.94 (s, 3H), 3.81 (m, 3H), 3.55 (m, 1H), 3.14 (m, 1H), 2.27 (m, 2H).

Example 199: Preparation of 1-acryloyl-azetidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-ethoxy-quinazolin-6-yl}-amide

The procedure of Example 170 was repeated except for using azetidine-1,2-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (85 mg, 25%).

^{1}H-NMR (CD_3OD, 300MHz): δ 9.10 (d, 1H), 8.74 (d, 1H), 8.64 (d, 1H), 8.09 (m, 2H), 7.90 (d, 1H), 7.77 (m, 2H), 7.57 (m, 1H), 7.35 (m, 1H), 6.53 (m, 2H), 6.02 (dd, 1H), 5.46 (s, 2H), 5.36 (m, 1H), 4.51 (m, 2H), 2.84 (m, 2H).

Example 200: Preparation of 1-acryloyl-azetidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using azetidine-1,3-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (70 mg, 26%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.04 (s, 1H), 8.64 (m, 2H), 8.20 (s, 1H), 7.98 (bs, 1H), 7.89 (d, 1H), 7.80 (m, 1H), 7.70 (d, 1H), 7.54 (dd, 1H), 7.27 (m, 2H), 7.02 (d, 1H), 6.43 (m, 1H), 6.26 (m, 1H), 5.76 (m, 1H), 5.32 (s, 2H), 4.61 (m,1 H), 4.40 (m, 3H), 4.07 (s, 3H), 3.61 (m, 1H).

Example 201: Preparation of (3S)-1-acryloyl-piperidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using (3*S*)-piperidine-1,3-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (50 mg, 30%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.95 (bs, 1H), 8.60 (m, 3H), 8.29 (bs, 1H), 7.84 (d, 1H), 7.75 (m, 1H), 7.66 (d, 1H), 7.50 (dd, 1H), 7.24 (m, 2H), 6.98 (d, 1H), 6.57 (m, 1H), 6.31 (m, 1H), 5.73 (m, 1H), 5.28 (s, 2H), 4.78 (m, 1H), 4.02 (m, 1H), 3.97 (s, 3H), 3.20 (m, 1H), 2.57 (m, 1H), 2.18 (m, 3H), 1.90 (m, 1H), 1.57 (m, 1H).

Example 202: Preparation of *N*-((1*S*)-1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-ethyl)-*N*-ethyl-acrylamide

The procedure of Example 166 was repeated except for using (2*S*)-2-(*t*-buthoxycarbonyl-ethyl-amino)-propionic acid instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (7 mg, 7%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.17 (s, 1H), 8.83 (s, 1H), 8.53 (m, 2H), 7.78 (m, 1H), 7.70 (td, 1H), 7.61 (s, 1H), 7.58 (d, 1H), 7.45 (dd, 1H), 7.16 (s,

1H), 7.14 (s, 1H), 6.92 (d, 1H), 6.53 (m, 1H), 5.75 (dd, 1H), 5.21 (s, 2H), 4.08 (m, 1H), 3.95 (s, 3H), 3.48 (q, 2H), 1.45 (d, 3H), 1.19 (t, 3H).

Example 203: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(2-fluoro-ethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[3-chloro-4-(2-fluoro-ethoxy)-phenyl]-7-methoxy-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (110 mg, 34%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.99 (s, 1H,) 8.62 (s, 1H), 7.83 (d, 1H), 7.60 (s, 1H), 7.56 (dd, 1H), 7.00 (d, 1H), 6.51 (m, 2H), 5.83 (dd, 1H), 4.88 (t, 1H), 4.73 (t, 1H), 4.50 (m, 1H), 4.35 (t, 1H), 4.26 (t, 1H), 3.98 (s, 3H), 3.48 (m, 2H), 2.20 (m, 1H), 1,98 (m,1H), 1.89 (m,2H).

Example 204: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenyl]-7-methoxy-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (19 mg, 11%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.86 (s, 1H), 8.85 (s, 1H), 8.73 (s, 1H), 8.72 (s, 1H), 8.21 (d, 1H), 8.11 (d, 1H), 7.93-7.98 (m, 2H), 7.85 (dd, 1H), 7.43 (d, 1H), 6.37-6.44 (m, 2H), 5.82-5.86 (m, 1H), 5.46 (s, 2H), 4.80 (m, 1H), 3.96 (s, 3H), 3.51 (m, 2H), 2.24 (m, 1H), 1.78-1.99 (m, 3H).

Example 205: Preparation of (2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-butyramide

The procedure of Example 166 was repeated except for using (2*S*)-2-(*t*-buthoxycarbonylamino)-butanoic acid instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (180 mg, 32%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.86 (s, 1H), 8.73 (s, 1H), 8.59 (m, 2H), 7.76 (m, 3H), 7.65 (d, 1H), 7.49 (m, 1H), 7.25 (m, 1H), 7.19 (s, 1H), 6.96 (d, 1H), 6.39 (m, 1H), 6.23 (m, 1H), 5.75 (m, 1H), 5.27 (s, 2H), 4.66 (m, 1H), 4.00 (s, 3H), 2.04 (m, 2H), 1.05 (t, 3H).

Example 206: Preparation of *N*-(2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-2-fluoro-ethyl)-acrylamide

The procedure of Example 166 was repeated except for using 3-*t*-buthoxycarbonylamino-2-fluoro-propionic acid instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (59 mg, 17%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.65 (s, 1H), 8.34 (d, 1H), 8.22 (s, 1H), 7.70 (td, 1H), 7.67 (s, 1H), 7.50 (d, 1H), 7.37 (dd, 1H), 7.18 (m, 1H), 7.02 (s, 1H), 6.94 (d, 1H), 6.03 (m, 2H), 5.45 (dd, 1H), 5.15 (m, 1H), 5.06 (s, 2H), 3.86 (s, 3H), 3.75 (m, 1H), 3.66 (m, 1H).

Example 207: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-7-(1-methyl-piperidin-4-ylmethoxy)-quinazolin-6-yl}-amide

385 mg of (2*S*)-pyrrolidine-2-carboxylic acid [4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino-7-(1-methyl-piperidin-4-ylmethoxy)-quinazolin-6-yl]-amide as a starting material was dissolved in 10 ml of THF, and cooled to 0℃.

0.09 ml of acrylic acid and 0.1 ml of pyridine were added thereto, and the resulting solution was reacted with 0.37 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride at 0℃ for 30 mins and then stirred for 2 hours while heating to room temperature. The reacted solution was extracted with a mixture of chloroform and isopropanol after adding water, washed with water and saturated saline solution, dried over anhydrous sodium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (68 mg, 16%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.71 (s, 1H), 8.55 (d, 1H), 8.40 (s, 1H), 7.89 (m, 2H), 7.70 (d, 1H), 7.56 (dd, 1H), 7.38 (m, 1H), 7.13 (m, 2H), 6.72 (m, 1H), 6.35 (m, 1H), 5.83 (m, 1H), 5.24 (s, 2H), 3.99 (d, 2H), 2.91 (m, 2H), 2.32 (s, 3H), 2.15 (m, 3H), 1.94 (m, 2H), 1.48 (m, 2H).

Example 208: Preparation of (1*R*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2-methoxy-ethoxy)-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

75 μl of acrylic acid was dissolved in 4 ml of THF, and cooled to 0℃. 180 μl of pyridine and 520 ml of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added thereto, the resulting solution was reacted with 284 mg of 2-amino-*N*-[4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2-methoxy-ethoxy)-quinazolin-6-yl]-propionamide dissolved in 4 ml of THF as a starting material for 30 mins, and then stirred for 3 hours while heating to room temperature. The reacted solution was washed with saturated sodium bicarbonate solution, extracted with a mixture of chloroform and methanol, dried over sodium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (87 mg, 28%).

^{1}H-NMR (DMSO-d_6 300MHz): δ 9.71 (s, 1H), 9.42 (s, 1H), 8.84 (s, 1H), 8.61 (m, 1H), 8.59 (s, 1H), 8.47 (s, 1H), 7.96 (d, 1H), 7.88 (td, 1H), 7.67 (dd, 1H), 7.58 (d, 1H), 7.36 (m, 1H), 7.28 (s, 1H), 7.23 (d, 1H), 6.38 (m, 1H), 6.17 (m, 1H), 5.69 (m, 1H), 5.29 (s, 1H), 4.70 (m, 1H), 4.32 (t, 2H), 3.77 (t, 2H), 3.35 (s, 3H), 1.41 (d, 3H).

