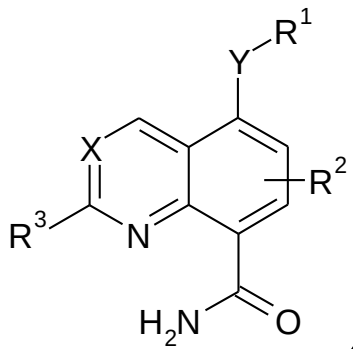
Claims

We claim:

1. A compound according the following Formula (I),



(I)

or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, wherein

X is N, or C-R^4;

Y is N-R^5, O, or absent;

R^1 is L^1-R^6, L^1-R^6-L^2-R^7;

R^2 is H, Hal, OH, OA, CN, NH_2, or NHA;

R^3 is H, CH_3, or $C(Hal)_3$;

R^4 is H, Hal, OH, COOH, NH_2, or CN;

R^5 is H, LA or monocyclic alkyl having 3, 4, 5, 6, or 7 ring atoms, in which one or two CH_2 groups may be replaced by a -NH- group, or

R^5, R^1 together form monocyclic alkyl having 3, 4, 5, 6, or 7 ring atoms, in which one or two CH_2 groups may be replaced by an O atom and/or an –NH-, -NA-, -N(L^1-R^6)-, -CHA-, -CA_2-, CH(L^1-R^6)- or -CO- group, and which monocyclic alkyl may be substituted by NH_2;

L^1, L^2 are independently a single bond, or unbranched or branched alkyl having 1, 2, 3, 4 or 5 C atoms, which may be unsubstituted, or mono- or disubstituted with Hal, OH, NH_2, NH(LA), N$(LA)_2$, and wherein one or two CH_2 groups may be replaced by an O atom or by a -CO-, -NH-, -N(LA)-, -CONH-, -N(LA)COO- or -NHCO- group;

R^6 is Ar or monocyclic alkyl having 3, 4, 5, 6, or 7 ring atoms, in which one or two CH_2 groups may be replaced by an O atom and/or an –NH-, -NA-, -CHA-, -CO- or -CONHA- group;

Ar is a mono- or bicyclic aromatic homo- or heterocycle having 0, 1, 2, 3 or 4 N, O and/or S atoms and 5, 6, 8, 9, or 10 skeleton atoms, which may be unsubstituted or, indenpendently of one another, mono-, di- or trisubstituted by Hal, A, OA, OH, NH_2, or NHA;

A is an unbranched or branched linear or cyclic alkyl having 1, 2, 3, 4, 5 or 6 C atoms, in which one or two CH_2 groups may be replaced by an O atom and/or an –NH-, -NHCOAr or –CONHAr group in which 1-3 H atoms may be replaced by Hal, and in which one or two CH_3 groups may be replaced by NH_2, OH, NH(LA) or $N(LA)_2$ group;

LA is unbranched or branched, linear alkyl having 1, 2, 3, or 4 C atoms wherein 1, 2 or 3 H atoms may be replaced by Hal (*e.g.*, methyl, ethyl, and trifluoromethyl); and

Hal is F, Cl, Br or I.

2. The compound according to Claim 1, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, in which the residues not designated in greater detail have the meaning indicated for Formula (I), but in which

in Subformula 1

X is N,

Y is $N\text{-}R^5$,

in Subformula 2

X is N,

Y is $N\text{-}R^5$,

R^5, R^1 together form monocyclic alkyl having 3, 4, 5, 6, or 7 ring atoms, in which one or two CH_2 groups may be replaced by an –NH-, -NA-, $-N(L^1\text{-}R^6)$-, -CHA-, $-CA_2$-, $CH(L^1\text{-}R^6)$- or -CO- group, and which monocyclic alkyl may be substituted by NH_2,

in Subformula 3

X is N,

Y is N-R^5,

R^5, R^1 together form monocyclic alkyl having 4, 5 or 6 ring atoms, in which one CH_2 group is replaced by an -N(L^1-R^6)- group, and which monocyclic alkyl may be substituted by NH_2,

in Subformula 4

X is N,

Y is N-R^5,

R^5, R^1 together form monocyclic alkyl having 4, 5 or 6 ring atoms, in which one CH_2 group is replaced by an -N(L^1-R^6)- group, and which monocyclic alkyl may be substituted by NH_2,

L^1 is a bond, -CONH-, -NHCO-, -$CONHCH_2$-, CH_2CONH-,

in Subformula 5

X is N,

Y is N-R^5,

R^5, R^1 together form monocyclic alkyl having 4, 5 or 6 ring atoms, in which one CH_2 group is replaced by an -N(L^1-R^6)- group, and which monocyclic alkyl may be substituted by NH_2,

