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(71) Applicant: AGENCY FOR SCIENCE, TECHNOLOGY AND RESEARCH [SG/SG]; 1 Fusionopolis Way, #20-10 Connexis North Tower, Singapore 138632 (SG).

(72) Inventor: NACRO, Kassoum; c/o Experimental Therapeutic Centre, 31 Biopolis Way, Nanos, #03-01, Singapore 138669 (SG).

(74) Agent: SPRUSON & FERGUSON (ASIA) PTE LTD; P.O. Box 1531, Robinson Road Post Office, Singapore 903031 (SG).

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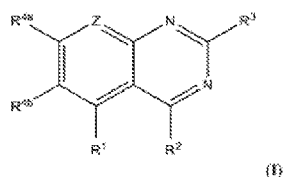
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(54) Title: GLYCINE METABOLISM MODULATORS AND USES THEREOF



(57) Abstract: The present invention relates to a compound of general formula (I) and/or its solvates, hydrates and pharmaceutically acceptable salts, which are modulators of glycine metabolism. The present invention also relates to the methods for their preparation, pharmaceutical compositions containing these compounds and uses of these compounds in the treatment of disorders/conditions/diseases involving, relating to or associated with glycine metabolism or a pathway where glycine decarboxylase (GLDC, or glycine cleavage system) plays a role. In a preferred embodiment the disorders/conditions/disease is cancer, inflammatory conditions, Alzheimer's disease, metabolic disorders and CNS disorders.



Description

Title of Invention: Glycine Metabolism Modulators and Uses Thereof

Technical Field

The present invention generally relates to quinazoline compounds as glycine metabolism modulators, a process for preparing the same, and its use as a medicament or in the treatment of diseases, disorders and conditions associated with glycine metabolism. The present invention also relates to the use of the compound in the preparation of a medicament for the treatment of diseases, disorders and conditions associated with glycine metabolism, a method of treating a disease, disorder or condition associated with glycine metabolism, and a pharmaceutical composition comprising the compound.

Background Art

The Warburg effect describes the condition whereby cancer cells exhibit an increased glycolysis, generally, in a poorly vascularized tumour microenvironment. This supports rapid proliferation by sustaining biosynthetic pathways that generate precursors for macromolecular synthesis, such as the pentose phosphate pathway in ribonucleotide production, the regeneration of nicotinamide adenine dinucleotide (NAD⁺) from reduced nicotinamide adenine dinucleotide (NADH) through pyruvate reduction into lactate, the serine-glycine biosynthetic pathway and one-carbon metabolism. In particular, the serine-glycine biosynthetic pathway and the glycine metabolism play a crucial role in DNA replication, and cancer cells are reprogrammed to hyperactivate this glycolytic shunt in driving oncogenesis.

Glycine decarboxylase an important component of the glycine metabolism, also known as glycine cleavage system P-protein or GLDC, is part of a system comprising a series of four enzymes found exclusively in the inner mitochondria of the cell. In plants and mammals, this system is triggered in response to high levels of glycine. GLDC is responsible for regulating levels of intracellular glycine by the degradation of glycine to release carbon dioxide and generate one-carbon units in the form of 5'-methylene tetrahydrofolate for serine and purine synthesis. GLDC dysfunction and its affected pathways manifest itself in a number of clinical pathologies. Deleterious mutations in components of the glycine cleavage system are associated with poor prognoses in newborns and infants due to glycine encephalopathy. Conversely, an overactive glycine cleavage system arising from gene duplications or triplications encoding GLDC, are reported in schizophrenic, psychotic and familial glioblastoma patients. The glycine cleavage system has been proposed as a target for pharmacological inhibition to treat psychosis and cancer.

In cancer, GLDC is found to be upregulated in tumor-initiating cells in non-small cell lung cancer patients, as well as other cancers, especially in ovarian and germ cell tumors. Clonal growth of these

tumour initiating cells was reduced with GLDC knockdown *in vitro* and in SCID mice. Molecular studies demonstrate that GLDC is sufficient in driving tumorigenesis in tumor-initiating cells from non-small cell lung cancer patients. Further studies reveal that sensitivity to GLDC inhibition in cancer cell lines was determined by the levels of GLDC's proximal enzyme, serine hydroxymethyltransferase 2 (SHMT2, mitochondrial form), suggesting dependencies within the glycine-serine pathways for cancer cell survival. A strong correlation has been reported between increased expression of genes coding for mitochondrial serine/glycine/folate metabolism (including GLDC) and lower IC₅₀ values for methotrexate, a clinical drug which interferes with folate metabolism. It is postulated that patients with this feature are likely to benefit from treatment with methotrexate. This raises the possibility that sub-population of cancers can be effectively treated with new molecule entities which can modulate an overactive serine-glycine-folate metabolism.

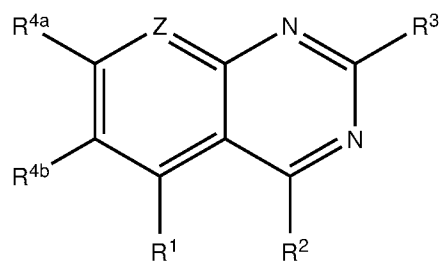
Levels of GLDC and its related enzymes in serine biosynthesis, one-carbon metabolism and the glycine cleavage system have been proposed as biomarkers to predict clinical outcomes in cancer. The high expression of GLDC observed in primary NSCLC tumors was shown to be significantly associated with a higher risk of patient mortality. Additionally, higher expression of enzymes in the glycine biosynthesis pathway has been found to be associated with greater mortality in six independent cohorts of early-stage breast cancer patients. GLDC expression levels has been found to vary between breast cancer sub-types; high GLDC levels in the tumor and stroma of HER-2-positive cancers as well as invasive lobular carcinoma, while levels of GLDC in triple negative breast cancers were found to be low.

In neurobiology, a clinical study of psychotic individuals with four copies of the GLDC gene were predicted to possess low glycine levels due to an overactive glycine cleavage system, resulting in N-methyl-D-aspartate receptor-mediated hypofunction. Treatment of these individuals with dietary glycine showed dramatic clinical improvements. A separate study revealed, to a high degree of significance, a single nucleotide polymorphism in the GLDC gene as a response biomarker to citalopram/escitalopram treatment for depression in a cohort of 512 patients suffering from major depressive disorder. These findings highlight GLDC as a potential target worth investigating for therapeutic intervention of psychological disorders. However, to-date, there have not been any known compounds that are effective for targeting GLDC and are efficient GLDC modulators.

There is therefore a need to provide a compound that overcomes or at least ameliorates, one or more of the disadvantages described above.

Summary

In an aspect, there is provided a compound of general formula (I) and/or its solvates, hydrates and pharmaceutically acceptable salts



(I)

wherein

Z represents N or C-R^{4c};

R¹ represents -Q¹-R⁶;

Q¹ represents a direct bond, -NH-, -C(O)-NH-, -C(O)-, alkynyl, alkenyl, or alkyl;

R² represents a group -Q³-R¹⁹, -N(R¹⁸)-Q²-COOH, -N(R¹⁸)-Q²-CN or -N(R¹⁸)-Q²-tetrazolyl;

Q³ represents a direct bond, -NH-, -N(R²⁰)- or -N(R²⁰)-alkyl-;

R¹⁹ represents optionally substituted cycloalkyl or optionally substituted non-aromatic heterocyclyl which has in each case 6 to 7 ring members and 1 to 3 heteroatoms selected from N, O or S and may be optionally benzo- or heteroaromatic-fused or may be optionally spirocyclic extended;

R²⁰ represents optionally substituted alkyl;

wherein R¹⁸ represents hydrogen, alkyl or cycloalkyl;

Q² represents a direct bond, alkyl, cycloalkyl, alkylcycloalkyl or cycloalkylalkyl;

R³ represents hydrogen, amino, alkyl, alkylthio, haloalkyl, nitro, alkylamino, dialkylamino, acyl or cyano;

R^{4a} and R^{4c} independently of each other represent hydrogen, amino, alkyl, alkoxy, alkylthio, halogen, haloalkyl, nitro, alkylamino, dialkylamino, acyl or cyano;

R^{4b} represents hydrogen, amino, alkyl, alkoxy, alkylthio, halogen, haloalkyl, nitro, alkylamino, dialkylamino, or acyl;

R⁶ represents an optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl or optionally substituted aromatic or non-aromatic heterocyclyl which is optionally heteroaryl- or aryl-fused.

Advantageously, the compound may be able to effectively target glycine cleavage system P-protein (GLDC). Further advantageously, this may in turn modulate levels of glycine metabolism, allowing for treatment of diseases, disorders or conditions associated with glycine metabolism. In particular, the compound having the structure of formula (I), due to specific structure-activity relationships

between the target receptor and the compound may be able to effectively interact with the receptor, and therefore modulate the activity of the target protein.

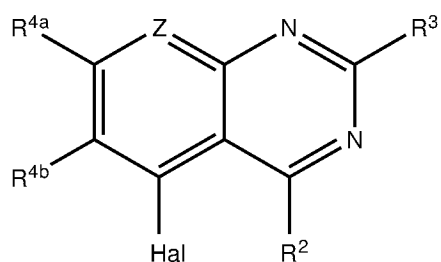
In an embodiment, the compound may comprise, at the R⁶ position, an optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl or optionally substituted aromatic or non-aromatic heterocyclyl which is optionally heteroaryl- or aryl-fused. Advantageously, this may, in combination with the structure of formula (I), further improve the structure-activity relationship between the compound and the target protein.

Further, advantageously each of the components within the molecule may be separately optimized in terms of position at which they are incorporated and substituents which they may have. This may in turn result in the modulation of the activity and physico-chemical properties of the compound. This suggests that the compounds may be modified accordingly so that it can be tailored to have different efficacy towards different targets for a variety of indications or applications.

Advantageously, the compounds are small with molecular weight of less than 500. Small size molecules may be less toxic and may have fewer occurrences of adverse drug effects while maintaining a high level of activity. Further advantageously, the compounds have planar chirality that may influence how the compounds interact and bind with the target protein.

In another aspect, there is provided a process for making a compound of formula (I) as defined herein wherein

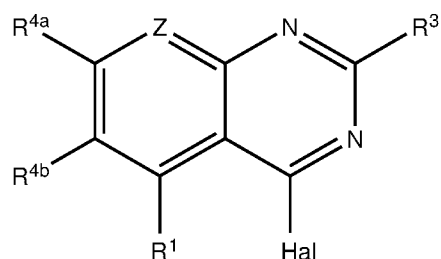
(a) a compound of formula (II),



(II)

wherein R², R³, R^{4a}, R^{4b} and Z are as defined herein and Hal represents halogen, preferably chlorine,

or a compound of formula (III),



(III)

wherein R^1 , R^3 , R^{4a} , R^{4b} and Z are as defined herein and Hal represents halogen, preferably chlorine, is reacted in an organic solvent in the presence of a base and optionally L-proline with an amine of formula (IV)

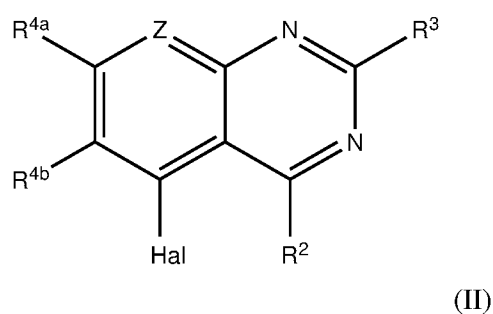
R^1 -H (IV)

or (IV)' respectively,

R^2 -H (IV)'

wherein R^1 and R^2 are as defined herein;

or (b) a compound of formula (II),



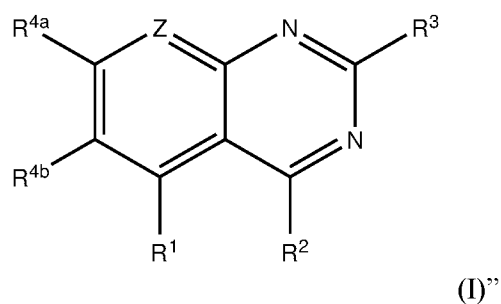
wherein R^2 , R^3 , R^{4a} , R^{4b} and Z are as defined herein and Hal represents halogen, preferably bromine,

is reacted in an organic solvent or organic solvent/water mixture in the presence of a base and a palladium catalyst with a boronic acid of formula (V),

R^1 -B(OH)₂ (V)

wherein R^1 is as defined herein;

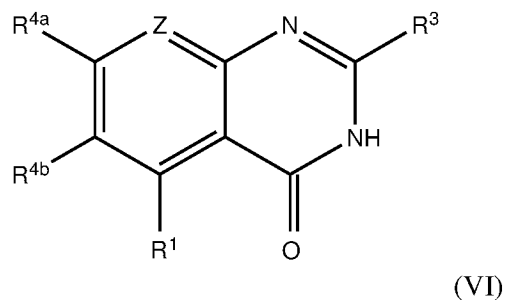
or (c) a compound of formula (I)'',



R^1 , R^2 , R^3 , R^{4a} , R^{4b} and Z are as defined herein and wherein R^2 carries a $-\text{COO}-\text{C}_1-\text{C}_3$ -alkyl or $-\text{SO}_2-\text{O}-\text{C}_1-\text{C}_3$ -alkyl ester group,

is converted in an organic solvent or organic solvent/water mixture in the presence of a base into an acid group carrying compound,

or (d) a compound of formula (VI),



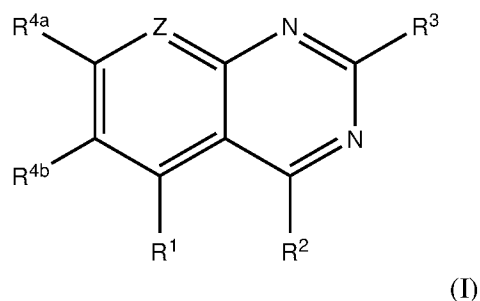
R^1 , R^3 , R^{4a} , R^{4b} and Z are as defined herein,

is reacted in the presence of a dehydrating agent, preferably phosphoryl chloride, with an amine of formula (IV),

R^2 -H (IV),

herein R^2 is as defined herein,

or (e) a compound of the formula (I),



wherein R^1 , R^2 , R^3 , R^{4a} , R^{4b} and Z are as defined herein and wherein R^2 is carrying a cyano group,

is reacted in an organic solvent optionally in the presence of an amine with a triazide, preferably an alkali metal triazide, and in all alternatives (a) to (e) the reaction product is isolated.