Example 209: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-yl}-amide

230 mg of (2*S*)-pyrrolidine-2-carboxylic acid [4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino-7-(3-morpholin-4-ylpropoxy)-quinazolin-6-yl]-amide as a starting material was dissolved in 10 ml of THF, and cooled to 0℃. The solution was reacted with 0.05 ml of acrylic acid, 0.06 ml of pyridine and 0.21 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride at 0℃ for 30 min and at room temperature for 3 hours. The reacted solution was extracted with a mixture of isopropanol and chloroform (1 : 3) after adding water, washed with saturated saline solution, dried over anhydrous sodium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (120 mg, 48%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.98 (s, 1H), 8.91 (s, 1H), 8.59 (m, 2H), 7.95 (bs, 1H), 7.84 (d, 1H), 7.76 (m, 1H), 7.65 (d, 1H), 7.52 (dd, 1H), 7.26 (m, 1H), 7.18 (s, 1H), 6.96 (d, 1H), 6.53 (m, 2H), 5.81 (m, 1H), 5.27 (s, 2H), 4.95 (m, 1H), 4.18 (t, 2H), 3.73 (m, 5H), 3.61 (m, 1H), 2.65 (m, 4H), 2.52 (m, 4H), 2.15 (m, 2H), 2.04 (m, 1H), 1.95 (m, 1H).

Example 210: Preparation of *N*-({4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-methyl)-acrylamide

The procedure of Example 145 was repeated except for using *tert*-buthoxycarbonylamino-acetic acid instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (36 mg, 10%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.78 (s, 1H), 8.59 (s, 1H), 8.58 (d, 1H), 7.91 (d, 1H), 7.78 (td, 1H), 7.69 (d, 1H), 7.58 (dd, 1H), 7.25 (m, 1H), 7.22 (s, 1H), 7.03 (d, 1H), 6.42 (dd, 1H), 6.26 (dd, 1H), 5.79 (dd, 1H), 5.30 (s, 2H), 4.22 (s, 2H), 4.05 (s, 3H).

Example 211: Preparation of *N*-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-methyl)-acrylamide

170 mg of 2-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-acetamide as a starting material was dissolved in 5 ml of THF, and cooled to 0℃. The solution was reacted with 0.04 ml of acrylic acid, 0.06 ml of pyridine and 134 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride at 0℃ for 1 hour and at room temperature for 5 hours. The reacted solution was extracted with chloroform after adding saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- ethylacetate : methanol = 10 : 1) to obtain the title compound (51 mg, 27%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.75 (s, 1H), 8.58 (s, 1H), 7.86 (d, 1H), 7.56 (dd, 1H), 7.36 (m, 1H), 7.24 (d, 2H), 7.19 (s, 1H), 6.99 (t, 1H), 6.96 (d, 1H), 6.40 (dd, 1H), 6.27 (dd, 1H), 5.79 (dd, 1H), 5.15 (s, 2H), 4.22 (s, 2H), 4.01 (s, 3H).

Example 212: Preparation of (3*S*)-3-acryloylamino-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-butyramide

36 mg of (3*S*)-amino-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-butyramide as a starting material was dissolved in 3 ml of THF, and cooled to 0℃. The solution was reacted with 0.01 ml of acrylic acid, 0.01 ml of pyridine and 0.042 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride at 0℃ for 30 mins and at room temperature for 2 hours. The reacted solution was extracted with a mixture of chloroform and isopropanol after adding water, washed with saturated saline solution, dried over anhydrous sodium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- ethylacetate : methanol = 15 : 1) to obtain the title compound (6 mg, 15%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.09 (s, 1H), 8.61 (m, 2H), 7.89 (d, 1H), 7.76 (m, 1H), 7.66 (m, 1H), 7.51 (dd, 1H), 7.24 (m, 2H), 7.01 (d, 1H), 6.42 (m, 1H), 6.36 (m, 1H), 5.87 (dd, 1H), 5.30 (s, 2H), 4.05 (s, 3H), 4.03 (m, 1H), 2.03 (d, 2H), 1.25 (d, 3H).

Example 213: Preparation of (2S)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-yl}-amide

302 mg of (2*S*)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-yl}-amide as a starting material was dissolved in 10 ml of THF, and cooled to 0℃. The solution was reacted with 0.15 ml of acrylic acid, 0.18 ml of pyridine and 0.53 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride at 0℃ for 30 mins and at room temperature for 2 hours. The reacted solution was extracted with a mixture of chloroform and isopropanol after adding water, washed with saturated saline solution, dried over anhydrous sodium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- ethylacetate : methanol = 30 : 1) to obtain the title compound (31 mg, 9%).

^{1}H-NMR (CD_3OD, 300MHz): δ 9.71 (s, 1H), 8.79 (d, 1H), 8.66 (s, 1H), 8.13 (m, 2H), 7.95 (d, 1H), 7.81 (dd, 1H), 7.62 (m, 1H), 7.45 (s, 1H), 7.38 (d, 1H), 6.93 (m, 1H), 6.61 (m, 1H), 6.07 (m, 1H), 5.50 (s, 2H), 4.58 (t, 2H), 4.12 (t, 2H), 4.02 (m, 1H), 2.49 (m, 2H), 2.32 (m, 2H).

Example 214: Preparation of (1*S*)-*N*-(1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

205 mg of (2*S*)-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-yl}-propionamide as a starting material was dissolved in 10 ml of a mixture of THF and water (3 : 1), and reacted with 0.047 ml of acryloylchloride at room temperature for 1 hour after adding 97 mg of sodium bicarbonate. The reacted solution was extracted with a mixture of chloroform and isopropanol after adding water, washed with saturated saline solution, dried over anhydrous sodium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- ethylacetate : methanol = 30 : 1) to obtain the title compound (55 mg, 24%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.71 (s, 1H), 9.42 (s, 1H), 8.83 (s, 1H), 8.6 1(d, 1H), 8.47 (s, 1H), 7.49 (d, 1H), 7.66 (dd, 1H), 7.46 (m, 1H), 7.25 (m, 5H), 6.34 (m, 1H), 6.21 (m, 1H), 5.68 (m, 1H), 5.24 (s, 2H), 4.70 (m, 1H), 4.32 (t, 2H), 3.78 (t, 2H), 1.41 (d, 3H).

Example 215: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-yl}-amide

288 mg of (2*S*)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-yl}-amide as a starting material was dissolved in 10 ml of THF, and cooled to 0℃. The solution was reacted with 0.07 ml of acrylic acid, 0.17 ml of pyridine and 0.29 g

of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride at 0℃ for 30 mins and at room temperature for 2 hours. The reacted solution was extracted with a mixture of chloroform and isopropanol after adding water, washed with saturated saline solution, dried over anhydrous sodium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- ethylacetate : methanol = 30 : 1) to obtain the title compound (52 mg, 17%).

^{1}H-NMR (DMSO-d6, 300MHz): δ 9.78 (s, 1H), 9.54 (s, 1H), 8.82 (s, 1H), 8.47 (d, 1H), 7.67 (m, 1H), 7.43 (m, 1H), 7.26 (m, 5H), 6.69 (m, 1H), 6.23 (m, 1H), 5.78 (m, 1H), 5.24 (s, 2H), 4.76 (m, 1H), 4.35 (t, 2H), 3.78 (t, 2H), 3.64 (m, 2H), 2.11 (m, 2H), 2.01 (m, 2H).

Example 216: Preparation of (1*S*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

300 mg of (2*S*)-amino-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-ethoxy-quinazolin-6-yl}-propionamide as a starting material was dissolved in 9 ml of THF and 3 ml of water, and reacted with 0.06 ml of acryloylchloride at room temperature for 1 hour after adding 153 mg of sodium bicarbonate. The reacted solution was extracted with a mixture of chloroform and isopropanol after adding water, washed with saturated saline solution, dried over anhydrous sodium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- ethylacetate : methanol = 15 : 1) to obtain the title compound (11 mg, 3%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.05 (bs, 1H), 8.90 (s, 1H), 8.60 (m, 2H), 7.84 (d, 1H), 7.76 (m, 1H), 7.66 (m, 1H), 7.49 (m, 2H), 7.23 (m, 2H), 6.98 (d, 1H), 6.41 (m, 1H), 6.19 (m, 2H), 5.77 (m, 1H), 5.29 (s, 2H), 4.84 (m, 1H), 4.23 (m, 2H), 2.02 (d, 3H), 1.55 (t, 3H).