R^6 is phenyl, which is unsubstituted, or independently mono-, di- or trisubstituted by Hal, $C(Hal)_3$, CH_3, $C(Hal)_3O$,

in Subformula 6

X is N,

Y is N-R^5,

X is N,

Y is N-R^5,

R^5, R^1 together form monocyclic alkyl having 4, 5 or 6 ring atoms, in which one CH_2 group is replaced by an -N(L^1-R^6)- group, and which monocyclic alkyl may be substituted by NH_2,

L^1 is a bond, -CONH-, -NHCO-, -$CONHCH_2$-, CH_2CONH-,

R^6 is phenyl, which is unsubstituted, or independently mono-, di- or trisubstituted by Hal, $C(Hal)_3$, CH_3, CH_3O, $C(Hal)_3O$,

in Subformula 7

X is N,

Y is NH,

R^1 is L^1-R^6-L^2-R^7,

L^1, L^2 are a bond,

R^6 monocyclic alkyl having 4, 5 or 6 ring atoms, in which one CH_2 group is replaced by an -NH-, group,

R^7 is phenyl, which is unsubstituted, or independently mono-, di- or trisubstituted by Hal, $C(Hal)_3$, CH_3, CH_3O, $C(Hal)_3O$,

in Subformula 8

X is N,

Y is NH,

R^1 is L^1-R^6-L^2-R^7,

L^1, L^2 are a bond,

R^6 is piperidyl or pyrrolidinyl,

R^7 is phenyl, which is mono- or disubstituted by Hal, $C(Hal)_3$, CH_3, CH_3O, $C(Hal)_3O$,

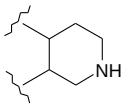
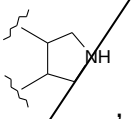
in Subformula 9

X is N,

Y is NH,

R^1 is L^1-R^6-L^2-R^7,

L^1, L^2 are a bond,

R^6 is  or ,

R^7 is phenyl, which is mono- or disubstituted by Hal, $C(Hal)_3$, CH_3, CH_3O, $C(Hal)_3O$,

in Subformula 10

X is N,

Y is NH,

R^1 is L^1-R^6,

R^6 is phenyl, which is unsubstituted, or independently mono-, di- or trisubstituted by Hal, $C(Hal)_3$, CH_3, CH_3O, $C(Hal)_3O$.

~~3. The compound according to Claim 1, wherein the compound is selected from the~~ group consisting of:
5-((4-(4-(trifluoromethoxy)phenyl)pyrrolidin-3-yl)amino)quinazoline-8-carboxamide (trans_racemic),
5-((4-phenylpiperidin-3-yl)amino)quinazoline-8-carboxamide (trans_racemic),
5-((4-(3-fluoro-4-(trifluoromethyl)phenyl)piperidin-3-yl)amino)quinazoline-8-carboxamide(trans_racemic),
5-((-4-(3-(trifluoromethoxy)phenyl)pyrrolidin-3-yl)amino)quinoline-8-carboxamide (trans_racemic)
5-((4-(3-(trifluoromethyl)phenyl)pyrrolidin-3-yl)amino)quinazoline-8-carboxamide,
5-((4-(4-chloro-3-fluorophenyl)piperidin-3-yl)amino)quinazoline-8-carboxamide,
5-((4-(3-chloro-4-fluorophenyl)piperidin-3-yl)amino)quinazoline-8-carboxamide,
5-(((3R,4R)-4-(3-chloro-4-fluorophenyl)piperidin-3-yl)amino)quinazoline-8-carboxamide,
5-((4-(4-fluorophenyl)piperidin-3-yl)amino)quinazoline-8-carboxamide,
or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios.

4. A pharmaceutical composition comprising a compound according to any of claims 1 to 3, and/or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, as active ingredient, together with a pharmaceutically acceptable carrier.

5. A compound of any of claims 1 to 3, and/or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, for use as a medicament.

6. A compound of any of claims 1 to 3, and/or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, for treating hyperproliferative diseases.

7. The compound of claim 6, and/or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, wherein the disease is selected from the group consisting of cancer, inflammation, pancreatitis or kidney disease, pain, benign hyperplasia of the skin, restenosis, prostate, diseases related to vasculogenesis or angiogenesis, tumor angiogenesis, skin diseases selected

from psoriasis, eczema, and sclerodema, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma and Kaposi's sarcoma.

8. Use of a compound of any of claims 1 to 3, or and/or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, for the preparation of a medicament for the treatment of hyperproliferative diseases.