Advantageously, the process may provide a facile route to preparing the compounds as defined above. The synthesis may not require harsh reaction conditions or toxic reagents, and may be performed efficiently without the need of multiple purification steps. Advantageously, the process may also be suitable for large-scale synthesis of the compound as defined above.

In another aspect, there is provided a compound of formula (I) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof for use as a medicament.

Advantageously, the compound may still have the same advantages as discussed above, even in the form of pharmaceutically acceptable salts, hydrates or solvates.

In another aspect, there is provided a compound of formula (I) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof for use in the treatment of diseases, disorders and conditions associated with glycine metabolism.

In another aspect, there is provided a compound of formula (I) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof for use in the treatment of diseases, disorders and conditions which are selected from cancer, inflammation, Alzheimer's disease, metabolic disorders, neurological disorders and central nervous system disorders.

In another aspect, there is provided the use of a compound of formula (I) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof in the manufacture of a medicament for the treatment of a disease, disorder or condition associated with glycine metabolism.

In another aspect, there is provided a method of treating a disease, disorder or condition associated with glycine metabolism in a subject in need of such treatment, comprising administering to said subject a compound of formula (I) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof.

Advantageously, the compound or its pharmaceutically acceptable salts, hydrates or solvates thereof may be useful in the treatment of diseases, disorders and conditions associated with glycine metabolism, as the compound as defined above may be effective at modulating proteins involved in glycine and serine metabolism.

In particular, the compound or its pharmaceutically acceptable salts, hydrates or solvates thereof may be useful in the treatment of cancer, inflammation, Alzheimer's disease, metabolic disorders, neurological disorders and central nervous system disorders which are caused as a result of anomalies in glycine metabolism.

In another aspect, there is provided a pharmaceutical composition comprising a compound of formula (I) as defined above or pharmaceutically acceptable salts, hydrates and solvates thereof and a pharmaceutically acceptable excipient.

Advantageously, the pharmaceutical composition may have the same advantages as the compounds as defined above, even with a pharmaceutically acceptable excipient.

In another aspect, there is provided a pharmaceutical composition comprising a compound of formula (I) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof and a pharmaceutically acceptable excipient for treatment of a disease, disorder or condition associated with glycine metabolism.

Definitions

In this specification a number of terms are used which are well known to a skilled addressee. Nevertheless for the purposes of clarity a number of terms will be defined. The following words and terms used herein shall have the meaning indicated:

In the definitions of a number of substituents below it is stated that “the group may be a terminal group or a bridging group”. This is intended to signify that the use of the term is intended to encompass the situation where the group is a linker between two other portions of the molecule as well as where it is a terminal moiety. Using the term alkyl as an example, some publications would use the term “alkylene” for a bridging group and hence in these other publications there is a distinction between the terms “alkyl” (terminal group) and “alkylene” (bridging group). In the present application no such distinction is made and most groups may be either a bridging group or a terminal group.

"Acyl" refers to an R-C(=O)- group in which the R group may be an optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl or optionally substituted heteroaryl group as defined herein. Examples of acyl include acetyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the carbonyl carbon.

"Acylamino" refers to an R-C(=O)-NH- group in which the R group may be an alkyl, cycloalkyl, heterocycloalkyl; aryl or heteroaryl group as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

"Acyloxy" refers to an R-C(=O)-O- group in which the R group may be an alkyl, cycloalkyl, heterocycloalkyl; aryl or heteroaryl group as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

"Alkylcarbonyloxy" refers to an R-C(=O)-O- group in which the R group may be an alkyl; alkyl group as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

"Acylothio" refers to an R-C(=O)-SH- group in which the R group may be an alkyl, cycloalkyl, heterocycloalkyl; aryl or heteroaryl group as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the sulphur atom.

"Alkenyl" as a group or part of a group denotes an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched preferably having 2-12 carbon atoms, more preferably 2-10 carbon atoms, most preferably 2-6 carbon atoms, in the normal chain. The group may contain a plurality of double bonds in the normal chain and the orientation about each is independently E or Z. Exemplary alkenyl groups include, but are not limited to, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl and nonenyl. The group may be a terminal group or a bridging group.

"Alkanoyl" refers to an alkyl-C=O group in which alkyl is as defined herein. Preferred alkanoyl groups are C₁-C₆ alkanoyl groups. The group may be a terminal group or a bridging group.

If the group is a terminal group it is bonded to the remainder of the molecule through the carbon atom of the carbonyl group.

“Alkenoyl” refers to an alkenyl-C=O group in which alkenyl is as defined herein. Preferred alkenoyl groups are C₁-C₆ alkenoyl groups. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the carbon atom of the carbonyl group.

“Alkenyloxy” refers to an alkenyl-O- group in which alkenyl is as defined herein. Preferred alkenyloxy groups are C₁-C₆ alkenyloxy groups. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

“Alkenylamino” includes both mono-alkenylamino and dialkenylamino, unless specified. “Mono-alkenylamino” means a alkenyl-NH- group, in which alkenyl is as defined herein. “Dialkenylamino” means a (alkenyl)₂N- group, in which each alkenyl may be the same or different and are each as defined herein for alkenyl. The alkenyl group is preferably a C₁-C₆ alkenyl group with at least one carbon-carbon double bond and which may be straight or branched. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom. The term “alkenylamine” may be used when the group is a terminal group.

“Alkyl” as a group or part of a group refers to a straight or branched aliphatic hydrocarbon group, preferably a C₁-C₁₂ alkyl, more preferably a C₁-C₁₀ alkyl, most preferably C₁-C₆ unless otherwise noted. Examples of suitable straight and branched C₁-C₆ alkyl substituents include methyl, ethyl, n-propyl, 2-propyl, n-butyl, sec-butyl, t-butyl, hexyl, and the like. The group may be a terminal group or a bridging group.

“Alkylaryl” refers to an alkyl-aryl group in which alkyl and aryl moieties are as defined herein. Preferred alkenyloxy groups are C₁-C₄-alkylaryl having 6 or 10 carbon atoms in the aryl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the aryl group.

“Alkylamino” includes both mono-alkylamino and dialkylamino, unless specified. “Mono-alkylamino” means a alkyl-NH- group, in which alkyl is as defined herein. “Dialkylamino” means a (alkyl)₂N- group, in which each alkyl may be the same or different and are each as defined herein for alkyl. The alkyl group is preferably a C₁-C₆ alkyl group. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

“Alkylaminoalkyl” refers to an alkyl-N-alkyl group, in which each alkyl may be the same or different and are each as defined herein for alkyl. The alkyl group is preferably a C₁-C₆ alkyl group. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

"Alkyloxy" refers to an alkyl-O- group in which alkyl is as defined herein. Preferably the alkyloxy is a C₁-C₆alkyloxy. Examples include, but are not limited to, methoxy and ethoxy. The group may be a terminal group or a bridging group. The term alkyloxy may be used interchangeably with the term "alkoxy".

"Alkylloxycarbonyl" or "alkoxycarbonyl" refers to an alkyl-O-C(=O)- group in which alkyl is as defined herein. The alkyl group is preferably a C₁-C₆ alkyl group. Examples include, but are not limited to, methoxycarbonyl and ethoxycarbonyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the carbonyl carbon.

"Alkylsulfonyl" refers to an alkyl-S(=O)₂- group in which alkyl is as defined above. The alkyl group is preferably a C₁-C₆ alkyl group. Examples include, but not limited to methylsulfonyl and ethylsulfonyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the sulfur atom.

"Alkylsulfonyloxy" refers to an alkyl-S(=O)₂-O- group in which alkyl is as defined above. The alkyl group is preferably a C₁-C₆ alkyl group. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the sulfur atom.

"Alkylthio" refers to an alkyl-SH group in which alkyl is as defined above. The alkyl group is preferably a C₁-C₆ alkyl group. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the sulfur atom.

"Alkylthioalkyl" refers to alkyl-S-alkyl group in which alkyl group is as defined above. The alkyl group is preferably a C₁-C₆ alkyl group. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the carbon atom of an alkyl group.

"Alkynyl" as a group or part of a group means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched preferably having from 2-12 carbon atoms, more preferably 2-10 carbon atoms, more preferably 2-6 carbon atoms in the normal chain. Exemplary structures include, but are not limited to, ethynyl and propynyl. The group may be a terminal group or a bridging group.

"Alkinoyl" refers to an alkynyl-C=O group in which alkynyl is as defined herein. Preferred alkynyl groups are C₁-C₆ alkinoyl groups. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the carbon atom of the carbonyl group.

"Alkynylamino" or "alkynylamino" includes both mono-alkynylamino and dialkynylamino, unless specified. "Mono-alkynylamino" means a alkynyl-NH- group, in which alkynyl is as defined herein. "Dialkynylamino" means a (alkynyl)₂N- group, in which each alkynyl may be the same or different and are each as defined herein for alkynyl. The alkynyl group is preferably a C₁-C₆ alkynyl group containing a carbon-carbon triple bond and which may be straight or branched. The group may

be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

"Amino" refers to groups of the form $\text{-NR}_a\text{R}_b$ wherein R_a and R_b are individually selected from the group including but not limited to hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, and optionally substituted aryl groups.

"Aminoalkyl" means an NH_2 -alkyl- group in which the alkyl group is as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkyl group. The "alkylamine" may be interchangeably used.

"Aryl" as a group or part of a group denotes (i) an optionally substituted monocyclic, or fused polycyclic, aromatic carbocycle (ring structure having ring atoms that are all carbon) preferably having from 5 to 12 atoms per ring. Examples of aryl groups include phenyl, naphthyl, and the like; (ii) an optionally substituted partially saturated bicyclic aromatic carbocyclic moiety in which a phenyl and a C_{5-7} cycloalkyl or C_{5-7} cycloalkenyl group are fused together to form a cyclic structure, such as tetrahydronaphthyl, indenyl or indanyl. The group may be a terminal group or a bridging group. Typically an aryl group is a $\text{C}_6\text{-C}_{18}$ aryl group.

"Arylalkyl" or "alkylaryl" means an aryl-alkyl- group in which the aryl and alkyl moieties are as defined herein. Preferred arylalkyl groups contain a C_{1-5} alkyl moiety. Exemplary arylalkyl groups include benzyl, phenethyl, 1-naphthalenemethyl and 2-naphthalenemethyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkyl group.

A "bond" is a linkage between atoms in a compound or molecule. The bond may be a single bond, a double bond, or a triple bond.

"Cyanate" refers to an $\text{R-O-C}\equiv\text{N}$ group in which the R group may be alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group as defined herein. Examples of cyano include acetonitrile. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

"Cyano" refers to an R-CN group in which the R group may be alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group as defined herein. Examples of cyano include acetonitrile. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the carbon atom.

"Cyanoalkylheteroaryl" refers to a R-CN group in which the R group may be alkyl and heteroaryl moieties and as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the carbon atom.

"Cycloalkenyl" means a non-aromatic monocyclic or multicyclic ring system containing at least one carbon-carbon double bond and preferably having from 5-10 carbon atoms per ring. Exemplary monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl or cycloheptenyl.

The cycloalkenyl group may be substituted by one or more substituent groups. A cycloalkenyl group typically is a C₃-C₁₂ alkenyl group. The group may be a terminal group or a bridging group.

"Cycloalkyl" refers to a saturated monocyclic or fused or bridged or spiro polycyclic, carbocycle preferably containing from 3 to 9 carbons per ring, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, unless otherwise specified. It includes monocyclic systems such as cyclopropyl and cyclohexyl, bicyclic systems such as decalin, and polycyclic systems such as adamantane. A cycloalkyl group typically is a C₃-C₁₂ alkyl group. The group may be a terminal group or a bridging group.

"Cycloalkylalkyl" refers to a cycloalkyl-alkyl- group in which the cycloalkyl and alkyl moieties are as defined herein. Exemplary monocycloalkylalkyl groups include cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl and cycloheptylmethyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkyl group.

"Cycloalkylheteroaryl" refers to a cycloalkyl-heteroaryl- group in which the cycloalkyl and heteroaryl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the cycloalkyl group.