Example 217: Preparation of *N*-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-ylcarbamoyl}-methyl)-acrylamide

320 mg of 2-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-yl}-acetamide as a starting material was dissolved in 10 ml of THF, and cooled to 0℃. The solution was reacted with 0.06 ml of acrylic acid, 0.1 ml of pyridine and 234 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride at 0℃ for 1 hour and at room temperature for 5 hours. The reacted solution was extracted with a mixture of chloroform and isopropanol after adding saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- ethylacetate : methanol = 30 : 1) to obtain the title compound (96 mg, 27%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.78 (s, 1H), 8.52 (s, 1H), 7.84 (d, 1H), 7.55 (dd, 1H), 7.35 (m, 1H), 7.23 (m, 2H), 7.15 (s, 1H), 7.02 (t, 1H), 6.98 (d, 1H), 6.38 (dd, 1H), 6.30 (dd, 1H), 5.76 (dd, 1H), 5.15 (s, 2H), 4.31 (m, 2H), 4.24 (s, 2H), 3.87 (m, 2H), 3.50 (s, 3H).

Example 218: Preparation of *N*-({4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-ylcarbamoyl}-methyl)-acrylamide

320 mg of 2-amino-*N*-{4-[3-chloro-4-(3-pyridin-2-ylmethoxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-yl}-acetamide as a starting material was dissolved in 10 ml of THF, and cooled to 0℃. The solution was reacted with 0.07 ml of acrylic acid, 0.11 ml of pyridine and 257 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride at 0℃ for 1 hour and at room temperature for 5.5 hours. The reacted solution was extracted with a mixture of chloroform and isopropanol after adding saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and distilled under a

reduced pressure, and the resulting residue was subjected to column chromatography (eluent- ethylacetate : methanol = 10 : 1) to obtain the title compound (45 mg, 12%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.80 (s, 1H), 8.57 (d, 1H), 8.55 (s, 1H), 7.89 (d, 1H), 7.79 (td, 1H), 7.70 (d, 1H), 7.57 (dd, 1H), 7.28 (m, 1H), 7.18 (s, 1H), 7.02 (d, 1H), 6.42 (dd, 1H), 6.29 (dd, 1H), 5.77 (dd, 1H), 5.29 (s, 2H), 4.32 (m, 2H), 4.25 (s, 2H), 3.87 (m, 2H), 3.50 (s, 3H).

Example 219: Preparation of (1*S*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

500 mg of (2*S*)-2-amino-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(3-morpholin-4-ylpropoxy)-quinazolin-6-yl}-propionamide as a starting material was dissolved in 12 ml of THF and 4 ml of water, and reacted with 0.08 ml of acryloylchloride at room temperature for 1.5 hours after adding 213 mg of sodium bicarbonate. The reacted solution was extracted with a mixture of chloroform and isopropanol after adding water, washed with water and saturated saline solution, dried over anhydrous sodium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- ethylacetate : methanol = 15 : 1) to obtain the title compound (180 mg, 33%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.12 (s, 1H), 8.83 (s, 1H), 8.58 (d, 1H), 8.55 (s, 1H), 7.90 (s, 1H), 7.75 (m, 2H), 7.64 (d, 1H), 7.45 (dd, 1H), 7.24 (m, 1H), 7.13 (s, 1H), 6.91 (d, 1H), 6.79 (d, 1H), 6.37 (m, 1H), 6.20 (m, 1H), 5.72 (m, 1H), 5.23 (s, 2H), 4.80 (m, 1H), 4.14 (t, 2H), 3.71 (m, 4H), 2.56 (t, 2H), 2.47 (m, 4H), 2.06 (m, 2H), 1.50 (d, 3H).

Example 220: Preparation of (1*S*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(3-methoxypropoxy)-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

400 mg of (2*S*)-2-amino-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(3-methoxypropoxy)-quinazolin-6-yl}-propionamide as a starting material was dissolved in 10 ml of THF and 3 ml of water, and reacted with 0.07 ml of acryloylchloride at room temperature for 1.5 hours after adding 188 mg of sodium bicarbonate. The reacted solution was extracted with a mixture of chloroform and isopropanol after adding water, washed with water and saturated saline solution, dried over anhydrous sodium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- ethylacetate : methanol = 15 : 1) to obtain the title compound (110 mg, 25%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.12 (s, 1H), 8.86 (s, 1H), 8.58 (m, 2H), 7.75 (m, 2H), 7.64 (m, 2H), 7.45 (dd, 1H), 7.26 (m, 1H), 7.17 (s, 1H), 6.94 (d, 1H), 6.53 (d, 1H), 6.39 (m,1 H), 6.20 (m, 1H), 5.75 (m, 1H), 5.26 (s, 2H), 4.82 (m, 1H), 4.22 (t, 2H), 3.63 (t, 2H), 3.37 (s, 3H), 2.17 (m, 2H), 1.52 (d, 3H); [M+H]+: 591.3.

Example 221: Preparation of (2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-4-methylsulfanyl-butyramide

297 mg of (2*S*)-2-amino-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-4-methylsulfanyl-butyramide as a starting material was dissolved in 9 ml of THF and 3 ml of water, and reacted with 0.05 ml of acryloylchloride at room temperature for 1.5 hours after adding 139 mg of sodium bicarbonate. The reacted solution was extracted with a mixture of chloroform and isopropanol after adding water, washed with water and saturated saline solution, dried over anhydrous sodium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- ethylacetate : methanol = 15 : 1) to obtain the title compound (81 mg, 25%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.90 (s, 1H), 8.82 (s, 1H), 8.59 (m, 2H), 7.75 (m,2H), 7.65 (m, 2H), 7.48 (dd, 1H), 7.24 (m, 1H), 7.16 (s, 1H), 6.96 (d, 1H), 6.84 (d, 1H), 6.38 (m, 1H), 6.20 (m, 1H), 5.75 (m, 1H), 5.27 (s, 2H), 4.95 (m, 1H), 3.96 (s, 3H), 2.66 (m, 2H), 2.22 (m, 2H), 2.14 (s, 3H); [M+H]+: 593.2.

Example 222: Preparation of (2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(2-emthoxyethoxy)-quinazolin-6-yl}-4-methylsulfanyl-butyramide

300 mg of (2*S*)-2-amino-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-yl}-4-methylsulfanyl-butyramide as a starting material was dissolved in 9 ml of THF and 3 ml of water, and reacted with 0.05 ml of acryloylchloride at room temperature for 1.5 hours after adding 130 mg of sodium bicarbonate. The reacted solution was extracted with a mixture of chloroform and isopropanol after adding water, washed with water and saturated saline solution, dried over anhydrous sodium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- ethylacetate : methanol = 15 : 1) to obtain the title compound (80 mg, 25%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.79 (s, 1H), 8.56 (m, 2H), 7.88 (d, 1H), 7.78 (m, 1H), 7.70 (d, 1H), 7.56 (dd, 1H), 7.28 (m, 1H), 7.19 (s, 1H), 7.02 (d, 1H), 6.50 (m, 1H), 6.28 (m, 1H), 5.76 (dd, 1H), 5.28 (s, 2H), 4.92 (m, 1H), 4.32 (m, 2H), 3.88 (m, 2H), 3.06 (s, 3H), 2.65 (m, 2H), 2.25 (m, 2H), 2.14 (s, 3H); [M+H]+: 637.3.

Example 223: Preparation of (2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-4-methanesulfinyl-butyramide

81 mg of 2-amino-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-4-methylsulfanyl-butyramide as a starting material was dissolved in 3 ml of THF and 1 ml of water, and reacted

with 0.05 ml of acryloylchloride at room temperature for 1 hour after adding 37 mg of sodium bicarbonate. The reacted solution was extracted with a mixture of chloroform and isopropanol after adding water, washed with water and saturated saline solution, dried over anhydrous sodium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- ethylacetate : methanol = 15 : 1) to obtain the title compound (62 mg, 70%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.73 (s, 1H), 8.56 (m, 2H), 7.84 (d, 1H), 7.76 (m, 1H), 7.69 (d, 1H), 7.55 (dd, 1H), 7.28 (m, 1H), 7.13 (s, 1H), 7.01 (d, 1H), 6.35 (m, 2H), 5.78 (dd, 1H), 5.27 (s, 2H), 4.87 (m, 1H), 3.97 (s, 3H), 2.96 (m, 2H), 2.65 (s, 3H), 2.48 (m, 2H); [M+H]+: 609.3.