9. Use according to claim 9 wherein the disease is selected from the group consisting of cancer, inflammation, pancreatitis or kidney disease, pain, benign hyperplasia of the skin, restenosis, prostate, diseases related to vasculogenesis or angiogenesis, tumor angiogenesis, skin diseases selected from psoriasis, eczema, and sclerodema, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma and Kaposi's sarcoma.

10. A method for treating hyperproliferative diseases, comprising administering to a subject a compound of any of claims 1 to 3, and/or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios.

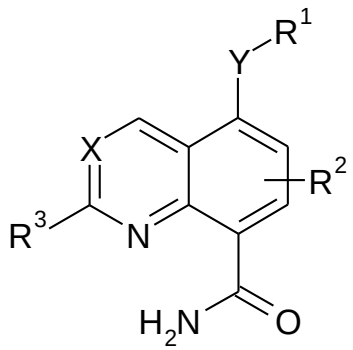
11. The method of claim 10, wherein the disease is selected from the group consisting of cancer, inflammation, pancreatitis or kidney disease, pain, benign hyperplasia of the skin, restenosis, prostate, diseases related to vasculogenesis or angiogenesis, tumor angiogenesis, skin diseases selected from psoriasis, eczema, and sclerodema, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma and Kaposi's sarcoma.

12. Set (kit) consisting of separate packs of an effective amount of a compound according to any of Claims 1 to 3 and/or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, and an effective amount of a further medicament active ingredient.

Claims

We claim:

1. A compound of Formula (I),



(I)

or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, wherein

X is N;

Y is N-R^5, O, or absent;

R^1 is L^1-R^6, or L^1-R^6-L^2-R^7;

R^2 is H, Hal, OH, OA, CN, NH_2, or NHA;

R^3 is H, CH_3, or $C(Hal)_3$;

R^4 is H, Hal, OH, COOH, NH_2, or CN;

R^5 is H, LA or monocyclic alkyl having 3, 4, 5, 6, or 7 ring atoms, wherein one or two CH_2 groups may be replaced by a -NH- group, or

R^5, R^1 together form a monocyclic alkyl ring having 3, 4, 5, 6, or 7 ring atoms, wherein one or two CH_2 groups may be replaced by an O atom and/or an –NH-, -NA-, -N(L^1-R^6)-, -CHA-, -CA_2-, CH(L^1-R^6)- or -CO- group, and wherein monocyclic alkyl ring may be substituted by NH_2;

L^1, L^2 are each independently a single bond, or unbranched or branched alkyl having 1, 2, 3, 4 or 5 C atoms, which may be unsubstituted, or mono- or disubstituted with Hal, OH, NH_2, NH(LA), N$(LA)_2$, and wherein one or two CH_2 groups may be replaced by an O atom or by a -CO-, -NH-, -N(LA)-, -CONH-, -N(LA)COO- or -NHCO- group;

R^6, R^7 are each independently Ar or a monocyclic alkyl ring having 3, 4, 5, 6, or 7 ring atoms, wherein one or two CH_2 groups may be replaced by an O atom and/or an –NH-, -NA-, -CHA-, -CO- or -CONHA- group;

each Ar is independently a mono- or bicyclic aromatic homo- or heterocycle having 0, 1, 2, 3 or 4 N, O and/or S atoms and 5, 6, 8, 9, or 10 skeleton atoms, which may be unsubstituted or, independently of one another, mono-, di- or trisubstituted by Hal, A, OA, OH, NH_2, or NHA;

each A is independently an unbranched or branched linear or cyclic alkyl having 1, 2, 3, 4, 5 or 6 C atoms, wherein one or two CH_2 groups may be replaced by an O atom and/or an –NH-, -NHCOAr or –CONHAr group wherein 1-3 H atoms may be replaced by Hal, and wherein one or two CH_3 groups may be replaced by NH_2, OH, NH(LA) or $N(LA)_2$ group;

each LA is independently an unbranched or branched, linear alkyl having 1, 2, 3, or 4 C atoms wherein 1, 2 or 3 H atoms may be replaced by Hal; and

each Hal is independently F, Cl, Br or I.

2. The compound according to Claim 1, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, X is N and Y is N-R^5.

3. The compound according to claim 1. or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, wherein X is N; Y is N-R^5; R^5 and R^1 together form a monocyclic alkyl ring having 3, 4, 5, 6, or 7 ring atoms, wherein one or two CH_2 groups may be replaced by an –NH-, -NA-, -N(L^1-R^6)-, -CHA-, -CA_2-, -CH(L^1-R^6)-, or –CO- group, and wherein the monocyclic alkyl ring is optionally substituted by NH_2.