"Cycloalkyloxy" refers to a cycloalkyl-O- group in which cycloalkyl is as defined herein. Preferably the cycloalkyloxy is a C₁-C₆cycloalkyloxy. Examples include, but are not limited to, cyclopropanoxy and cyclobutanoxo. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

"Cycloalkenyloxy" refers to a cycloalkenyl-O- group in which the cycloalkenyl is as defined herein. Preferably the cycloalkenyloxy is a C₁-C₆cycloalkenyloxy. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

"Cycloamino" refers to a saturated monocyclic, bicyclic, or polycyclic ring containing at least one nitrogen in at least one ring. Each ring is preferably from 3 to 10 membered, more preferably 4 to 7 membered. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

"Haloalkyl" refers to an alkyl group as defined herein in which one or more of the hydrogen atoms has been replaced with a halogen atom selected from the group consisting of fluorine, chlorine, bromine and iodine. A haloalkyl group typically has the formula C_nH_(2n+1-m)X_m wherein each X is independently selected from the group consisting of F, Cl, Br and I. In groups of this type n is typically from 1 to 10, more preferably from 1 to 6, most preferably 1 to 3. m is typically 1 to 6, more preferably 1 to 3. Examples of haloalkyl include fluoromethyl, difluoromethyl and trifluoromethyl.

"Haloalkenyl" refers to an alkenyl group as defined herein in which one or more of the hydrogen atoms has been replaced with a halogen atom independently selected from the group consisting of F, Cl, Br and I.

“Haloalkynyl” or “haloalkinyl” refers to an alkynyl group as defined herein in which one or more of the hydrogen atoms has been replaced with a halogen atom independently selected from the group consisting of F, Cl, Br and I.

"Halogen" represents chlorine, fluorine, bromine or iodine.

“Haloheteroarylalkyl” refers to a heteroarylalkyl group as defined herein in which one or more of the hydrogen atoms has been replaced with a halogen atom independently selected from the group consisting of F, Cl, Br and I.

“Haloheterocycloalkyl” refers to a heterocycloalkyl group as defined herein in which one or more of the hydrogen atoms has been replaced with a halogen atom independently selected from the group consisting of F, Cl, Br and I.

“Haloalkoxy” refers to an alkoxy group as defined herein in which one or more of the hydrogen atoms has been replaced with a halogen atom independently selected from the group consisting of F, Cl, Br and I.

“Haloalkenyloxy” refers to an alkenyloxy group as defined herein in which one or more of the hydrogen atoms has been replaced with a halogen atom independently selected from the group consisting of F, Cl, Br and I.

“Heteroalkyl” refers to a straight- or branched-chain alkyl group preferably having from 2 to 12 carbons, more preferably 2 to 6 carbons in the chain, one or more of which has been replaced by a heteroatom selected from S, O, P and N. Exemplary heteroalkyls include alkyl ethers, secondary and tertiary alkyl amines, amides, alkyl sulfides, and the like. Examples of heteroalkyl also include hydroxyC₁-C₆alkyl, C₁-C₆alkyloxyC₁-C₆alkyl, aminoC₁-C₆alkyl, C₁-C₆alkylaminoC₁-C₆alkyl, and di(C₁-C₆alkyl)aminoC₁-C₆alkyl. The group may be a terminal group or a bridging group.

"Heteroalkyloxy" refers to an heteroalkyl-O- group in which heteroalkyl is as defined herein. Preferably the heteroalkyloxy is a C₁-C₆heteroalkyloxy. The group may be a terminal group or a bridging group.

"Heteroaryl" either alone or part of a group refers to groups containing an aromatic ring (preferably a 5 or 6 membered aromatic ring) having one or more heteroatoms as ring atoms in the aromatic ring with the remainder of the ring atoms being carbon atoms. The aromatic rings may be monocyclic, fused or bridged or spiro polycyclic ring fused with another aromatic ring (preferably a 5 or 6 membered aromatic ring). Suitable heteroatoms include nitrogen, oxygen and sulphur. Examples of heteroaryl include tetrazolyl, triazolyl, pyrimidinyl, pyrazinyl, thiophenyl, furanyl, indazolyl, benzoxazolyl, benzofuranyl, benzothiophenyl, indolyl, pyrrolyl, oxazolyl, pyrazolyl, thiazolyl, quinolinyl, imidazolyl, purinyl, oxadiazolonyl. A heteroaryl group is typically a C₁-C₁₈ heteroaryl group. A heteroaryl group may comprise 3 to 8 ring atoms. A heteroaryl group may comprise 1 to 3 heteroatoms independently selected from the group consisting of N, O and S. The group may be a terminal group or a bridging group.

"Heteroarylalkyl" or "alkylheteroaryl" means a heteroaryl-alkyl group in which the heteroaryl and alkyl moieties are as defined herein. Preferred heteroarylalkyl groups contain a lower alkyl moiety. Exemplary heteroarylalkyl groups include pyridylmethyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkyl group.

"Heteroarylalkenyl" means a heteroaryl-alkenyl- group in which the heteroaryl and alkenyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkenyl group.

"Heteroarylamino" refers to groups containing an aromatic ring (preferably 5 or 6 membered aromatic ring) having at least one nitrogen and at least another heteroatom as ring atoms in the aromatic ring, preferably from 1 to 3 heteroatoms in at least one ring. Suitable heteroatoms include nitrogen, oxygen and sulphur. Arylamino and aryl is as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

"Heterocyclic" or "heterocyclyl" refers to saturated, partially unsaturated or fully unsaturated monocyclic, bicyclic or polycyclic ring system containing at least one heteroatom selected from the group consisting of nitrogen, sulfur and oxygen as a ring atom. Examples of heterocyclic moieties include heterocycloalkyl, heterocycloalkenyl and heteroaryl.

"Heterocycloalkenyl" refers to a heterocycloalkyl as defined herein but containing at least one double bond. A heterocycloalkenyl group typically is a C₂-C₁₂ heterocycloalkenyl group. The group may be a terminal group or a bridging group.

"Heterocycloalkyl" refers to a saturated monocyclic, fused or bridged or spiro polycyclic ring containing at least one heteroatom selected from nitrogen, sulfur, oxygen, preferably from 1 to 3 heteroatoms in at least one ring. Each ring is preferably from 3 to 10 membered, more preferably 4 to 7 membered. Examples of suitable heterocycloalkyl substituents include pyrrolidinyl, piperidinyl, azepanyl, piperazinyl, dioxanyl, morpholinyl, pyrazolinidyl, morpholinyl, thiomorpholinyl, tetrahydropyridinyl, tetrahydropyrazolopyridine, oxotetrahydroquinolinyl, azabicycloheptanyl, azabicyclooctanyl, azaspirocyclooctanyl or dioxazaspirodecanyl. A heterocycloalkyl group typically is a C₂-C₁₂ heterocycloalkyl group. A heterocycloalkyl group may comprise 3 to 9 ring atoms. A heterocycloalkyl group may comprise 1 to 3 heteroatoms independently selected from the group consisting of N, O and S. The group may be a terminal group or a bridging group.

"Heterocycloalkylalkyl" refers to a heterocycloalkyl-alkyl- group in which the heterocycloalkyl and alkyl moieties are as defined herein. Exemplary heterocycloalkylalkyl groups include (2-tetrahydrofuryl)methyl, (2-tetrahydrothiofuranyl) methyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkyl group.

"Heterocycloalkylalkenyl" refers to a heterocycloalkyl-alkenyl- group in which the heterocycloalkyl and alkenyl moieties are as defined herein. The group may be a terminal group or a

bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkenyl group.

“Heterocycloalkylheteroaryl” means a heterocycloalkyl-heteroaryl- group in which the heterocycloalkyl and heteroaryl moieties are as defined herein. Exemplary heterocycloalkylheteroaryl groups include pyrrolopyridinyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the heteroalkyl group.

“Heterocycloalkylalkylaryl” refers to a heterocycloalkyl-alkyl-aryl- group in which the heterocycloalkyl, alkyl and aryl moieties are as defined herein. Preferably the heterocycloalkylalkylaryl is a C₆-C₁₂heterocycloalkylalkylaryl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the aryl group.

“Heterocycloalkyloxy” refers to a heterocycloalkyl-O- group in which the heterocycloalkyl is as defined herein. Preferably the heterocycloalkyloxy is a C₁-C₆heterocycloalkyloxy. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

“Heterocycloamino” refers to a saturated monocyclic, bicyclic, or polycyclic ring containing at least one nitrogen and at least another heteroatom selected from nitrogen, sulfur, oxygen, preferably from 1 to 3 heteroatoms in at least one ring. Each ring is preferably from 3 to 10 membered, more preferably 4 to 7 membered. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

“Hydroxyalkyl” refers to an alkyl group as defined herein in which one or more of the hydrogen atoms has been replaced with an OH group. A hydroxyalkyl group typically has the formula C_nH_(2n+1-x)(OH)_x. In groups of this type n is typically from 1 to 10, more preferably from 1 to 6, most preferably from 1 to 3. x is typically from 1 to 6, more preferably from 1 to 4.

“Nitro” refers to an R-NO₂ group in which the R group may be alkyl, cycloalkyl, heterocycloalkyl; aryl or heteroaryl group as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

“Nitroalkyl” refers to an R-NO₂ group in which the R group may be alkyl, as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

“Nitroalkenyl” refers to an R-NO₂ group in which the R group may be alkenyl, as defined herein. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

“Nitroalkinyl” or “nitroalkynyl” refers to an R-NO₂ group in which the R group may be alkynyl, as defined herein. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

“Nitroheterocyclyl” refers to an R-NO_2 group in which the R group may be heterocyclyl, as defined herein. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

“Patient,” as used herein, refers to an animal, preferably a mammal, and most preferably a human.

“Phosphinyl” refers to an -O-P(=O)(OH)_2 group. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

“Phosphono” refers to an R-P(=O)(OH)_2 group R group may be alkyl, cycloalkyl, heterocycloalkyl; aryl or heteroaryl group as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the phosphorus atom.

“Subject” refers to a human or an animal.

“Sulfonyl” means an R-S(=O)_2 - group in which the R group may be OH, alkyl, cycloalkyl, heterocycloalkyl; aryl or heteroaryl group as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the sulfur atom.

“Sulfonylamino” means an $\text{R-S(=O)}_2\text{-NH-}$ group. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

“Thio” means an R-SH group in which the R group may be alkyl, cycloalkyl, heterocycloalkyl; aryl or heteroaryl group as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the sulphur atom.

It is understood that included in the family of compounds of Formula (I) are isomeric forms including diastereoisomers, enantiomers, tautomers, and geometrical isomers in “E” or “Z” configurational isomer or a mixture of E and Z isomers. It is also understood that some of the isomeric forms including planar chirality compounds in “R” or “S” configuration. It is also understood that some isomeric forms such as diastereomers, enantiomers, and geometrical isomers can be separated by physical and/or chemical methods and by those skilled in the art.

Some of the compounds of the disclosed embodiments may exist as single stereoisomers, racemates, and/or mixtures of enantiomers and /or diastereomers. All such single stereoisomers, racemates and mixtures thereof, are intended to be within the scope of the subject matter described and claimed.

Additionally, Formula (I) is intended to cover, where applicable, solvated as well as unsolvated forms of the compounds. Thus, each formula includes compounds having the indicated structure, including the hydrated as well as the non-hydrated forms.

Further, it is possible that compounds of the invention may contain more than one asymmetric carbon atom. In those compounds, the use of a solid line to depict bonds to asymmetric carbon atoms is meant to indicate that all possible stereoisomers are meant to be included. The use of a solid line to depict bonds to one or more asymmetric carbon atoms in a compound of the invention and the use of a solid or dotted wedge to depict bonds to other asymmetric carbon atoms in the same compound is meant to indicate that a mixture of diastereomers is present.

The term “optionally substituted” as used herein means the group to which this term refers may be unsubstituted, or may be substituted with one or more groups independently selected from alkyl, hydroxyalkyl, aminoalkyl, alkenyl, alkynyl, thioalkyl, alkylthioalkyl, cycloalkyl, cycloalkenyl, five to six membered optionally benzo-fused heterocycloalkyl having 1 to 3 hetero atoms selected from N, O or S, C₆ or C₁₀-aryl, halogen, -COOH, -CONH₂, alkoxycarbonyl, haloalkyl, haloalkinyl, hydroxyl (OH), alkoxy, alkoxyalkyl, thioalkoxy, alkenyloxy, haloalkoxy, haloalkenyloxy, nitro, amino, nitroalkyl, nitroalkenyl, nitroalkinyl, five to six ring membered optionally benzo-fused nitro-heterocyclyl having 1 to 3 hetero atoms selected from N, O or S, alkylaminoalkyl, alkylamino, dialkylamino, alkenylamine, alkynylamino, acyl, alkenoyl, alkinoyl, acylamino, diacylamino, acyloxy, alkylsulfonyloxy, five to six ring membered optionally benzo-fused heterocyclylalkyl having 1 to 3 hetero atoms selected from N, O or S, five to six ring membered optionally benzo-fused heterocycliloxy having 1 to 3 hetero atoms selected from N, O or S, five to six ring membered optionally benzo-fused heterocyclylamino having 1 to 3 hetero atoms selected from N, O or S, five to six ring membered optionally benzo-fused haloheterocycloalkyl having 1 to 3 hetero atoms selected from N, O or S, alkylsulfonyl, alkylcarbonyloxy, alkylthio, acylthio, phosphorus-containing groups such as phosphono and phosphinyl, aryl having 6 to 10 carbon atoms, five to six ring membered optionally benzo-fused heteroaryl having 1 to 3 hetero atoms selected from N, O or S, C₁-C₄-alkylaryl having 6 or 10 carbon atoms in the aryl, five to six ring membered optionally benzo-fused C₁-C₆-alkylheteroaryl having 1 to 3 hetero atoms selected from N, O or S, cyano, cyanate, isocyanate, -C(O)NH(C₁-C₆-alkyl), -NH-C(O)-(C₁-C₆-alkyl), -C(O)N(C₁-C₆-alkyl)₂, -CH₂N(C₁-C₆-alkyl)₂, phenyl, naphthyl, cyclohexyl, cyclohexenyl, pyrrolopyridinyl, pyridinyl, pyrimidinyl, pyrazinyl, thiophenyl, furanyl, indazolyl, benzoxazolyl, benzofuranyl, benzothiophenyl, indolyl, pyrrolyl, oxazolyl, pyrazolyl, thiazolyl, quinolinyl, imidazolyl, purinyl, dioxanyl, morpholinyl, piperazinyl, piperidinyl, pyrrolidinyl, azepanyl, piperazinyl, pyrazolinidyl, morpholinyl, thiomorpholinyl, tetrahydropyridinyl, tetrahydropyrazolopyridine, oxotetrahydroquinolinyl, azabicycloheptanyl, azabicyclooctanyl, azaspirocyclooctanyl, dioxazaspirodecanyl, oxadiazolonyl, tetrazolyl,