Example 224: Preparation of (2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-methyl-butyramide

474 mg of (2*S*)-2-amino-*N*-{4-[3-chloro-4-(pyridin-2-yllmethoxy)-phenylamino]-quinazolin-6-yl}-3-methyl-butyramide as a starting material was dissolved in 10 ml of THF, and cooled to 0℃. The solution was reacted with 0.11 ml of acrylic acid, 0.16 ml of pyridine and 380 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride at 0℃ for 1 hour and at room temperature for 1.5 hours. The reacted solution was extracted with chloroform after adding saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was stirred in ethylacetate and filtered under a reduced pressure to obtain the title compound (178 mg, 34%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.42 (s, 1H), 9.76 (s, 1H), 8.60 (s, 1H), 8.54 (d, 1H), 8.44 (s, 1H), 8.30 (d, 1H), 7.90 (d, 1H), 7.82 (m, 2H), 7.69 (d, 1H), 7.61 (dd, 1H), 7.52 (d, 1H), 7.31 (m, 1H), 7.19 (d, 1H), 6.40 (dd, 1H), 6.09 (dd, 1H), 5.58 (dd, 1H), 5.23 (s, 2H), 4.38 (t, 1H), 2.05 (m, 1H), 0.91 (m, 6H).

Example 225: Preparation of (2*S*)-2-acryloylamino-4-methyl-pentanoic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

480 mg of (2*S*)-2-amino-4-methyl-pentanoic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide was dissolved in 10 ml of THF, cooled to 0℃, and the resulting solution was treacted with 0.1 ml of acrylic acid, 0.16 ml of pyridine and 376 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride at 0℃ for 1 hour and at room temperature for 2 hours. The resulting solution was treated with saturated sodium bicarbonate, extracted with chloroform, dried over anhydrous sodium sulfate, filtered and distilled under a reduced pressure. The resulting residue was subjected to column chromatography (eluent- ethylacetate : methanol = 30 : 1) to obtain the title compound of formula (162 mg, 31%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.43 (s, 1H), 9.76 (s, 1H), 8.60 (s, 1H), 8.53 (d, 1H), 8.44 (s, 1H), 8.39 (d, 1H), 7.92 (d, 1H), 7.82 (td, 2H), 7.70 (d, 1H), 7.60 (dd, 1H), 7.52 (d, 1H), 7.30 (m, 1H), 7.19 (d, 1H), 6.30 (dd, 1H), 6.08 (dd, 1H), 5.57 (dd, 1H), 5.22 (s, 2H), 4.57 (m, 1H), 1.50 (m, 3H), 0.87 (m, 6H).

The inventive compounds prepared in the Examples were formulated as follows:

Preparation Example 1

Tablets for oral administration comprising each of the compounds of formula (I) obtained in Examples 1 to 225 as an active ingredient were prepared based on the recipes of Table 1.

Table 1

Ingredient	Amount per formulation
Active compound	100 mg

Corn starch	80 mg
Lactose	80 mg
Magnesium stearate	5 mg

Preparation Example 2

Gelatin capsules for oral administration comprising each of the compounds of formula (I) obtained in Examples 1 to 225 as an active ingredient were prepared based on the recipes of Table 2.

Table 2

Ingredient	Amount per formulation
Active compound	100 mg
Corn starch	40 mg
Lactose	80 mg
Crystalline cellulose	80 mg
Magnesium stearate	5 mg

Preparation Example 3

Injection formulations comprising each of the compounds of formula (I) obtained in Examples 1 to 225 as an active ingredient were prepared based on the recipes of Table 3, wherein in case a salt of the compound of formula (I) was used, pH values was not manupulated.

Table 3

Ingredient	Amount per formulation
Active compound	20 mg
5% glucose solution	10 ml

HCl (1N)	to adjust pH 4

Preparation Example 4

Injection formulations comprising each of the compounds of formula (I) obtained in Examples 1 to 225 as an active ingredient were prepared based on the recipes of Table 4.

Table 4

Ingredient	Amount per formulation
Active compound	20 mg
Polyethyleneglycol 400	2 ml
Sterile water	8 ml

Test Example 1: Inhibition of EGFR enzyme

10 μl of EGFR (EGFR type 1 kinase) was added to each well of a 96-well microplate. As an EGFR inhibitor, 10 μl each of the serially diluted solution of the compounds obtained in Examples 1 to 225, Iressa (astrazeneca) or Tarceba (Roche) was added to each well, and the plate was incubated at room temperature for 10 mins. 10 μl of Poly (Glu, Tyr) 4 : 1 and 10 μl of ATP were successively added thereto to initiate kinase reaction, and the resulting mixture was incubated at room temperature for 1 hour. 10 μl of 100 mM EDTA was added to each well and stirred for 5 mins to terminate the kinase reaction. 10 μl of 10 X anti-phosphotyrosine antibody (Pan Vera), 10 μl of 10 X PTK (protein tyrosine kinase) green tracer (Pan Vera) and 30 μl of FP (fluorescence polarization) dilutied buffer were added to the reacted solution, and incubated in dark at room temperature for 30 mins. FP values of each well were determined using VICTORIII fluorescence meter (Perkin Elmer) at 488 nm, and IC_{50}, the concentration at which 50% inhibition was observed, was determined,

wherein the maximum value was the polarized light value measured for the well untreated with EGFR inhibitor and the minimum value corresponded to 100% inhibition. The calulation and analysis of IC_{50} were carried out by using Microsoft Excel, and the results were shown in Table 5.

Test Example 2: Test of cancer cell growth inhibition

A skin cancer cell line, A431 (ATCC: CRL-1555), a skin cancer cell line, SK-Br3 (ATCC: HTB-30), and a colon and rectal cancer cell line , SW-620 (ATCC: CCL-227) were used to test the degrees of cancer cell growth inhibition using a culture medium, DEME (Dulbecco's Modified Eagle's Medium) including 4.5 g/ℓ of glucose and 1.5 g/ℓ of sodium bicarbonate and supplemented with 10% FBS (fetal bovine serum).

The cancer cell lines stored in a liquid nitrogen tank were each quickly thawed at 37℃, and centrifuged to remove the medium. The resulting cell pellet was mixed with a culture medium, incubated in a culture flask at 37℃ under 5% CO_2 for 2 to 3 days, and the medium was removed. The remaining cells were washed with DPBS (Dulbecco's Phosphate Buffered Saline) and separaed from the flask by using Tripsin-EDTA, and the separated cells were diluted with a culture medium to a concentration of 100,000 A431 cells/ml or in case of SK-Br3, 200,000 cells/ml. 100 μl of the diluted cell solution was added to each well of a 96-well plate, which was incubated at 37℃ under 5% CO_2 for 1 day.

The compounds obtained in Examples 1 to 225 as well as conventional EGFR inhibitors, Iressa and Tarceva were each dissolved in 99.5% DMSO to a concentration of 25 mM. In case that the test compound was not soluble in DMSO, a small amount of 1% HCl was added thereto and treated in a 40℃ water bath for 30 mins until complete dissolution was attained. The test compound solution was diluted with a culture medium to a final concentration of 100 μM, then diluted 10 time serially to 10^{-6} (final concentration of DMSO was less than 1%).

The medium was removed from each well of the 96-well microplate, 100 μl of a diluted test compound solution was added to each well holding

cultured cells, and the microplate was incubated at 37℃ under 5% CO_2 for 72 hours. After removing the medium from the plate, 50 μl of 10% trichloroacetic acid was added to each well, and the plate was kept at 37℃ for 1 hour to fix the cells to the bottom of the plate. 10% trichloroacetic acid was removed from each well, the plate was dried, 100 μl of an SRB (Sulforhodamine-B) dye solution was added thereto, and reacted for 10 mins. The SRB dye solution was prepared by dissolving SRB in 1% acetic acid to a concentration of 0.4%. After removing the dye solution, the plate was washed with water, and dried. When the dye solution was not removed by water, 1% acetic acid was used. 150 μl of 10 mM trisma base was added to each well, and the absorbance at 570 nm was determined with a microplate reader. IC_{50}, the concentration at which 50% inhibition occurs, was evaluated by regarding the difference between the final concentration of cells and the initial concentration of the cells incubated in a well untreated with the test compound as 100%. The calculation of IC_{50} was carried out by using Microsoft Excel, and the results are shown in Table 5.