4. The compound according to Claim 1, wherein the compound is selected from the group consisting of:

5-((4-(4-(trifluoromethoxy)phenyl)pyrrolidin-3-yl)amino)quinazoline-8-carboxamide (trans_racemic),

5-((4-phenylpiperidin-3-yl)amino)quinazoline-8-carboxamide (trans_racemic),

5-((4-(3-fluoro-4-(trifluoromethyl)phenyl)piperidin-3-yl)amino)quinazoline-8-carboxamide(trans_racemic),

5-((-4-(3-(trifluoromethoxy)phenyl)pyrrolidin-3-yl)amino)quinoline-8-carboxamide (trans_racemic)
5-((4-(3-(trifluoromethyl)phenyl)pyrrolidin-3-yl)amino)quinazoline-8-carboxamide,
5-((4-(4-chloro-3-fluorophenyl)piperidin-3-yl)amino)quinazoline-8-carboxamide,
5-((4-(3-chloro-4-fluorophenyl)piperidin-3-yl)amino)quinazoline-8-carboxamide,
5-(((3R,4R)-4-(3-chloro-4-fluorophenyl)piperidin-3-yl)amino)quinazoline-8-carboxamide, and
5-((4-(4-fluorophenyl)piperidin-3-yl)amino)quinazoline-8-carboxamide,
or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios.

5. A pharmaceutical composition comprising a compound of claim 1, and/or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, as active ingredient, together with a pharmaceutically acceptable carrier.

6. A kit consisting of separate packs of an effective amount of a compound of claim 1 and/or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, and an effective amount of a further medicament active ingredient.

7. The compound according to claim 1, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, wherein, X is N; Y is N_R^5; and R^5 and R^1 together form a monocyclic alkyl ring having 4, 5 or 6 ring atoms, wherein one CH_2 group is replaced by an _N(L^1-R^6)_ group, and wherein the monocyclic alkyl ring is optionally substituted by NH_2.

8. The compound according to claim 1, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, wherein, X is N; Y is N_R^5; R^5 and R^1 together form a monocyclic alkyl ring having 4, 5 or 6 ring atoms, wherein one CH_2 group is replaced by an _N(L^1-R^6)_ group, and wherein the monocyclic alkyl ring is optionally substituted by NH_2; and L^1 is a bond, _CONH_, _NHCO_, _CONHCH$_2$_, or CH$_2$CONH_.

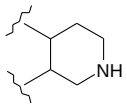
9. The compound according to claim 1, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, wherein, X is N; Y is N_R^5; R^5 and R^1 together form a monocyclic alkyl ring having 4, 5 or 6 ring atoms, wherein one CH_2 group is replaced by an _N(L^1-R^6)_ group, and wherein the monocyclic alkyl is optionally substituted by NH_2; and R^6 is phenyl, which is unsubstituted, or independently mono-, di- or trisubstituted by Hal, $C(Hal)_3$, CH_3, or $C(Hal)_3O$.

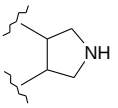
10. The compound according to claim 1, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, wherein, X is N; Y is N_R^5; R^5 and R^1 together form a monocyclic alkyl ring having 4, 5 or 6 ring atoms, wherein one CH_2 group is replaced by an _N(L^1-R^6)_ group, and wherein the monocyclic alkyl ring is optionally substituted by NH_2; L^1 is a bond, _CONH_, _NHCO_, _CONHCH$_2$_, or CH_2CONH_; and R^6 is phenyl, which is unsubstituted, or independently mono-, di- or trisubstituted by Hal, $C(Hal)_3$, CH_3, CH_3O, or $C(Hal)_3O$.

11. The compound according to claim 1, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, wherein, X is N; Y is NH; R^1 is L^1-R^6-L^2-R^7; L^1 and L^2 are a bond; R^6 is a monocyclic alkyl ring having 4, 5 or 6 ring atoms, wherein one CH_2 group is replaced by an _NH_, group; and R^7 is phenyl, which is unsubstituted, or independently mono-, di- or trisubstituted by Hal, $C(Hal)_3$, CH_3, CH_3O, or $C(Hal)_3O$.

12. The compound according to claim 1, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, wherein, X is N; Y is NH; R^1 is L^1-R^6-L^2-R^7; L^1 and L^2 are a bond; R^6 is piperidyl or pyrrolidinyl; and R^7 is phenyl, which is mono- or disubstituted by Hal, $C(Hal)_3$, CH_3, CH_3O, or $C(Hal)_3O$.

13. The compound according to claim 1, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, wherein, X is N; Y is NH; R^1 is L^1-R^6-L^2-R^7; L^1 and L^2 are a bond; R^6 is



or 

, and R^7 is phenyl, which is mono- or disubstituted by Hal, $C(Hal)_3$, CH_3, CH_3O, or $C(Hal)_3O$.