Preferably, the alkyl is an optionally substituted C₁-C₆ alkyl, the alkenyl is an optionally substituted C₁-C₆ alkenyl, the alkynyl is a C₁-C₁₂ alkynyl, the thioalkyl is an optionally substituted C₁-C₆ thioalkyl comprising 1 or 2 sulfur atoms, the alkyloxy is an optionally substituted C₁-C₆ alkyl-O-group, the cycloalkyl is an optionally substituted C₃-C₉ cycloalkyl, the cycloalkylalkyl is an optionally substituted C₃ to C₉ cycloalkylalkyl, the cycloalkenyl is an optionally substituted C₃-C₉ cycloalkenyl, the heterocycloalkyl is an optionally substituted heterocycloalkyl having a ring atom number of 3 to 8 and having 1 to 3 heteroatoms independently selected from the group consisting of N, O and S, the

cycloalkoxy is an optionally substituted cycloalkoxy having a ring atom number of 3 to 8 and having 1 or 2 oxygen atoms, the cycloamino is an optionally substituted cycloamino having a ring atom number of 3 to 8 and having 1 or 2 nitrogen atoms, halo is selected from the group consisting of fluoro, chloro, bromo and iodo, haloalkyl is an optionally substituted C₁-C₆ haloalkyl having at least one halo group selected from the group consisting of fluoro, chloro, bromo and iodo, haloalkenyl is an optionally substituted C₁-C₆ haloalkenyl having at least one halo group selected from the group consisting of fluoro, chloro, bromo and iodo, haloalkynyl is an optionally substituted C₁-C₆ haloalkynyl having at least one halo group selected from the group consisting of fluoro, chloro, bromo and iodo, haloalkoxy is an optionally substituted C₁-C₆ haloalkoxy having at least one halo group selected from the group consisting of fluoro, chloro, bromo and iodo, haloalkenyloxy is an optionally substituted C₁-C₆ haloalkenyloxy having at least one halo group selected from the group consisting of fluoro, chloro, bromo and iodo, alkenyloxy is an optionally substituted C₁-C₆ alkenyloxy having at least one oxygen atom, heteroalkyl is an optionally substituted C₂-C₆ alkyl having a least one heteroatom selected from the group consisting of N, O, P and S, heteroalkyloxy is an optionally substituted C₂-C₆ alkyl having at least one oxygen atom and at least one other heteroatom selected from the group consisting of N, O, P and S, hydroxyalkyl is a substituted alkyl having the formula C_nH_(2n+1-x)(OH)_x where n is 1 to 10, haloalkenyloxy is an optionally substituted C₁-C₆ alkenyloxy having at least one oxygen atom and at least one other substituent selected from the group consisting of fluoro, chloro, bromo and iodo, the nitroalkyl is an optionally substituted C₁-C₆ alkyl having at least one nitro group, the nitroalkenyl is an optionally substituted C₁-C₆ alkenyl having at least one nitro group, the nitroalkynyl is an optionally substituted C₁-C₆ alkynyl having at least one nitro group, the nitroheterocyclyl is an optionally substituted heterocycloalkyl having a ring atom number of 3 to 8 and having 1 to 3 heteroatoms independently selected from the group consisting of N, O and S and having at least one nitro group, the optionally substituted aryl is an optionally substituted C₆-C₁₈ aryl, the cycloalkylheteroaryl is an optionally substituted heteroaryl having a ring atom number of 3 to 8 and having 1 to 3 heteroatoms independently selected from the group consisting of N, O and S and with C₁-C₆ cycloalkyl group, the heteroaryl is an optionally substituted heteroaryl having a ring atom number of 3 to 8 and having 1 to 3 heteroatoms independently selected from the group consisting of N, O and S, alkylamino is an optionally substituted alkyl-NH- group having a C₁-C₆ alkyl group, dialkylamino is an optionally substituted (alkyl)₂N- group having a C₁-C₆ alkyl group, alkylaminoalkyl is an optionally substituted alkyl-NH-alkyl group having a C₁-C₆ alkyl group, alkenylamine is an optionally substituted alkenyl-NH- group having a C₁-C₆ alkenyl group, alkynyl amino is an optionally substituted alkynyl-NH- group having a C₁-C₆ alkynyl group, alkyloxycarbonyl is a an optionally substituted C₁-C₁₆ alkyloxy having a carbonyl group, alkanoyl is an optionally substituted C₁-C₆ alkyl having a carbonyl group, alkenoyl is an optionally substituted C₁-C₆ alkenyl having a carbonyl group, alkynoyl is an optionally substituted C₁-C₆ alkynyl having a carbonyl group, acyl is an optionally substituted R-C(=O)- group in which the R group may be a C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl having 1 to 3 heteroatoms independently selected from the group consisting of N, O and S, acylamino is an optionally substituted R-C(=O)-NH- group in which the R group may be a C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl having 1 to 3 heteroatoms independently selected from the group consisting of N, O and S, aryl having a ring atom number of 3 to 8 or heteroaryl group having a ring atom number of 3 to 8 and having 1 to 3 heteroatoms independently selected from the group consisting of N, O and S, the acyloxy is a C₁-C₆ acyloxy, the alkylsulfonyloxy is an optionally substituted C₁-C₆ alkyl-O- group having at least one sulfonyl group,

the heterocycloalkylalkylaryl is a heterocycloalkylalkylaryl having a ring atom number of 3 to 8 and having 1 to 3 heteroatoms independently selected from the group consisting of N, O and S and C₁-C₆ alkyl group and C₁-C₆ aryl group, the heterocycloalkenyl is a heterocycloalkenyl having a ring atom number of 3 to 8 and having 1 to 3 heteroatoms independently selected from the group consisting of N, O and S, the heterocycloalkyl is a heterocycloalkyl having a ring atom number of 3 to 8 and having 1 to 3 heteroatoms independently selected from the group consisting of N, O and S, the heterocycloalkylalkyl is an optionally substituted C₃ to C₉ cycloalkylalkyl having 1 to 3 heteroatoms independently selected from the group consisting of N, O and S, the heterocycloalkylalkenyl is an optionally substituted C₃ to C₉ cycloalkylalkenyl having 1 to 3 heteroatoms independently selected from the group consisting of N, O and S, the heterocycloalkyloxy is an optionally substituted C₃ to C₉ cycloalkyl having 1 to 3 heteroatoms independently selected from the group consisting of N, O and S and an optionally substituted C₁-C₆ alkyl-O- group, the heterocycloamino is an optionally substituted heterocycloalkyl having a ring atom number of 3 to 8 and having 1 to 3 heteroatoms independently selected from the group consisting of N, O and S and an amino group, the haloheterocycloalkyl is an optionally substituted heterocycloalkyl having a ring atom number of 3 to 8 and having 1 to 3 heteroatoms independently selected from the group consisting of N, O and S and a halo group selected from the group consisting of fluoro, chloro, iodo and bromo, the alkylsulfonyl is an optionally substituted C₁-C₆ alkyl group having at least one sulfonyl group, the alkylcarbonyloxy is an optionally substituted C₁-C₆ alkyl group having at least one carbonyl group and at least one hydroxy group, the alkylthio is an optionally substituted C₁-C₆ alkyl group having at least one thiol group, alkylthioalkyl is an optionally substituted C₁-C₆ alkyl group having at least one thiol group and another C₁-C₆ alkyl group, the acylthio is R-C(=O)-S in which R group may be a C₁-C₆ alkyl, C₃-C₁₂ cycloalkyl, C₃-C₁₂ heterocycloalkyl having 1 to 3 heteroatoms independently selected from the group consisting of N, O and S, aryl having a ring atom number of 3 to 8 or heteroaryl group having a ring atom number of 3 to 8 and having 1 to 3 heteroatoms independently selected from the group consisting of N, O and S, the heteroarylalkyl or alkylheteroaryl is an optionally substituted heteroaryl having a ring atom number of 3 to 8 and having 1 to 3 heteroatoms independently selected from the group consisting of N, O and S and a C₁-C₁₂ alkyl, the heteroarylalkenyl is an optionally substituted heteroaryl having a ring atom number of 3 to 8 and having 1 to 3 heteroatoms independently selected from the group consisting of N, O and S and a C₁-C₁₂ alkenyl, the heteroarylamino is an optionally substituted heteroaryl having a ring atom number of 3 to 8 and having 1 to 3 heteroatoms independently selected from the group consisting of N, O and S and an amino group, the heteroaryloxy is an optionally substituted heteroaryl having a ring atom number of 3 to 8 and having at least one oxygen group, the arylalkyl or alkylaryl is an optionally substituted heteroaryl having a ring atom number of 3 to 8 and having 1 to 3 heteroatoms independently selected from the group consisting of N, O and S and a C₁-C₆ alkyl or the aryloxy is an optionally substituted heteroaryl having a ring atom number of 3 to 8 and having at least one oxygen atom.

The term "pharmaceutically acceptable salts" refers to salts that retain the desired biological activity of the above-identified compounds, and include pharmaceutically acceptable acid addition salts and base addition salts. Suitable pharmaceutically acceptable acid addition salts of compounds of Formula (I) may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, sulfuric, and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, heterocyclic carboxylic and sulfonic classes of

organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, fumaric, maleic, alkyl sulfonic, arylsulfonic. Additional information on pharmaceutically acceptable salts can be found in Remington's Pharmaceutical Sciences, 19th Edition, Mack Publishing Co., Easton, PA 1995. In the case of agents that are solids, it is understood by those skilled in the art that the inventive compounds, agents and salts may exist in different crystalline or polymorphic forms, all of which are intended to be within the scope of the present disclosure and specified formulae.

The term "therapeutically effective amount" or "effective amount" is an amount sufficient to effect beneficial or desired clinical results. An effective amount can be administered in one or more administrations. An effective amount is typically sufficient to palliate, ameliorate, stabilize, reverse, slow or delay the progression of the disease state.

The word "substantially" does not exclude "completely" e.g. a composition which is "substantially free" from Y may be completely free from Y. Where necessary, the word "substantially" may be omitted from the definition of the invention.

Unless specified otherwise, the terms "comprising" and "comprise", and grammatical variants thereof, are intended to represent "open" or "inclusive" language such that they include recited elements but also permit inclusion of additional, unrecited elements.

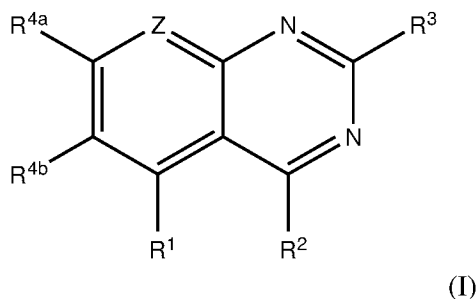
As used herein, the term "about", in the context of concentrations of components of the formulations, typically means $\pm 10\%$ of the stated value, more typically $\pm 7.5\%$ of the stated value, more typically $\pm 5\%$ of the stated value, more typically $\pm 4\%$ of the stated value, more typically $\pm 3\%$ of the stated value, more typically, $\pm 2\%$ of the stated value, even more typically $\pm 1\%$ of the stated value, and even more typically $\pm 0.5\%$ of the stated value.

Throughout this disclosure, certain embodiments may be disclosed in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the disclosed ranges. Accordingly, the description of a range should be considered to have specifically disclosed all the possible sub-ranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed sub-ranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

Certain embodiments may also be described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the disclosure. This includes the generic description of the embodiments with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

Detailed Description of Embodiments

The present disclosure provides a compound of general formula (I) and/or its solvates, hydrates and pharmaceutically acceptable salts



wherein

Z represents N or C-R^{4c};

R¹ represents -Q¹-R⁶;

Q¹ represents a direct bond, -NH-, -C(O)-NH-, -C(O)-, alkynyl, alkenyl, or alkyl;

R² represents a group -Q³-R¹⁹, -N(R¹⁸)-Q²-COOH, -N(R¹⁸)-Q²-CN or -N(R¹⁸)-Q²-tetrazolyl;

Q³ represents a direct bond, -NH-, -N(R²⁰)- or -N(R²⁰)-alkyl-;

R¹⁹ represents optionally substituted cycloalkyl or optionally substituted non-aromatic heterocyclyl which has in each case 6 to 7 ring members and 1 to 3 heteroatoms selected from N, O or S and may be optionally benzo- or heteroaromatic-fused or may be optionally spirocyclic extended;;

R²⁰ represents optionally substituted alkyl;

wherein R¹⁸ represents hydrogen, alkyl or cycloalkyl;

Q² represents a direct bond, alkyl, cycloalkyl, alkylcycloalkyl or cycloalkylalkyl;

R³ represents hydrogen, amino, alkyl, alkylthio, haloalkyl, nitro, alkylamino, dialkylamino, acyl or cyano;

R^{4a} and R^{4c} independently of each other represent hydrogen, amino, alkyl, alkoxy, alkylthio, halogen, haloalkyl, nitro, alkylamino, dialkylamino, acyl or cyano;

R^{4b} represents hydrogen, amino, alkyl, alkoxy, alkylthio, halogen, haloalkyl, nitro, alkylamino, dialkylamino, or acyl;

R⁶ represents an optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl or optionally substituted aromatic or non-aromatic heterocyclyl which is optionally heteroaryl- or aryl-fused.