Table 5

Example	IC_{50} (μM)			
	EGFR	A431	SK-Br-3	SW-620
1-5	-	0.408	0.359	-
2-4	-	0.206	0.245	>10
4	-	0.179	0.010	>10
5-3	-	0.315	0.106	>10
7-2	-	0.740	0.261	-
8	-	0.308	0.190	-
9	-	0.060	0.007	>10
11	-	0.252	0.113	-
17	-	0.713	0.182	-
18	-	0.157	0.29	>10
19	-	0.335	0.427	-

Example	IC_{50} (μM)			
	EGFR	A431	SK-Br-3	SW-620
20-2	0.030	0.948	0.151	-
21	-	0.455	0.016	>10
22	0.003	0.058	0.003	>10
23	-	0.316	0.359	-
24	-	0.232	0.105	>10
25	-	0.138	0.133	>10
26	-	0.801	0.872	-
27	-	0.085	0.010	>10
28	-	0.197	0.065	>10
29	-	0.310	0.054	>10
30	-	0.119	0.038	>10
32	-	0.312	0.163	-
33	-	0.348	0.131	-
34	-	0.896	0.141	-
37	-	0.137	0.160	-
39-2	-	0.482	0.045	>10
40	-	0.327	0.084	>10
41	-	0.936	0.172	-
42-2	-	0.340	0.102	>10
43	-	0.390	0.115	-
44	-	0.043	0.006	>10
48	-	0.828	0.131	-
50-2	-	0.845	0.099	-
53-2	-	0.124	0.258	-
54	-	0.321	0.046	>10
56	-	0.613	0.051	-
57	-	0.625	0.043	-

Example	IC_{50} (μM)

Example	IC_{50} (μM)			
	EGFR	A431	SK-Br-3	SW-620
61	-	0.168	0.098	>10
64	-	0.698	0.212	-
77	-	0.208	0.086	>10
79	-	0.065	0.003	>10
85-2	-	0.012	0.003	>10
87-2	-	0.095	0.035	>10
88	-	0.732	0.062	-
89	-	0.173	0.019	>10
90	-	0.423	0.628	-
91	-	0.603	0.445	-
92	-	0.293	0.080	-
93	-	0.324	0.033	>10
94	-	0.245	0.070	-
95	-	0.994	0.331	-
98	-	0.079	0.184	-
101	-	0.786	0.021	>10
102	-	0.345	0.080	>10
103	-	0.227	0.042	>10
104	-	0.254	0.022	>10
106	-	0.359	0.048	-
107	-	0.641	0.051	-
114	-	0.136	0.216	-
115-2	-	0.117	0.038	>10
117	-	0.336	0.040	>10
118	-	0.735	0.161	-
119	-	0.161	0.069	-
121	-	0.616	0.069	-
122	-	0.617	0.085	-

	EGFR	A431	SK-Br-3	SW-620
123	-	0.240	0.036	>10
124	-	0.584	0.107	-
125	-	0.272	0.083	-
126	-	0.099	0.091	-
128	-	0.489	0.585	-
129-2	-	0.490	0.345	-
131	0.004	0.037	0.003	-
132-2	-	0.880	0.662	-
133	-	7.261	1.110	-
134	-	0.193	0.004	-
135	-	0.123	0.092	-
136	-	0.828	1.713	-
137	-	0.100	0.044	-
138	-	0.102	0.054	-
139-5	0.005	0.069	0.047	-
140	-	0.102	0.102	-
141-4	-	1.327	0.804	-
142-2	0.002	0.019	0.004	-
143	0.001	0.010	0.002	-
144	-	0.073	0.008	-
145	0.004	0.032	0.025	-
146	0.004	0.032	0.040	-
147	0.002	0.021	0.019	-
148	-	0.034	0.004	-
149	-	0.054	0.002	-
150	-	0.036	0.006	-
151	-	0.105	0.003	-
152	-	0.166	0.004	-
Example	IC_{50} (μM)			

	EGFR	A431	SK-Br-3	SW-620
153	-	0.394	0.029	-
154	-	0.086	0.005	-
155	-	0.350	0.012	-
156	-	0.513	0.019	-
157	-	5.592	0.123	-
158	-	0.583	0.048	-
159	-	0.462	0.223	-
160	-	6.934	0.437	-
161	-	0.680	0.019	-
162	-	0.286	0.028	-
163	-	1.400	0.060	-
164	-	0.105	0.012	-
165	-	0.215	0.005	-
166	0.003	0.027	0.003	-
167	0.002	0.017	0.004	-
168	-	0.068	0.006	-
169	-	0.079	0.024	-
170	-	0.199	0.002	-
171	-	0.306	0.031	-
172	-	10	4.519	-
173	-	0.552	0.029	-
174	-	0.956	0.035	-
175	-	0.048	0.026	-
176	-	0.517	0.034	-
177	-	0.078	0.009	-
178	0.004	0.050	0.003	-
179	-	0.121	0.017	-

Example	IC_{50} (μM)			
	EGFR	A431	SK-Br-3	SW-620

180	-	0.438	0.063	-
181	-	0.218	0.013	-
182	-	0.128	0.009	-
183	0.002	0.013	0.003	-
184	-	1.425	0.114	-
185	-	0.022	0.003	-
186	-	0.026	0.008	-
187	-	0.022	0.003	-
188	-	0.024	0.006	-
189	0.001	0.009	0.002	-
190	0.002	0.013	0.006	-
191	-	0.056	0.003	-
192	-	0.036	0.006	-
193	-	0.075	0.022	-
194	-	0.093	0.056	-
195	-	0.119	0.044	-
196	-	0.088	0.025	-
197	-	0.259	0.196	-
198	-	0.047	0.024	-
199	-	0.145	0.096	-
200	-	0.332	0.008	-
201	-	0.148	0.025	-
202	-	0.105	0.006	-
203	-	0.269	0.034	-
204	-	0.085	0.030	-
205	0.002	0.017	0.019	-
206	-	0.017	0.010	-

Example	IC_{50} (μM)			
	EGFR	A431	SK-Br-3	SW-620

208	0.002	0.011	0.003	-
209	-	0.044	0.003	-
211	0.002	0.016	0.006	-
212	-	0.098	0.009	-
213	-	0.034	0.004	-
214	-	0.022	0.006	-
215	-	0.059	0.011	-
216	0.002	0.013	0.008	-
217	0.002	0.014	0.003	-
218	0.002	0.016	0.004	-
219	0.002	0.017	0.007	-
220	-	0.022	0.021	-
221	-	0.028	0.023	-
222	-	0.025	0.009	-
223	-	0.054	0.032	-
224	-	0.049	0.012	-
225	-	0.042	0.021	-
Iressa	1.147	0.028	0.206	>10
Tarceva	>1.7	0.059	0.891	>10

As shown in Table 5, each of the inventive compounds showed an excellent anticancer activity by effectively inhibiting EGFR kinase, arresting the growth of EGFR overexpressed A431 and Erb-B2 overexpressed SK-Br3 at a low drug concentration, while the inventive compounds did not inhibit the growth of SW-620 not having overexpressed EGFR and Erb-B2.

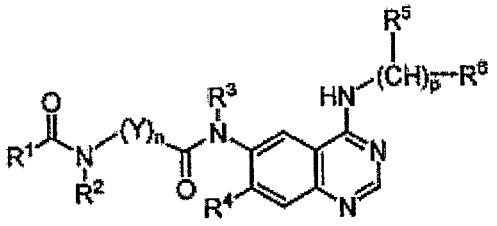
Therefore, the compounds of formula (I) of the present invention can selectively inhibit the growth of specific cancer cells induced by epithelial growth factor with reduced side effects.

While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and

changes may be made and also fall within the scope of the invention as defined by the claims that follow.

What is claimed is:

1. A quinazoline derivative of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein,

R^1 is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkylamino, C_{1-6}dialkylamino, C_{1-6}alkylthio, aryl or heteroaryl which is optionally substituted with X;

R^2 and R^3 are each independently hydrogen, hydroxy, C_{1-6}alkyl, C_{3-7}cycloalkyl, hydroxyC_{1-5}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl or C_{1-6}dialkylaminoC_{1-6}alkyl;

Y is -($CR^{11}R^{12}$)-, aryl or heteroaryl, R^{11} and R^{12} being each independently hydrogen, halogen, hydroxy, amino, nitro, cyano, thiol, carboxylic acid, carbamoyl; C_{1-6}alkyl, C_{1-6}alkylamino, C_{1-6}dialkylamino, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, C_{1-6}alkyloxysulfonyl, C_{1-6}alkylaminosulfonyl, C_{1-6}dialkylaminosulfonyl, C_{1-6}alkanoyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkylcarbamoyl, C_{1-6}dialkylcarbamoyl, C_{1-6}alkylthiocarbonyl, C_{1-6}alkanoyloxy, C_{1-6}alkyloxycarbonyloxy, C_{1-6}alkylaminocarbonyloxy, C_{1-6}dialkylaminocarbonyloxy, C_{1-6}alkylthiocarbonyloxy, C_{1-6}alkanoylamino, C_{1-6}alkoxycarbonylamino, C_{1-6}alkyl or C_{1-6}dialkylureido, C_{1-6}alkyl, C_{1-6}dialkylguanidino, aryl, or heteroaryl which is optionally substitutied with substituent Z, or optionally fused to each other to form a 3 to 8-membered non-aromatic ring, or R^{11} or R^{12} may be fused to R^2 or R^3 to form together with the carbon and nitrogen they are attached to a 4 to 8-membered non-aromatic ring;

R^4 is hydrogen, halogen, hydroxy, amino, or C_{1-6}alkyl, C_{1-6}alkoxy or C_{1-6}alkylamino optionally substituted with R^{13}, R^{13} being halogen, cyano,

trifluoromethyl, trifluoromethoxy, C_{1-6}alkoxy, C_{1-6}alkylamino, C_{1-5}dialkylamino, aryl or heteroaryl);

R^5 is hydrogen or C_{1-3}alkyl;

R^6 is R^{14}, aryl or heteroaryl optionally substituted with R^{15}, R^{14} and R^{15} being each independently hydrogen, halogen, trifluoromethyl, trifluoromethoxy, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylamino, C_{1-6}dialkylamino, or aryl, heteroaryl, arylalkyl, heteroarylalkyl, arylalkoxy, heteroarylalkoxy, aryloxy, heteroaryloxy, aryloxycarbonyl, heteroaryloxycarbonyl, arylcarbonyl, heteroarylcarbonyl, arylcarbamoyl, heteroarylcarbamoyl, arylsulfonyl or heteroarylsulfonyl optionally substituted with R^{16}, wherein R^{16} is halogen, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylamino or C_{1-6}dialkylamino;

n is an integer in the range of 1 to 6;

p is 0 or 1;

X and Z are each independently hydrogen, halogen, nitro, hydroxy, amino, cyano, thiol, carboxylic acid, carbamoyl, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkylamino, C_{1-6}dialkylamino, C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylcarbonyl, C_{1-6}alkylthiocarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbamoyl, C_{1-6}dialkylcarbamoyl, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, C_{1-6}alkoxycarbonyloxy, C_{1-6}alkylaminocarbonyloxy, C_{1-6}dialkylaminocarbonyloxy, C_{1-6}alkylthiocarbonyloxy, C_{1-6}alkanoylamino, C_{1-6}alkoxycarbonylamino, C_{1-6}alkylureido, C_{1-6}dialkylureido, C_{1-6}alkylguanidino, C_{1-6}dialkylguanidino, C_{1-6}alkoxysulfonyl, C_{1-6}alkylaminosulfonyl, C_{1-6}dialkylaminosulfonyl, C_{1-6}alkylsulfamoyl, C_{1-6}alkylaminosulfamoyl, C_{1-6}dialkylaminosulfamoyl, aryl or heteroaryl; wherein

aryl is C_{5-12} monocylic or bicyclic aryl;

heteroaryl is a 5 to 13-membered heteroaromatic or non-aromatic group containing one or more of the elements selected from the group consisting of N, O, S, SO and SO_2; and

The optionally substituted aryl and heteroaryl each has one or more substituents selected from the group consisting of halogen, hydroxy, amino, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylamino and C_{1-6}dialkylamino.

2. The compound of claim 1, wherein R^1 is preferably methyl, cyclopropyl, trifluoromethyl, cyanomethyl, chloromethyl, phenyl, methoxy, phenoxy, benzyloxy, methoxymethyl, acetoxymethyl, dimethylaminoethoxymethyl, methoxyethoxymethyl, methylthiomethyl, methanesulfinylmethyl, methanesulfonylmethyl, dimethylaminomethyl, morpholinomethyl, 4-methylpiperazinylmethyl, methanesulfonylethylaminomethyl, methoxyethylaminomethyl, ethoxycarbonyl, ethylamino, furan-3-yl, furan-2-yl-methylamino, benzamino, benzylamino, *t*-buthoxy, 3-methyl-isoxazol-5-yl, 5-methyl-isoxazol-4-yl, 1*H*-pyrazol-4-yl, vinyl, penta-1,3-dienyl, cyclopentenyl, 2-phenylvinyl, 2-methylvinyl, 2,2-dimethylvinyl, 1-methylvinyl, 2-phenylethynyl, 2-methylethynyl, 2-(bromomethyl)vinyl, 2-(dimethylaminomethyl)vinyl, 2-(morpholinomethyl)vinyl, 2-(4-methylpiperazinylmethyl)vinyl, 2-((*N*-methyl-(2-hydroxyethyl)amino)methyl)vinyl or 2-(methanesulfonylethylaminomethyl)vinyl;

R^2 and R^3 are preferably each independently hydrogen, methyl, ethyl or 3-(*N,N*-dimethylamino)propyl;

R^4 is preferably hydrogen, amino, hydroxyl, fluoro, chloro, methoxy, ethoxy, methoxyethoxy, methoxypropoxy, ethylsulfanyl, cyclopropylmethoxy, cyclopentyloxy, 2,2,2-trifluoroethoxy, 2-fluoroethoxy, *N,N*-dimethylamino, morpholinopropoxy or 4-methylpiperadinylmethoxy;

R^5 is preferably hydrogen;

R^6 is preferably 1-phenyl-ethyl, 3-ethynyl-phenyl, biphenyl, 3-chloro-4-fluoro-phenyl, 3-chloro-4-(3-fluoro-benzyloxy)-phenyl, 3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenyl, 4-[2-(6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-phenyl, *N*-phenyl-benzamid-4-yl, 3-chloro-4-(pyridin-2-ylmethoxy)-phenyl, 3-chloro-4-(pyridin-3-ylmethoxy)-phenyl, 3-chloro-4-(6-methyl-pyridin-2ylmethoxy)-phenyl, 3-chloro-4-(pyridin-4-ylmethoxy)-phenyl, 3-methyl-4-(pyridin-2-ylmethoxy)-phenyl, 1-pyridin-2-ylmethyl-1*H*-indazol-5-yl, 1-(3-fluoro-benzyl)-1*H*-indazol-5-yl, 1-penta-2,4-dienyl-1*H*-indazol-5-yl, 3-chloro-4-(2-fluoroethoxy)-phenyl, 2-methyl-1*H*-indol-5-yl or 1-benzyl-1*H*-indazol-5-yl;

Y is preferably -($CR^{11}R^{12}$)-, aryl or heteroaryl, R^{11} and R^{12} being each independently hydrogen, amino, hydroxyl, halogen, C_{1-6}alkyl, C_{1-3}alkenyl, C_{1-6}alkylC_{1-6}alkyl, hydroxylC_{1-3}alkyl, diC_{1-3}alkylaminoC_{1-3}alkyl, C_{1-3}alkoxyC_{1-3}alkyl, C_{1-3}alkylsulfonylC_{1-3}alkyl, C_{1-3}alkylsulfinylC_{1-3}alkyl, C_{1-3}alkylsulfanylC_{1-3}alkyl, carboxyC_{1-3}alkyl, C_{1-3}alkoxycarbonylC_{1-3}alkyl, diC_{1-3}alkylamino, C_{1-3}alkoxy, C_{1-6}alkanoyloxy, C_{1-6}alkylcarbamoyl, aryl, heteroaryl, or C_{1-3}alkylsubstitutied with aryl or heteroaryl, the aryl or heteroaryl is phenyl, naphtyl, furan, thiophene, imidazole, triazole, pyridine, oxazole, isoxazole, thiazole, indole, quinoline, isoquinoline, quinazoline, aziridine, azetidine, pyrrolidine, piperidine, morpholine, piperazine, thiomorpholine or 4-pyridone, optionally, fused to each other to form a 3 to 8-membered non-aromatic ring, or R^{11} or R^{12} may be fused to R^2 or R^3 to form together with the carbon and nitrogen they are attached to a 4 to 8-membered non-aromatic ring; and

Preferable n is an integer in the range of 1 to 4.