In the compound of Formula (I), Q^1 may represent a single bond, -NH-, C₂-C₄-alkynyl, C₂-C₄-alkenyl, or C₁-C₆-alkyl. Q^1 may be C₂-alkynyl, C₂-C₃-alkenyl, or C₁-C₃-alkyl. Q^1 may represent a single bond or a -C≡C- group. Q^1 may be -C≡C-C≡C- group. Where R^6 exists, Q^1 is a single bond, that is R^6 is bonded directed to the quinazoline ring (in such instance, R^1 represents R^6).

R^6 may represent an optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl or optionally substituted aromatic or non-aromatic heterocyclyl which is optionally heteroaryl- or aryl-fused. R^6 may be a optionally substituted C₆ or C₁₀-aryl, optionally substituted C₃-C₈-cycloalkyl, optionally substituted C₃-C₈-cycloalkenyl or in each case optionally substituted and optionally heteroaryl- or benzo-fused, aromatic or non-aromatic heterocyclyl having in each case 5 to 7 ring members and 1 to 3 heteroatoms selected from N, O or S in the ring linked to Q^1 .

Where R^6 is an optionally substituted aryl, R^6 may represent an optionally substituted phenyl or naphthyl, optionally substituted cyclohexyl, optionally substituted cyclohexenyl, or in each case optionally substituted pyrrolopyridinyl, pyridinyl, pyrimidinyl, pyrazinyl, thiophenyl, furanyl, indazolyl, benzoxazolyl, benzofuranlyl, benzothiophenyl, indolyl, pyrrolyl, oxazolyl, pyrazolyl, thiazolyl, quinolinyl, imidazolyl, purinyl, dioxanyl, morpholinyl, piperazinyl or piperidinyl.

Where R^6 has one or more optional substituents, the one or more optional substituents of R^6 may be independently selected from C₁-C₆-alkyl, C₁-C₆-alkoxy, hydroxy-C₁-C₆-alkyl, amino-C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkinyl, thio-C₁-C₆-alkyl, C₁-C₄-alkyl-thio-C₁-C₄-alkyl, C₃-C₈-cycloalkyl, C₃-C₈-cycloalkenyl, optionally benzo- or heteroaryl-fused heterocycloalkyl having 5 to 7 ring members and 1 to 3 hetero atoms selected from N,O or S, C₆ or C₁₀-aryl, halogen, -COOH, -CONH₂, C₁-C₆-alkoxycarbonyl, halo-C₁-C₆-alkyl, halo-C₂-C₆-alkinyl, hydroxyl (OH), C₁-C₆-alkoxy, C₁-C₄-alkoxy-C₁-C₄-alkyl, thio-C₁-C₆-alkoxy, C₂-C₆-alkenyloxy, halo-C₁-C₆-alkoxy, halo-C₂-C₆-alkenyloxy, nitro, amino, nitro-C₁-C₆-alkyl, nitro-C₂-C₆-alkenyl, nitro-C₂-C₆-alkinyl, five to six ring membered optionally benzo-fused nitro-heterocycloalkyl having 5 to 7 ring members and 1 to 3 hetero atoms selected from N,O or S, C₁-C₄-alkylamino-C₁-C₄-alkyl, C₁-C₆-alkylamino, di-C₁-C₆-alkylamino, C₂-C₆-alkenylamino, C₂-C₆-alkinylamino, C₁-C₆-acyl, C₂-C₆-alkenoyl, C₂-C₆-alkinoyl, C₁-C₆-acylamino, di-C₁-C₆-acylamino, C₁-C₆-acyloxy, C₁-C₆-alkylsulfonyloxy, C₁-C₆-alkylsulfonyl, optionally benzo-fused heterocycloalkyl-C₁-C₄-alkyl having 5 to 7 ring members and 1 to 3 hetero atoms selected from N, O or S, optionally benzo-fused heterocycloalkyloxy having 5 to 7 ring members and 1 to 3 hetero atoms selected from N,O or S, optionally benzo-fused heterocycloalkylamino having 5 to 7 ring members and 1 to 3 hetero atoms selected from N,O or S, optionally benzo-fused halo-heterocycloalkyl having 5 to 7 ring members and 1 to 3 hetero atoms selected from N,O or S, C₁-C₆-alkylsulfonyl, C₁-C₆-alkylcarbonyloxy, C₁-C₆-alkylthio, C₁-C₆-acylthio, phosphorus-containing groups such as phosphono and phosphinyl, aryl having 6 to 10 carbon atoms, five to six ring membered optionally benzo-fused heteroaryl, C₁-C₄-alkylaryl having 6 or 10 carbon atoms in the aryl group, five to six ring membered optionally benzo-fused C₁-C₆-alkylheteroaryl having 5 to 7 ring members and 1 to 3 hetero atoms selected from N, O or S, cyano, cyanate, isocyanate, -C(O)NH(C₁-C₆-alkyl), -NH-C(O)-(C₁-C₆-alkyl), -C(O)N(C₁-C₆-alkyl)₂ or -CH₂N(C₁-C₆-alkyl)₂.

Specifically, the one or two optional substituents of R^6 may be selected from methyl, ethyl, propyl, butyl, C₁-C₃-alkoxy, hydroxy-C₁-C₆-alkyl, amino-C₁-C₃-alkyl, amino-carbonyl, C₂-C₄-alkenyl, C₂-C₃-

alkinyl, thio-C₁-C₃-alkyl, cyclopropyl, cyclopentyl, cyclohexyl, C₃-C₆-cyclohexenyl, C₃-C₆-cyclopentenyl, morpholinyl, phenyl, fluorine, chlorine, bromine, -COOH, -CONH₂, C₁-C₃-alkoxycarbonyl, fluoro-C₁-C₆-alkyl, chloro-C₁-C₆-alkyl, hydroxyl (-OH), methoxy, C₁-C₃-alkoxy-C₁-C₄-alkyl, fluoro-C₁-C₃-alkoxy, chloro-C₁-C₃-alkoxy, nitro, amino, C₁-C₃-alkylamino, di-(C₁-C₃-alkyl)amino, C₁-C₃-acylamino, di-C₁-C₃-acylamino, C₁-C₃-acyloxy, C₁-C₃-alkylsulfonyloxy, C₁-C₃-alkylsulfonyl, optionally methyl substituted piperazinyl-C₁-C₄-alkyl, optionally methyl substituted morpholinyl-C₁-C₄-alkyl, optionally methyl substituted piperidinyl C₁-C₄-alkyl, C₁-C₃-alkylsulfonyl, C₁-C₃-alkylcarbonyloxy, C₁-C₃-alkylthio, C₁-C₆-acylthio, phenyl, five to six ring membered optionally benzo-fused heteroaryl, C₁-C₃-alkylphenyl, cyano, -C(O)NH(C₁-C₆-alkyl), -NH-C(O)-(C₁-C₃-alkyl), -C(O)N(C₁-C₆-alkyl)₂ or -CH₂N(C₁-C₆-alkyl)₂.

Specifically, R⁶ may be independently selected from the group consisting of furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, 1*H*-pyrrol-2-yl, 1*H*-pyrrol-3-yl, 1-methyl-1*H*-pyrrol-2-yl, 1-methyl-1*H*-pyrrol-3-yl, 5-methylthiophen-2-yl, 4-methylthiophen-2-yl, 3-methylthiophen-2-yl, 5-chlorothiophen-2-yl, 4-chlorothiophen-2-yl, 3-chlorothiophen-2-yl, morpholino, 3-methylcyclohex-1-enyl, 4-methylcyclohex-1-enyl, 5-methylcyclohex-1-enyl, 5-chloropyridin-3-yl, 5-chloropyridin-4-yl, 5-chloropyridin-2-yl, 2-chloropyridin-3-yl, 4-chloropyridin-3-yl, 6-chloropyridin-3-yl, 5-methylpyridin-3-yl, 2-methylpyridin-3-yl, 4-methylpyridin-3-yl, 6-methylpyridin-3-yl, 5-methylpyridin-2-yl, 5-methylpyridin-4-yl, 5-methylpyridin-6-yl, pyridin-4-yl, pyridin-3-yl, pyridin-2-yl, 1*H*-pyrrolo[2,3-*b*]pyridin-4-yl, 1*H*-pyrrolo[2,3-*b*]pyridin-5-yl, 1*H*-pyrrolo[2,3-*b*]pyridin-6-yl, 1*H*-indazol-4-yl, 1*H*-indazol-5-yl, 1*H*-indazol-6-yl, 1*H*-indazol-7-yl, benzofuran-4-yl, benzofuran-5-yl, benzofuran-6-yl, benzofuran-7-yl, 4-chloronaphthalen-1-yl, 2-chloronaphthalen-1-yl, 3-chloronaphthalen-1-yl, 5-chloronaphthalen-1-yl, 6-chloronaphthalen-1-yl, 7-chloronaphthalen-1-yl, 8-chloronaphthalen-1-yl, 4-chloronaphthalen-2-yl, 4-chloronaphthalen-3-yl, naphthalen-2-yl, naphthalen-1-yl, naphthalen-3-yl, naphthalen-4-yl, naphthalen-5-yl, naphthalen-6-yl, naphthalen-7-yl, naphthalen-8-yl, benzo[*b*]thiophen-5-yl, benzo[*b*]thiophen-4-yl, benzo[*b*]thiophen-6-yl, benzo[*b*]thiophen-7-yl, phenylethynyl, phenylbuta-1,3-diyn-1-yl, piperidin-1-yl, 3-methylpiperidin-1-yl, 2-methylpiperidin-1-yl, 4-methylpiperidin-1-yl, 3,5-dimethylpiperidin-1-yl, 2,4-dimethylpiperidin-1-yl, phenyl, 4-isopropylphenyl, 2-isopropylphenyl, 3-isopropylphenyl, 3-cyclopropylphenyl, 4-cyclopropylphenyl, 2-cyclopropylphenyl, 3-(trifluoromethyl)phenyl, 2-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, 3-(1,1-difluoroethyl)phenyl, 2-(1,1-difluoroethyl)phenyl, 4-(1,1-difluoroethyl)phenyl, 3-chlorophenyl, 2-chlorophenyl, 4-chlorophenyl, meta-tolyl, para-tolyl, ortho-tolyl, 2-ethylphenyl, 3-ethylphenyl, 4-ethylphenyl, 3-fluorophenyl, 2-fluorophenyl, 4-fluorophenyl, 3-(hydroxymethyl)phenyl, 2-(hydroxymethyl)phenyl, 4-(hydroxymethyl)phenyl, 3-(aminomethyl)phenyl, 2-(aminomethyl)phenyl, 4-(aminomethyl)phenyl, 4-methoxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-hydroxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 3-(tert-butyl)phenyl, 2-(tert-butyl)phenyl, 4-(tert-butyl)phenyl, 1,1'-biphenyl]-3-yl, 1,1'-biphenyl]-2-yl, 1,1'-biphenyl]-4-yl, 3-cyanophenyl, 2-cyanophenyl, 4-cyanophenyl, 3-methoxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 3-carboxyphenyl, 2-carboxyphenyl, 4-carboxyphenyl, 3-((4-methylpiperazin-1-yl)methyl)phenyl, 2-((4-methylpiperazin-1-yl)methyl)phenyl, 4-((4-methylpiperazin-1-yl)methyl)phenyl, 3-(methylsulfonyl)phenyl, 2-(methylsulfonyl)phenyl, 4-(methylsulfonyl)phenyl, 3-(ethylsulfonyl)phenyl, 2-(ethylsulfonyl)phenyl, 4-(ethylsulfonyl)phenyl, 3-vinylphenyl, 2-vinylphenyl, 4-vinylphenyl, 3-nitrophenyl, 2-nitrophenyl, 4-nitrophenyl, 3-(morpholinomethyl)phenyl, 2-(morpholinomethyl)phenyl, 4-(morpholinomethyl)phenyl, 3-carbamoylphenyl, 2-carbamoylphenyl, 4-carbamoylphenyl, 3-

(piperazin-1-ylmethyl)phenyl, 2-(piperazin-1-ylmethyl)phenyl, 4-(piperazin-1-ylmethyl)phenyl, 3-(dimethylcarbamoyl)phenyl, 2-(dimethylcarbamoyl)phenyl, 4-(dimethylcarbamoyl)phenyl, 3-(methylcarbamoyl)phenyl, 2-(methylcarbamoyl)phenyl, 4-(methylcarbamoyl)phenyl, 3-aminophenyl, 2-aminophenyl, 4-aminophenyl, 3-(trifluoromethoxy)phenyl, 2-(trifluoromethoxy)phenyl, 4-(trifluoromethoxy)phenyl, 3-(dimethylamino)phenyl, 2-(dimethylamino)phenyl, 4-(dimethylamino)phenyl, 3-(methylamino)phenyl, 2-(methylamino)phenyl, 4-(methylamino)phenyl, 4-acetamidophenyl, 2-acetamidophenyl, 3-acetamidophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 4-chloro-3-hydroxyphenyl, 5-chloro-3-hydroxyphenyl, 3-chloro-5-(trifluoromethyl)phenyl, 3-chloro-4-(trifluoromethyl)phenyl, 4-chloro-3-(trifluoromethyl)phenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 4-cyano-3-fluorophenyl, 5-cyano-3-fluorophenyl, 3-cyano-4-fluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 4-chloro-3-methylphenyl, 5-chloro-3-methylphenyl, 3-chloro-4-methylphenyl, 4-chloro-3-ethylphenyl, 5-chloro-3-ethylphenyl, 3-chloro-4-ethylphenyl, 3-chloro-4-fluorophenyl, 3-chloro-5-fluorophenyl, 4-chloro-3-fluorophenyl, 3-fluoro-4-methylphenyl, 3-fluoro-5-methylphenyl, and 4-fluoro-3-methylphenyl.