3. The compound of claim 1, which is selected from the group consisting of:

({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-methyl)-carbamic acid *t*-butylester;

N-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-methyl)-2-methoxy-acetamide;

N-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-methyl)-2-methanesulfonyl-acetamide;

N-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-methyl)-acrylamide;

(2*S*)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-(2-methoxy-acetylamino)-3-phenyl-propionamide;

(1*S*)-(1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-3-methanesulfanyl-propyl)-carbamic acid *t*-butylester;

(2*S*)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-(2-methoxy-acetylamino)-4-methanesulfanyl-butyramide;

(2*S*)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-(2-methanesulfonyl-acetamino)-4-methanesulfanyl-butyramide;

(2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-methanesulfanyl-butyramide;

(1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-cyclopropyl)-carbamic acid *t*-butylester;

(2*S*)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-(2-methoxy-acetylamino)-2-phenyl-acetamide;

(4*S*)-4-*t*-buthoxycarbonylamino-4-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-butyric acid methylester;

4-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-4-(2-methoxy-acetylamino)-butyric acid methylester;

4-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-4-(2-methoxy-acetylamino)-butyric acid;

2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-pyrrolidine-1-carboxylic acid *t*-butylester;

1-(2-methoxy-acetyl)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide;

1-(2-methanesulfonyl-acetyl)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide;

1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide;

(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid *t*-butylester;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-propionamide;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-propionamide;

N-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

3-phenyl-propionylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

hexa-2,4-dienonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

cyclopent-1-en carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

N-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-3-phenyl-acrylamide;

but-2-ynoylic acid(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

3-methyl-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

N-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-2-methyl-acrylamide;

N-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-2-cyano-acetamide;

3-methyl-isoxazol-5-carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

furan-3-carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

1*H*-pyrazol-4-carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

N-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-benzamide;

N-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-oxalamic acid ethylester;

cyclopropylcarboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

acetic acid 2-*t*-buthoxycarbonylamino-1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethylester;

acetic acid 1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-2-(2-methoxy-acetylamino)-ethylester;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-hydroxyl-3-(2-methoxy-acetylamino)-propionamide;

(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-carbamic acid *t*-butylester;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-2-methyl-propionamide;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-2-methyl-propionamide;

N-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-acrylamide;

(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-1-phenyl-ethyl)-carbamic acid *t*-butylester;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-3-phenyl-propionamide;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-3-phenyl-propionamide;

3-(2-methoxy-acetylamino)-thiophene-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide;

(2-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid *t*-butylester;

3-(2-methanesulfonyl-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-propionamide;

N-(2-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

{2-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-carbamic acid *t*-butylester;

N-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-3-(2-methanesulfonyl-acetylamino)-propionamide;

N-{2-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide;

4-bromo-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

4-dimethylamino-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

4-morpholin-4-yl-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

4-(4-methyl-piperazin-1-yl)-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

4-[(2-hydroxyl-ethyl)-methyl-amino]-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

4-(2-methanesulfonyl-ethylamino)-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

3-(2-chloro-acetylamide)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-morpholin-4-yl-acetylamino)-propionamide;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-dimethylamino-acetylamino)-propionamide;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(4-methyl-piperazin-1-yl)-acetylamino]-propionamide;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(2-methoxy-ethylamino)-acetylamino]-propionamide;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(2-methanesulfonyl-ethylamino)-acetylamino]-propionamide;

3-(2-chloro-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-propionamide;

N-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-3-(2-morpholin-4-yl-acetylamino)-propionamide;

3-(2-dimethylamino-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-propionamide;

N-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(4-methyl-piperazin-1-yl)-acetylamino]-propionamide;

3-[2-(2-methoxy-ethylamino)-acetylamino]-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-methylamino]-quinazolin-6-yl}-propionamide;

3-[2-(2-methanesulfonyl-ethylamino)-acetylamino]-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-propionamide;

N-{2-[4-(2-methyl-1*H*-indol-5-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide;

3-(2-methanesulfonyl-acetylamino)-*N*-[4-(1-phenyl-ethylamino)-quinazolin-6-yl]-propionamide;

N-{2-[4-(1-phenyl-ethylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide;

N-[2-(4-{4-[2-(6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-phenylamino}-quinazolin-6-ylcarbamoyl)-ethyl]-acrylamide;

{2-[4-(1-benzyl-1*H*-indazol-5-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-carbamic acid *t*-butylester;

N-[4-(1-benzyl-1*H*-indazol-5-ylamino)-quinazolin-6-yl]-3-(2-methanesulfonyl-acetylamino)-propionamide;

N-{2-[4-(1-benzyl-1*H*-imidazol-5-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide;

{2-[4-(4-phenylcarbamoyl-phenylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-carbamic acid *t*-butylester;

4-{6-[3-(2-methanesulfonyl-acetylamino)-propionylamino]-quinazolin-4-ylamino}-*N*-phenyl-benzamide;

4-[6-(3-acryloylamino-propionylamino)-quinazolin-4-ylamino]-*N*-phenyl-benzamide;

N-[4-(biphenyl-4-ylamino)-quinazolin-6-yl]-3-(2-methanesulfonyl-acetylamino)-propionamide;

N-{2-[4-(biphenyl-4-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide;

N-{2-[4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide;

(3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-carbamic acid *t*-butylester;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-methoxy-acetylamino)-butyramide;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-methanesulfonyl-acetylamino)-butyramide;

4-acryloylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-butyramide;

N-(3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-benzamide;

N-(3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-oxalamic acid ethylester;

cyclopropylcarboxylic acid (3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-amide;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-cyano-acetylamino)-butyramide;

furan-3-carboxylic acid (3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-amide;

1*H*-pyrazol-4-carboxylic acid (3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-amide;

{3-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-ylcarbamoyl]-propyl}-carbamic acid *t*-butylester;

N-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-4-(2-methanesulfonyl-acetylamino)-butyramide;

4-acryloylamino-*N*-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-butyramide;

(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-ylcarbonyl}-propyl)-carbamic acid *t*-butylester;

4-(2-methanesulfonyl-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide;

4-acryloylamino-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide;

4-(2-chloro-acetylamino)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-butyramide;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-morpholin-4-yl-acetylamino)-butyramide;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-dimethylamino-acetylamino)-butyramide;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-[2-(4-methyl-piperazin-1-yl)-acetylamino]-butyramide;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-[2-(2-methoxy-ethylamino)-acetylamino]-butyramide;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-[2-(2-methanesulfonyl-ethylamino)-acetylamino]-butyramide;

4-(2-chloro-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide;

N-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-4-(2-morpholin-4-yl-acetylamino)-butyramide;

4-(2-dimethylamino-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide;

N-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-4-[2-(4-methyl-piperazin-1-yl)-acetylamino]-butyramide;

4-[2-(2-methanesulfonyl-ethylamino)-acetylamino]-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide;

4-[2-(2-methoxy-ethylamino)-acetylamino]-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide;

(4-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-butyl)-carbamic acid *t*-butylester;

5-(2-methoxy-acetylamino)-pentanoic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide;

5-(2-methanesulfonyl-acetylamino)-pentanoic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-pentylamino]-quinazolin-6-yl}-amide;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfanyl-acetylamino)-propionamide;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfinyl-acetylamino)-propionamide;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2,2,2-trifluoro-acetylamino)-propionamide;

3-acetylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide;

acetic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethylcarbamoyl)-methylester;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(2-dimethylamino-ethoxy)-acetylamino]-propionamide;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(3-ethyl-ureido)-propionamide;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(3-phenyl-ureido)-propionamide;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(3-furan-2-ylmethyl-ureido)-propionamide;

(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid methylester;

(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid phenylester;

(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid benzylester;

N-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-propionamide;

N-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-propionamide;

N-(2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

N-{4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-propionamide;

N-{4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-propionamide;

N-(2-{4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(2-methoxy-ethoxy)-acetylamino]-propionamide;

5-methyl-isoxazol-4-carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-methanesulfanyl-acetylamino)-butyramide;

N-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-methanesulfinyl-acetylamino)-butyramide;

N-[2-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-methyl-carbamoyl)-ethyl]-acrylamide;

N-[2-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-ethyl-carbamoyl)-ethyl]-acrylamide;

N-{2-[{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-(3-dimethylamino-propyl)-carbamoyl]-ethyl}-acrylamide;

N-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-*N*-methyl-acrylamide;

N-(2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-*N*-methyl-acrylamide;

N-(2-{4-[3-chloro-4-(6-methyl-pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

(2*S*)-1-acryloyl-pyrrolidin-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

(2*S*)-1-(1-oxo-butyn-2-yl)-pyrrolidin-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(6-methyl-pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

(3*R*,5*S*)-acetic acid 1-acryloyl-5-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-pyrrolidin-3-ylester;

(2*S*,4*R*)-1-acryloyl-4-hydroxyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