R¹ may represent optionally substituted phenyl or optionally substituted piperidinyl which is bonded via the nitrogen ring atom. R¹ may represent phenyl which is 3,4-substituted or 3,5-substituted with halogen and/or C₁-C₃-alkyl.

Where R¹ represents an optionally substituted phenyl, there may be one substituent present on the phenyl. This substituent of R¹ may be selected from the group consisting of 4-isopropylphenyl, 2-isopropylphenyl, 3-isopropylphenyl, 3-cyclopropylphenyl, 4-cyclopropylphenyl, 2-cyclopropylphenyl, 3-(trifluoromethyl)phenyl, 2-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, 3-(1,1-difluoroethyl)phenyl, 2-(1,1-difluoroethyl)phenyl, 4-(1,1-difluoroethyl)phenyl, 3-chlorophenyl, 2-chlorophenyl, 4-chlorophenyl, meta-tolyl, para-tolyl, ortho-tolyl, 2-ethylphenyl, 3-ethylphenyl, 4-ethylphenyl, 3-fluorophenyl, 2-fluorophenyl, 4-fluorophenyl, 3-(hydroxymethyl)phenyl, 2-(hydroxymethyl)phenyl, 4-(hydroxymethyl)phenyl, 3-(aminomethyl)phenyl, 2-(aminomethyl)phenyl, 4-(aminomethyl)phenyl, 4-methoxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-hydroxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 3-(tert-butyl)phenyl, 2-(tert-butyl)phenyl, 4-(tert-butyl)phenyl, 1,1'-biphenyl]-3-yl, 1,1'-biphenyl]-2-yl, 1,1'-biphenyl]-4-yl, 3-cyanophenyl, 2-cyanophenyl, 4-cyanophenyl, 3-methoxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 3-carboxyphenyl, 2-carboxyphenyl, 4-carboxyphenyl, 3-((4-methylpiperazin-1-yl)methyl)phenyl, 2-((4-methylpiperazin-1-yl)methyl)phenyl, 4-((4-methylpiperazin-1-yl)methyl)phenyl, 3-(methylsulfonyl)phenyl, 2-(methylsulfonyl)phenyl, 4-(methylsulfonyl)phenyl, 3-(ethylsulfonyl)phenyl, 2-(ethylsulfonyl)phenyl, 4-(ethylsulfonyl)phenyl, 3-vinylphenyl, 2-vinylphenyl, 4-vinylphenyl, 3-nitrophenyl, 2-nitrophenyl, 4-nitrophenyl, 3-(morpholinomethyl)phenyl, 2-(morpholinomethyl)phenyl, 4-(morpholinomethyl)phenyl, 3-carbamoylphenyl, 2-carbamoylphenyl, 4-carbamoylphenyl, 3-(piperazin-1-ylmethyl)phenyl, 2-(piperazin-1-ylmethyl)phenyl, 4-(piperazin-1-ylmethyl)phenyl, 3-(dimethylcarbamoyl)phenyl, 2-(dimethylcarbamoyl)phenyl, 4-(dimethylcarbamoyl)phenyl, 3-(methylcarbamoyl)phenyl, 2-(methylcarbamoyl)phenyl, 4-(methylcarbamoyl)phenyl, 3-aminophenyl, 2-aminophenyl, 4-aminophenyl, 3-(trifluoromethoxy)phenyl, 2-(trifluoromethoxy)phenyl, 4-(trifluoromethoxy)phenyl, 3-(dimethylamino)phenyl, 2-(dimethylamino)phenyl, 4-(dimethylamino)phenyl, 3-(methylamino)phenyl, 2-(methylamino)phenyl, 4-(methylamino)phenyl, 4-acetamidophenyl, 2-acetamidophenyl, and 3-acetamidophenyl.

R¹ may represent phenyl which is 3,4-disubstituted or 3,5-disubstituted with halogen and/or C₁-C₃-alkyl wherein R¹ may be further independently selected from the group consisting of 3,4-dichlorophenyl, 3,5-dichlorophenyl, 4-chloro-3-hydroxyphenyl, 5-chloro-3-hydroxyphenyl, 3-chloro-5-(trifluoromethyl)phenyl, 3-chloro-4-(trifluoromethyl)phenyl, 4-chloro-3-(trifluoromethyl)phenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 4-cyano-3-fluorophenyl, 5-cyano-3-fluorophenyl, 3-cyano-4-fluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 4-chloro-3-methylphenyl, 5-chloro-3-methylphenyl, 3-chloro-4-methylphenyl, 4-chloro-3-ethylphenyl, 5-chloro-3-ethylphenyl, 3-chloro-4-ethylphenyl, 3-chloro-4-fluorophenyl, 3-chloro-5-fluorophenyl, 4-chloro-3-fluorophenyl, 3-fluoro-4-methylphenyl, 3-fluoro-5-methylphenyl, 4-fluoro-3-methylphenyl.

R¹ may represent optionally substituted piperidinyl which is bonded via the nitrogen ring atom wherein one or two optional substituents of R¹ may be further independently selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl, hexyl.

R² may represent -Q³-R¹⁹.

R² may represent a group -N(R¹⁸)-Q²-COOH, -N(R¹⁸)-Q²-CN or -N(R¹⁸)-Q²-tetrazolyl.

Q³ may represent a direct bond, -NH-, -N(R²⁰)- or -N(R²⁰)-alkyl-. Q³ may be a direct bond, -NH-, -N(R²⁰)- or -N(R²⁰)-C₁-C₃-alkyl.

R¹⁹ may represent optionally substituted cycloalkyl or optionally substituted heterocyclyl which may be optionally heteroaryl- or aryl-fused or may be spirocyclic extended. R¹⁹ may represent optionally substituted C₃-C₈-cycloalkyl or optionally substituted non-aromatic heterocyclyl which has in each case 6 to 7 ring members and 1 to 3 heteroatoms selected from N, O or S and may be optionally benzo- or heteroaromatic-fused or may be optionally spirocyclic extended.

Specifically, R¹⁹ may represent optionally substituted cycloalkyl or optionally substituted piperidinyl, tetrahydropyranyl, thianyl, silianyl, azepanyl, oxepanyl, thiepanyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, tetrahydro-1,3,5-triazinyl, trioxanyl, trihianyl, diazepanyl, tetrahydropyridinyl, tetrahydropyrazolopyridine, oxotetrahydroquinolinyl, azabicycloheptanyl, azabicyclooctanyl, azaspirocyclooctanyl, dioxazaspirodecanyl.

Specifically, R¹⁹ may represent optionally substituted cycloalkyl or optionally substituted piperidinyl, azepanyl, piperazinyl, tetrahydropyrazolopyridine, oxotetrahydroquinolinyl.

R¹⁹ may be unsubstituted or substituted by at least one substituent selected from cyano, C₁-C₆-alkyl, cyano, halo-C₁-C₃-alkyl, cyano, C₃-C₈-cycloalkyl, cyano, halo-C₁-C₃-alkyl, -COOH, -C₁-C₃-alkyl-C(O)-NH₂, C₃-C₈-cycloalkyl-COOH, halo-C₃-C₈-cycloalkyl-COOH, piperidinyl-COOH, cyano-C₃-C₈-cycloalkyl-COOH, -SO₂H, -SO₃H, hydroxyl (OH), hydroxy-C₁-C₆-alkyl, =O (Oxo), -COCOOH, -CH(OH)-COOH, =CH-COOH, C₁-C₆-alkyl-COOH, halo-C₁-C₆-alkyl-COOH, cyano-C₁-C₆-alkyl-COOH, amino-C₁-C₆-alkyl-COOH, C₂-C₆-alkenyl-COOH, C₂-C₆-alkinyl-COOH, C₁-C₆-alkyl-OH, C₁-C₆-alkoxy-C₁-C₆-alkyl, C₂-C₆-alkenyl-OH, C₁-C₆-alkyl-SH, C₂-C₆-alkenyl-SH, -C(O)-NH-OH, -C(O)-NH-NH₂, -C(O)-NH-S(O)₂-C₁-C₃-alkyl, tetrazolyl, triazolyl, imidazolyl, oxadiazolonyl, oxadiazolyl, C₁-C₃-alkyl-tetrazolyl, C₁-C₃-alkyl-triazolyl, C₁-C₃-alkyl-imidazolyl, C₁-C₃-alkyl-oxadiazolonyl, C₁-C₃-alkyl-oxadiazolyl, halo-C₁-C₃-alkyl-tetrazolyl, halo-C₁-C₃-alkyl-triazolyl, halo-

C₁-C₃-alkyl-imidazolyl-, halo-C₁-C₃-alkyl-oxadiazolonyl-, halo-C₁-C₃-alkyl-oxadiazolyl, C₃-C₈-cycloalkyl-tetrazolyl, -C₃-C₈-cycloalkyl-triazolyl, C₃-C₈-cycloalkyl-imidazolyl, C₃-C₈-cycloalkyl-oxadiazolonyl-, C₃-C₈-cycloalkyl-oxadiazolyl, -C(O)-NH-tetrazolyl, -C(O)-NH-triazolyl, -C(O)-NH-imidazolyl, -C(O)-NH-oxadiazolonyl, -C(O)-NH-oxadiazolyl, -N(C₁-C₃-alkyl)-C₁-C₃-alkyl-tetrazolyl, C₂-C₆-alkenyl-cyano, C₂-C₆-alkinyl-cyano, C₃-C₆-cycloalkyl-tetrazolyl, C₃-C₆-cycloalkyl-triazolyl, C₃-C₆-cycloalkyl-imidazolyl, C₃-C₆-cycloalkylalkyl-oxadiazolonyl, C₃-C₆-cycloalkyl-oxadiazolyl, -CO-NH-tetrazolyl, -CO-NH-triazolyl, -CO-NH-imidazolyl, -CO-NH-oxadiazolonyl, -CO-NH-oxadiazolyl, cyano-C₁-C₃-alkyl-tetrazolyl, cyano-C₁-C₃-alkyl-triazolyl, cyano-C₁-C₃-alkyl-imidazolyl, cyano-C₁-C₃-alkyl-oxadiazolonyl, cyano-C₁-C₃-alkyl-oxadiazolyl, heterocyclyl substituted C₁-C₃-alkyl-tetrazolyl, heterocyclyl substituted C₁-C₃-alkyl-triazolyl, heterocyclyl substituted C₁-C₃-alkyl-imidazolyl, heterocyclyl substituted C₁-C₃-alkyl-oxadiazolonyl, heterocyclyl substituted C₁-C₃-alkyl-oxadiazolyl, heterocyclyl substituted C₁-C₃-alkyl-cyano wherein the heterocyclyl substituent can be selected from a 4 to 6 membered heterocyclic ring having 1 to three hetero atoms selected from N, O and S.

R¹⁹ may be unsubstituted or substituted by at least one substituent selected from cyano, C₃-C₈-cycloalkyl-cyano, C₁-C₃-alkyl-cyano, halo-C₁-C₃-alkyl, -COOH, C₁-C₃-alkyl-C(O)-NH₂, C₃-C₈-cycloalkyl-COOH, halo-C₃-C₈-cycloalkyl-COOH, piperidiny-COOH, -SO₂H, -SO₃H, hydroxy-C₁-C₆-alkyl, hydroxyl (OH), -COCO₂H, -CH(OH)-COOH, =CH-COOH, C₁-C₆-alkyl-COOH, halo-C₁-C₆-alkyl-COOH, cyano-C₁-C₆-alkyl-COOH, amino-C₁-C₆-alkyl-COOH, C₂-C₆-alkenyl-COOH, C₂-C₆-alkinyl-COOH, C₁-C₆-alkyl-OH, C₁-C₆-alkyl-O-C₁-C₆-alkyl, C₂-C₆-alkenyl-OH, C₁-C₆-alkyl-SH, C₂-C₆-alkenyl-SH, -C(O)-NH-OH, -C(O)-NH-NH₂, -C(O)-NH-S(O)₂-C₁-C₃-alkyl, tetrazolyl, triazolyl, imidazolyl, oxadiazolonyl, oxadiazolyl, C₁-C₃-alkyl-tetrazolyl, C₁-C₃-alkyl-triazolyl, C₁-C₃-alkyl-imidazolyl, C₁-C₃-alkyl-oxadiazolonyl, C₁-C₃-alkyl-oxadiazolyl, halo-C₁-C₃-alkyl-tetrazolyl, halo-C₁-C₃-alkyl-triazolyl, halo-C₁-C₃-alkyl-imidazolyl, halo-C₁-C₃-alkyl-oxadiazolonyl, halo-C₁-C₃-alkyl-oxadiazolyl, -N(C₁-C₃-alkyl)-C₁-C₃-alkyl-tetrazolyl, or =O (Oxo).

R¹⁹ may be unsubstituted or substituted by at least one substituent selected from cyano, cyano-C₁-C₃-alkyl, halo-C₁-C₃-alkyl, -COOH, -CH(OH)-COOH, =CH-COOH, -C₃-C₈-cycloalkyl-COOH, -SO₃H, C₁-C₆-alkyl-COOH, -C(O)-NH-OH, tetrazolyl, oxadiazolonyl, tetrazolyl-C₁-C₃-alkyl.

R¹⁹ may have further optional additional substituents that may be selected from C₁-C₆-alkyl, C₁-C₄-alkoxy, C₁-C₃-alkyl-N(C₁-C₃-alkyl)₂, hydroxy-C₁-C₆-alkyl, amino-C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkinyl, thio-C₁-C₆-alkyl, C₁-C₄-alkyl-thio-C₁-C₄-alkyl, C₃-C₈-cycloalkyl, C₃-C₈-cycloalkenyl, five to six ring membered optionally benzo-fused heterocycloalkyl having 1 to 3 hetero atoms selected from N, O or S, C₆ or C₁₀-aryl, halogen, -COOH, -CONH₂, C₁-C₆-alkoxycarbonyl, halo-C₁-C₆-alkyl, halo-C₂-C₆-alkinyl, hydroxyl (OH), C₁-C₆-alkoxy, C₁-C₄-alkoxy-C₁-C₄-alkyl, thio-C₁-C₆-alkoxy, C₂-C₆-alkenyl, halo-C₁-C₆-alkoxy, halo-C₂-C₆-alkenyl, nitro, amino, nitro-C₁-C₆-alkyl, nitro-C₂-C₆-alkenyl, nitro-C₂-C₆-alkinyl, five to six ring membered optionally benzo-fused nitro-heterocyclyl having 1 to 3 hetero atoms selected from N, O or S, C₁-C₄-alkylamino-C₁-C₄-alkyl, C₁-C₆-alkylamino, di-C₁-C₆-alkylamino, C₂-C₆-alkenylamine, C₂-C₆-alkinylamine, C₁-C₆-acyl, C₂-C₆-alkenoyl, C₂-C₆-alkynoyl, C₁-C₆-acylamino, di-C₁-C₆-acylamino, C₁-C₆-acyloxy, C₁-C₆-alkylsulfonyloxy, five to six ring membered optionally benzo-fused heterocyclyl-C₁-C₄-alkyl having 1 to 3 hetero atoms selected from N, O or S, five to six ring membered optionally benzo-fused heterocycliloxy having 1 to 3 hetero atoms selected from N, O or S, five to six ring membered optionally benzo-fused

heterocyclamino having 1 to 3 hetero atoms selected from N, O or S, five to six ring membered optionally benzo- fused halo-heterocycloalkyl having 1 to 3 hetero atoms selected from N, O or S, C₁-C₆-alkylsulfonyl, C₁-C₆-alkylcarbonyloxy, C₁-C₆-alkylthio, C₁-C₆-acylthio, phosphorus-containing groups such as phosphono and phosphinyl, aryl having 6 or 10 carbon atoms, five to six ring membered optionally benzo-fused heteroaryl having 1 to 3 hetero atoms selected from N, O or S, C₁-C₄-alkylaryl having 6 or 10 carbon atoms in the aryl, five to six ring membered optionally benzo-fused C₁-C₆-alkylheteroaryl having 1 to 3 hetero atoms selected from N, O or S, cyano, cyanate, isocyanate, -C(O)NH(C₁-C₆-alkyl), -NH-C(O)-(C₁-C₆-alkyl), -C(O)N(C₁-C₆-alkyl)₂ -CH₂-N(C₁-C₆-alkyl)₂;

Where R¹⁹ has two substituents, the two substituents may form a C₁-C₄-alkyl bridge; or two substituents of R¹⁹ together may form a C₃-C₆-cycloalkyl-COOH group together with the ring to which they are bonded or may form a pyrazol group which is optionally substituted by C₁-C₃-alkyl, -COOH, cyano or C₃-C₆-cycloalkyl.

Where R¹⁹ has further optional additional one to two substituents, the further optional additional one to two substituents may be selected from C₁-C₆-alkyl, hydroxy-C₁-C₆-alkyl, amino-C₁-C₆-alkyl, amino-C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkinyl, thio-C₁-C₆-alkyl, C₁-C₄-alkyl-thio-C₁-C₄-alkyl, C₃-C₈-cycloalkyl, C₃-C₈-cycloalkenyl, five to six membered optionally benzo-fused heterocycloalkyl having 1 to 3 hetero atoms selected from N, O or S, C₆ or C₁₀-aryl, halogen, -COOH, -CONH₂, C₁-C₆-alkoxycarbonyl, halo-C₁-C₆-alkyl, halo-C₂-C₆-alkinyl, hydroxyl (OH), C₁-C₆-alkoxy, C₁-C₄-alkoxy-C₁-C₄-alkyl, thio-C₁-C₆-alkoxy, C₂-C₆-alkenyloxy, halo-C₁-C₆-alkoxy, halo-C₂-C₆-alkenyloxy, nitro, amino, nitro-C₁-C₆-alkyl, nitro-C₂-C₆-alkenyl, nitro-C₂-C₆-alkinyl, five to six ring membered optionally benzo-fused nitro-heterocyclyl having 1 to 3 hetero atoms selected from N, O or S, C₁-C₄-alkylamino-C₁-C₄-alkyl, C₁-C₆-alkylamino, di-C₁-C₆-alkylamino, C₂-C₆-alkenylamine, C₂-C₆-alkinylamino, C₁-C₆-acyl, C₂-C₆-alkenoyl, C₂-C₆-alkinoyl, C₁-C₆-acylamino, di-C₁-C₆-acylamino, C₁-C₆-acyloxy, C₁-C₆-alkylsulfonyloxy, five to six ring membered optionally benzo-fused heterocyclyl-C₁-C₄-alkyl having 1 to 3 hetero atoms selected from N, O or S, five to six ring membered optionally benzo-fused heterocycliloxy having 1 to 3 hetero atoms selected from N, O or S, five to six ring membered optionally benzo-fused heterocyclamino having 1 to 3 hetero atoms selected from N, O or S, five to six ring membered optionally benzo-fused halo-heterocycloalkyl having 1 to 3 hetero atoms selected from N, O or S, C₁-C₆-alkylsulfonyl, C₁-C₆-alkylcarbonyloxy, C₁-C₆-alkylthio, C₁-C₆-acylthio, phosphorus-containing groups such as phosphono and phosphinyl, aryl having 6 to 10 carbon atoms, five to six ring membered optionally benzo-fused heteroaryl having 1 to 3 hetero atoms selected from N, O or S, C₁-C₄-alkylaryl having 6 or 10 carbon atoms in the aryl, five to six ring membered optionally benzo-fused C₁-C₆-alkylheteroaryl having 1 to 3 hetero atoms selected from N, O or S, cyano, cyanate, isocyanate, -C(O)NH(C₁-C₆-alkyl), -NH-C(O)-(C₁-C₆-alkyl), -C(O)N(C₁-C₆-alkyl)₂, or -CH₂N(C₁-C₆-alkyl)₂.

Where R¹⁹ has further optional additional substituents, the further optional additional substituents may be independently selected from the group consisting of a methyl, ethyl, trifluoromethyl, hydroxyl (OH), amino or halogen; or

R¹⁹ may represent optionally substituted piperidinyl which is bonded via the nitrogen ring atom and carries at least one substituent in the 2-position, 3-position and/or 4-position of the ring selected from

cyano, cyano-C₁-C₃-alkyl, halo-C₁-C₃-alkyl, -COOH, -CH(OH)-COOH, =CH-COOH, -C₃-C₈-cycloalkyl-COOH, -SO₃H, C₁-C₆-alkyl-COOH, -C(O)-NH-OH, tetrazolyl, oxadiazolonyl, tetrazolyl-C₁-C₃-alkyl.

R¹⁹ may represent piperidinyl bond via its N-atom which is substituted in the 2-position, 3-position and/or 4-position with a -COOH, -(CH₂)_m-COOH or tetrazolyl and m represents 1, 2 or 3.

R¹⁹ may be selected from the group consisting of 1-piperidine-3-carboxylic acid, (*R*)-1-piperidine-3-carboxylic acid, (*S*)-1-piperidine-3-carboxylic acid, 1-piperidine-2-carboxylic acid, (*R*)-1-piperidine-2-carboxylic acid, (*S*)-1-piperidine-2-carboxylic acid, 1-piperidine-4-carboxylic acid, (*R*)-1-piperidine-4-carboxylic acid, (*S*)-1-piperidine-4-carboxylic acid, 3-(1*H*-tetrazol-5-yl)piperidin-1-yl, (*R*)-3-(1*H*-tetrazol-5-yl)piperidin-1-yl, (*S*)-3-(1*H*-tetrazol-5-yl)piperidin-1-yl, 2-(1*H*-tetrazol-5-yl)piperidin-1-yl, (*R*)-2-(1*H*-tetrazol-5-yl)piperidin-1-yl, (*S*)-2-(1*H*-tetrazol-5-yl)piperidin-1-yl, 4-(1*H*-tetrazol-5-yl)piperidin-1-yl, (*R*)-4-(1*H*-tetrazol-5-yl)piperidin-1-yl, (*S*)-4-(1*H*-tetrazol-5-yl)piperidin-1-yl, 5-(1*H*-tetrazol-5-yl)piperidin-1-yl, (*R*)-5-(1*H*-tetrazol-5-yl)piperidin-1-yl, (*S*)-5-(1*H*-tetrazol-5-yl)piperidin-1-yl, 6-(1*H*-tetrazol-5-yl)piperidin-1-yl, (*R*)-6-(1*H*-tetrazol-5-yl)piperidin-1-yl, (*S*)-6-(1*H*-tetrazol-5-yl)piperidin-1-yl, piperidine-3-carbonitrile, (*R*)-piperidine-3-carbonitrile, (*S*)-piperidine-3-carbonitrile, piperidine-2-carbonitrile, (*R*)-piperidine-2-carbonitrile, (*S*)-piperidine-2-carbonitrile, piperidine-4-carbonitrile, (*R*)-piperidine-4-carbonitrile, (*S*)-piperidine-4-carbonitrile, piperidine-5-carbonitrile, (*R*)-piperidine-5-carbonitrile, (*S*)-piperidine-5-carbonitrile, piperidine-6-carbonitrile, (*R*)-piperidine-6-carbonitrile, (*S*)-piperidine-6-carbonitrile, piperidin-4-one, piperidin-2-one, piperidin-3-one, piperidin-5-one, piperidin-6-one, 4-hydroxypiperidine-3-carboxylic acid, 2-hydroxypiperidine-3-carboxylic acid, 5-hydroxypiperidine-3-carboxylic acid, 6-hydroxypiperidine-3-carboxylic acid, 4-hydroxypiperidine-2-carboxylic acid, 4-hydroxypiperidine-5-carboxylic acid, 4-hydroxypiperidine-6-carboxylic acid, 2-piperidin-3-yl-2-methylpropanoic acid, (*R*)-2-piperidin-3-yl-2-methylpropanoic acid, (*S*)-2-piperidin-3-yl-2-methylpropanoic acid, 2-piperidin-2-yl-2-methylpropanoic acid, (*R*)-2-piperidin-2-yl-2-methylpropanoic acid, (*S*)-2-piperidin-2-yl-2-methylpropanoic acid, 2-piperidin-4-yl-2-methylpropanoic acid, (*R*)-2-piperidin-4-yl-2-methylpropanoic acid, (*S*)-2-piperidin-4-yl-2-methylpropanoic acid, (*E*)-2-(1-piperidin-3-ylidene)acetic acid, (*Z*)-2-(1-piperidin-3-ylidene)acetic acid, (*E*)-2-(1-piperidin-2-ylidene)acetic acid, (*Z*)-2-(1-piperidin-2-ylidene)acetic acid, (*E*)-2-(1-piperidin-4-ylidene)acetic acid, (*Z*)-2-(1-piperidin-4-ylidene)acetic acid, 1'-[1,4'-bipiperidine]-3-carboxylic acid, (*R*)-1'-[1,4'-bipiperidine]-3-carboxylic acid, (*S*)-1'-[1,4'-bipiperidine]-3-carboxylic acid, 1'-[1,4'-bipiperidine]-2-carboxylic acid, (*R*)-1'-[1,4'-bipiperidine]-2-carboxylic acid, (*S*)-1'-[1,4'-bipiperidine]-2-carboxylic acid, 1'-[1,4'-bipiperidine]-4-carboxylic acid, (*R*)-1'-[1,4'-bipiperidine]-4-carboxylic acid, (*S*)-1'-[1,4'-bipiperidine]-4-carboxylic acid, *trans*-6-methylpiperidine-3-carboxylic acid, *cis*-6-methylpiperidine-3-carboxylic acid, 6-methylpiperidine-2-carboxylic acid, 6-methylpiperidine-4-carboxylic acid, 6-methylpiperidine-5-carboxylic acid, 2-methylpiperidine-3-carboxylic acid, 4-methylpiperidine-3-carboxylic acid, 5-methylpiperidine-3-carboxylic acid, 2-(1-piperidin-3-yl)propanoic acid, 2-(1-piperidin-2-yl)propanoic acid, 2-(1-piperidin-4-yl)propanoic acid, 2-(5-methylpiperidin-3-yl)acetic acid, 2-(5-methylpiperidin-2-yl)acetic acid, 2-(5-methylpiperidin-4-yl)acetic acid, 2-(5-methylpiperidin-6-yl)acetic acid, 2-(2-methylpiperidin-3-yl)acetic acid, 2-(4-methylpiperidin-3-yl)acetic acid, 2-(6-methylpiperidin-3-yl)acetic acid, morpholine-2-carboxylic acid, (*R*)-morpholine-2-carboxylic acid, (*S*)-morpholine-2-carboxylic acid, morpholine-3-carboxylic acid, (*R*)-morpholine-3-carboxylic acid, (*S*)-morpholine-3-