(2*S*,4*R*)-1-acryloyl-4-ethylsulfanyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

(2*S*,4*R*)-1-acryloyl-4-dimethylamino-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-4-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

2-(1-acryloyl-pyrrolidin-2-yl)-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-acetamide;

1-acryloyl-pyrrolidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

1-acryloyl-piperidine-4-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-amide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-(3-ethynyl-phenylamino)-quinazolin-6-yl]-amide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-amide;

(2*S*,4*R*)-1-acryloyl-4-ethanesulfonyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

(2*S*,4*R*)-1-acryloyl-4-methoxy-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

1-acryloyl-piperidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

1-acryloyl-azetidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

1-acryloyl-piperidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-fluoro-quinazolin-6-yl}-amide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

N-(2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

(2*S*)-1-acryloyl-pyrrolidin-2-carboxylic acid {7-methoxy-4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

2-(1-acryloyl-pyrrolidin-2-yl)-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-acetamide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-ethoxy-quinazolin-6-yl}-amide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-ethylsulfanyl-quinazolin-6-yl}-amide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-cyclopropylmethoxy-quinazolin-6-yl}-amide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-cyclopentyloxy-quinazolin-6-yl}-amide;

N-(2-{4-[3-chloro-4-(pyridin-4-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

(2*S*)-1-(4-dimethylamino-buten-2-oyl)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {7-chloro-4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {7-fluoro-4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

N-(2-{7-fluoro-4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

(2*S*)-1-acryloyl-2,5-dihydro-1*H*-pyrrol-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

(4*R*)-3-acryloyl-thiazolidin-4-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

1-acryloyl-azetidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

1-acryloyl-azetidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2,2,2-trifluoro-ethoxy)-quinazolin-6-yl]-amide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-dimethylamino-quinazolin-6-yl}-amide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [7-methoxy-4-(1-pyridin-2-ylmethyl-1*H*-indazol-5-ylamino)-quinazolin-6-yl]-amide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenylamino]-7-ethoxy-quinazolin-6-yl}-amide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2-fluoro-ethoxy)-quinazolin-6-yl]-amide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[1-(3-fluoro-benzyl)-1*H*-indazol-5-ylamino]-7-methoxy-quinazolin-6-yl}-amide;

(1*R*)-*N*-(1-{4-[3chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

(1*S*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

(1*S*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}ethyl)-N-methyl-acrylamide;

N-(2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-fluoro-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [7-methoxy-4-(1-penta-2,4-dienyl-1*H*-indazol-5-ylamino)-quinazolin-6-yl]-amide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(6-methyl-pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

1-acryloyl-azetidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-fluoro-quinazolin-6-yl}-amide;

1-acryloyl-piperidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

1-acryloyl-piperidine-4-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

1-acryloyl-pyrrolidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

1-acryloyl-azetidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-ethoxy-quinazolin-6-yl}-amide;

1-acryloyl-azetidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

(3S)-1-acryloyl-piperidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

N-((1*S*)-1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-ethyl)-*N*-ethyl-acrylamide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(2-fluoro-ethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

(2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-butyramide;

N-(2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-2-fluoro-ethyl)-acrylamide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-7-(1-methyl-piperidin-4-ylmethoxy)-quinazolin-6-yl}-amide;

(1*R*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2-methoxy-ethoxy)-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-yl}-amide;

N-({4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-methyl)-acrylamide

N-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-methyl)-acrylamide;

(3*S*)-3-acryloylamino-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-butyramide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-yl]-amide;

(1*S*)-*N*-{1-[4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide;

(2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-yl]-amide;

(1*S*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

N-{[4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-ylcarbamoyl]-methyl}-acrylamide;

N-({4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-ylcarbamoyl}-methyl]-acrylamide;

(1*S*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylemthoxy)-phenylamino]-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-ylcarbamoyl}-ethyl-acrylamide;

(1*S*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(3-methoxypropoxy)-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

(2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-4-methylsulfanyl-butyramide;

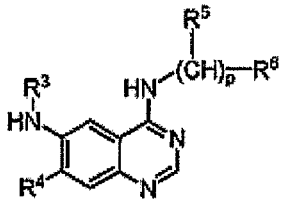
(2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-yl}-4-methylsulfanyl-butyramide;

(2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-4-methylsulfinyl-butyramide;

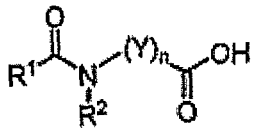
(2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-methyl-butyramide; and

(2*S*)-2-acryloylamino-4-methyl-pentanoic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide.

4. A process for preparing the quinazoline derivative of claim 1, which comprises the step of subjecting a compound of formula (IV) to a condensation reaction with a compound of formula (V):



(IV)

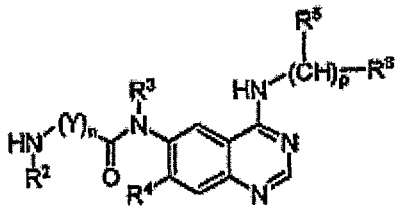


(V)

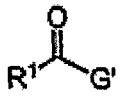
wherein,

R^1, R^2, R^3, R^4, R^5, R^6, Y, n and p have same meanings as defined in claim 1.

5. A process for preparing the quinazoline derivative of claim 1, which comprises the step of subjecting a compound of formula (II) to a condensation reaction with a compound of formula (IX):



(II)



(IX)

wherein,

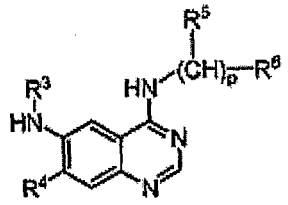
R^1, R^2, R^3, R^4, R^5, R^6, Y, n and p have same meanings as defined in claim 1, and G' is halogen, hydroxy or C_{1-6}alkanoyloxy.

6. The process of claim 4 or 5, wherein the condensation reation is carried out in the presence of a condensation reagent selected from the group consistin of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, *N,N*-dicyclohexyldiimide, C_{1-6}alkylchloroformate, carbonyldiimidazole and *O*-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate.

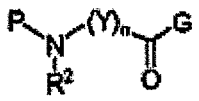
7. The process of claim 4 or 5, wherein the condensation reation is carried out in a solvent selected form the group consisting of methylene

chloride, chloroform, *N,N*-dimethylformamide, THF, 1,4-dioxane, acetonitrile and a mixture thereof at a temperature ranging from -20℃ to the boiling point of the solvent.

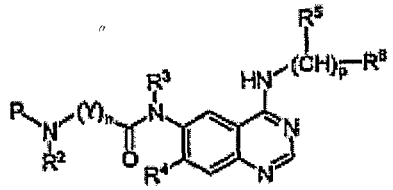
8. The process of claim 5, wherein the compound of formula (II) is prepared by subjecting a compound of formula (IV) to a condensation reaction with a compound of formula (VIII) to obtain a compound of formula (III), followed by removing the amine protecting group P from the compound of formula (III):



(IV)



(VIII)

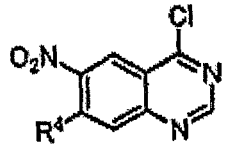


(III)

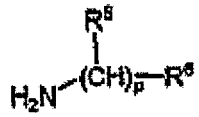
wherein,

R^2, R^3, R^4, R^5, R^6, Y, n and p have same meanings as defined in claim 1, P is an amine protecting group, and G is halogen, hydroxy or C_{1-6}alkanoyloxy.

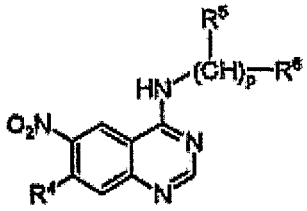
9. The process of claim 4 or 8, wherein the compound of formula (IV) is prepared by reacting a compound of formula (XVII) with a compound of formula (XX) to obtain a compound of formula (XVI), followed by reducing the compound of formula (XVI):



(XVII)



(XX)



(XVI)

wherein,

R^4, R^5, R^6 and p have same meanings as defined in claim 1.

10. A pharmaceutical composition for inhibiting the growth of cancer cells comprising the compound or salt defined in claim 1 as an active ingredient.

11. The composition of claim 10, which is administered in combination with an anticancer agent selected from the group consisting of cell signal transduction inhibitors, mitosis inhibitors, alkylating agents, antimetabolites, antibiotics, growth factor inhibitors, cell cycle inhibitors, topoisomerase inhibitors, biological reaction modifiers, antihormonal agents and antiandrogen.

12. The composition of claim 10, wherein the cancer cells are induced by epithelial growth factor.