carboxylic acid, 1-methylpiperazine-2-carboxylic acid, (*R*)-1-methylpiperazine-2-carboxylic acid, (*S*)-1-methylpiperazine-2-carboxylic acid, 1-methylpiperazine-3-carboxylic acid, (*R*)-1-methylpiperazine-3-carboxylic acid, (*S*)-1-methylpiperazine-3-carboxylic acid, 2-(1-piperidin-3-yl)-2-oxoacetic acid, (*R*)-2-(1-piperidin-3-yl)-2-oxoacetic acid, (*S*)-2-(1-piperidin-3-yl)-2-oxoacetic acid, 2-(1-piperidin-2-yl)-2-oxoacetic acid, (*R*)-2-(1-piperidin-2-yl)-2-oxoacetic acid, (*S*)-2-(1-piperidin-2-yl)-2-oxoacetic acid, 2-(1-piperidin-4-yl)-2-oxoacetic acid, (*R*)-2-(1-piperidin-4-yl)-2-oxoacetic acid, (*S*)-2-(1-piperidin-4-yl)-2-oxoacetic acid, 2-(1-piperidin-3-yl)-2-hydroxyacetic acid, (*R*)-2-(1-piperidin-3-yl)-2-hydroxyacetic acid, (*S*)-2-(1-piperidin-3-yl)-2-hydroxyacetic acid, 2-(1-piperidin-2-yl)-2-hydroxyacetic acid, (*R*)-2-(1-piperidin-2-yl)-2-hydroxyacetic acid, (*S*)-2-(1-piperidin-2-yl)-2-hydroxyacetic acid, 2-(1-piperidin-4-yl)-2-hydroxyacetic acid, (*R*)-2-(1-piperidin-4-yl)-2-hydroxyacetic acid, (*S*)-2-(1-piperidin-4-yl)-2-hydroxyacetic acid, 3-(2,2,2-trifluoroethyl)piperidin-1-yl, (*R*)-3-(2,2,2-trifluoroethyl)piperidin-1-yl, (*S*)-3-(2,2,2-trifluoroethyl)piperidin-1-yl, 2-(2,2,2-trifluoroethyl)piperidin-1-yl, (*R*)-2-(2,2,2-trifluoroethyl)piperidin-1-yl, (*S*)-2-(2,2,2-trifluoroethyl)piperidin-1-yl, 4-(2,2,2-trifluoroethyl)piperidin-1-yl, (*R*)-4-(2,2,2-trifluoroethyl)piperidin-1-yl, (*S*)-4-(2,2,2-trifluoroethyl)piperidin-1-yl, 3-3-azabicyclo[3.1.1]heptane-6-carboxylic acid, 3-3-azabicyclo[3.1.1]heptane-2-carboxylic acid, 2-(1-piperidin-4-yl)acetic acid, (*R*)-2-(1-piperidin-4-yl)acetic acid, (*S*)-2-(1-piperidin-4-yl)acetic acid, 2-(1-piperidin-2-yl)acetic acid, (*R*)-2-(1-piperidin-2-yl)acetic acid, (*S*)-2-(1-piperidin-2-yl)acetic acid, 2-(1-piperidin-3-yl)acetic acid, (*R*)-2-(1-piperidin-3-yl)acetic acid, (*S*)-2-(1-piperidin-3-yl)acetic acid, 5,5-difluoropiperidine-3-carboxylic acid, (*R*)-5,5-difluoropiperidine-3-carboxylic acid, (*S*)-5,5-difluoropiperidine-3-carboxylic acid, 5,5-difluoropiperidine-2-carboxylic acid, (*R*)-5,5-difluoropiperidine-2-carboxylic acid, (*S*)-5,5-difluoropiperidine-2-carboxylic acid, 5,5-difluoropiperidine-4-carboxylic acid, (*R*)-5,5-difluoropiperidine-4-carboxylic acid, (*S*)-5,5-difluoropiperidine-4-carboxylic acid, 5,5-difluoropiperidine-6-carboxylic acid, (*R*)-5,5-difluoropiperidine-6-carboxylic acid, (*S*)-5,5-difluoropiperidine-6-carboxylic acid, 2,2-difluoropiperidine-3-carboxylic acid, (*R*)-2,2-difluoropiperidine-3-carboxylic acid, (*S*)-2,2-difluoropiperidine-3-carboxylic acid, 4,4-difluoropiperidine-3-carboxylic acid, (*R*)-4,4-difluoropiperidine-3-carboxylic acid, (*S*)-4,4-difluoropiperidine-3-carboxylic acid, 6,6-difluoropiperidine-3-carboxylic acid, (*R*)-6,6-difluoropiperidine-3-carboxylic acid, (*S*)-6,6-difluoropiperidine-3-carboxylic acid, 2-(1-piperidin-4-ylidene)acetic acid, 2-(1-piperidin-3-ylidene)acetic acid, 2-(1-piperidin-2-ylidene)acetic acid, 2-(1-1,2,3,6-tetrahydropyridin-4-yl)acetic acid, 3-(trifluoromethyl)piperidin-1-yl, (*R*)-3-(trifluoromethyl)piperidin-1-yl, (*S*)-3-(trifluoromethyl)piperidin-1-yl, 2-(trifluoromethyl)piperidin-1-yl, (*R*)-2-(trifluoromethyl)piperidin-1-yl, (*S*)-2-(trifluoromethyl)piperidin-1-yl, 4-(trifluoromethyl)piperidin-1-yl, (*R*)-4-(trifluoromethyl)piperidin-1-yl, (*S*)-4-(trifluoromethyl)piperidin-1-yl, 8-azabicyclo[3.2.1]octane-2-carboxylic acid, 8-azabicyclo[3.2.1]octane-3-carboxylic acid, piperidin-3-ol, (*R*)-piperidin-3-ol, (*S*)-piperidin-3-ol, piperidin-2-ol, (*R*)-piperidin-2-ol, (*S*)-piperidin-2-ol, piperidin-4-ol, (*R*)-piperidin-4-ol, (*S*)-piperidin-4-ol, piperidin-3-yl-methanol, (*R*)-piperidin-3-yl-methanol, (*S*)-piperidin-3-yl-methanol, piperidin-2-yl-methanol, (*R*)-piperidin-2-yl-methanol, (*S*)-piperidin-2-yl-methanol, piperidin-4-yl-methanol, (*R*)-piperidin-4-yl-methanol, (*S*)-piperidin-4-yl-methanol, 1,4-dioxo-8-azaspiro[4.5]decane-6-carboxylic acid, 1,4-dioxo-8-azaspiro[4.5]decane-7-carboxylic acid, 2-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)acetic acid, 5-4,5,6,7-tetrahydro-2*H*-pyrazolo[4,3-*c*]pyridine-3-carboxylic acid, piperidine-3-carbohydrazide, (*R*)-piperidine-3-carbohydrazide, (*S*)-piperidine-3-carbohydrazide, piperidine-2-carbohydrazide, (*R*)-piperidine-2-carbohydrazide, (*S*)-piperidine-2-carbohydrazide, piperidine-4-

carbohydrazide, (*R*)-piperidine-4-carbohydrazide, (*S*)-piperidine-4-carbohydrazide, 5-(1-piperidin-3-yl-1,3,4-oxadiazol-2(3H)-one), (*R*)-5-(1-piperidin-3-yl-1,3,4-oxadiazol-2(3H)-one), (*S*)-5-(1-piperidin-3-yl-1,3,4-oxadiazol-2(3H)-one), 5-(1-piperidin-2-yl-1,3,4-oxadiazol-2(3H)-one), (*R*)-5-(1-piperidin-2-yl-1,3,4-oxadiazol-2(3H)-one), (*S*)-5-(1-piperidin-2-yl-1,3,4-oxadiazol-2(3H)-one), 5-(1-piperidin-4-yl-1,3,4-oxadiazol-2(3H)-one), (*R*)-5-(1-piperidin-4-yl-1,3,4-oxadiazol-2(3H)-one), (*S*)-5-(1-piperidin-4-yl-1,3,4-oxadiazol-2(3H)-one), azepane-4-carboxylic acid, (*R*)-azepane-4-carboxylic acid, (*S*)-azepane-4-carboxylic acid, azepane-2-carboxylic acid, (*R*)-azepane-2-carboxylic acid, (*S*)-azepane-2-carboxylic acid, azepane-3-carboxylic acid, (*R*)-azepane-3-carboxylic acid, (*S*)-azepane-3-carboxylic acid, N-(methylsulfonyl)piperidine-3-carboxamide, (*R*)-N-(methylsulfonyl)piperidine-3-carboxamide, (*S*)-N-(methylsulfonyl)piperidine-3-carboxamide, N-(methylsulfonyl)piperidine-2-carboxamide, (*R*)-N-(methylsulfonyl)piperidine-2-carboxamide, (*S*)-N-(methylsulfonyl)piperidine-2-carboxamide, N-(methylsulfonyl)piperidine-4-carboxamide, (*R*)-N-(methylsulfonyl)piperidine-4-carboxamide, (*S*)-N-(methylsulfonyl)piperidine-4-carboxamide, piperidine-3-sulfonic acid, (*R*)-piperidine-3-sulfonic acid, (*S*)-piperidine-3-sulfonic acid, piperidine-2-sulfonic acid, (*R*)-piperidine-2-sulfonic acid, (*S*)-piperidine-2-sulfonic acid, piperidine-4-sulfonic acid, (*R*)-piperidine-4-sulfonic acid, (*S*)-piperidine-4-sulfonic acid, N-hydroxypiperidine-3-carboxamide, (*R*)-N-hydroxypiperidine-3-carboxamide, (*S*)-N-hydroxypiperidine-3-carboxamide, N-hydroxypiperidine-2-carboxamide, (*R*)-N-hydroxypiperidine-2-carboxamide, (*S*)-N-hydroxypiperidine-2-carboxamide, N-hydroxypiperidine-4-carboxamide, (*R*)-N-hydroxypiperidine-4-carboxamide, (*S*)-N-hydroxypiperidine-4-carboxamide, 3-(1-piperidin-3-yl)propanoic acid, (*R*)-3-(1-piperidin-3-yl)propanoic acid, (*S*)-3-(1-piperidin-3-yl)propanoic acid, 3-(1-piperidin-2-yl)propanoic acid, (*R*)-3-(1-piperidin-2-yl)propanoic acid, (*S*)-3-(1-piperidin-2-yl)propanoic acid, 3-(1-piperidin-4-yl)propanoic acid, (*R*)-3-(1-piperidin-4-yl)propanoic acid, (*S*)-3-(1-piperidin-4-yl)propanoic acid, 2-(1-piperidin-3-yl)acetonitrile, (*R*)-2-(1-piperidin-3-yl)acetonitrile, (*S*)-2-(1-piperidin-3-yl)acetonitrile, 2-(1-piperidin-2-yl)acetonitrile, (*R*)-2-(1-piperidin-2-yl)acetonitrile, (*S*)-2-(1-piperidin-2-yl)acetonitrile, 2-(1-piperidin-4-yl)acetonitrile, (*R*)-2-(1-piperidin-4-yl)acetonitrile, (*S*)-2-(1-piperidin-4-yl)acetonitrile, 3-((1*H*-tetrazol-5-yl)methyl)piperidin-1-yl, (*R*)-3-((1*H*-tetrazol-5-yl)methyl)piperidin-1-yl, (*S*)-3-((1*H*-tetrazol-5-yl)methyl)piperidin-1-yl, 2-((1*H*-tetrazol-5-yl)methyl)piperidin-1-yl, (*R*)-2-((1*H*-tetrazol-5-yl)methyl)piperidin-1-yl, (*S*)-2-((1*H*-tetrazol-5-yl)methyl)piperidin-1-yl, 4-((1*H*-tetrazol-5-yl)methyl)piperidin-1-yl, (*R*)-4-((1*H*-tetrazol-5-yl)methyl)piperidin-1-yl, (*S*)-4-((1*H*-tetrazol-5-yl)methyl)piperidin-1-yl, 3-cyclohexanecarboxylic acid, (*R*)-3-cyclohexanecarboxylic acid, (*S*)-3-cyclohexanecarboxylic acid, 2-cyclohexanecarboxylic acid, (*R*)-2-cyclohexanecarboxylic acid, (*S*)-2-cyclohexanecarboxylic acid, 4-cyclohexanecarboxylic acid, (*R*)-4-cyclohexanecarboxylic acid, (*S*)-4-cyclohexanecarboxylic acid, 3-(methylamino)cyclohexane-1-carboxylic acid, 2-(methylamino)cyclohexane-1-carboxylic acid, 4-(methylamino)cyclohexane-1-carboxylic acid, 3-propanoic acid, 4-butanoic acid, 5-pentanoic acid, 6-hexanoic acid, 3-(methylamino)propanoic acid, 4-(methylamino)butanoic acid, 5-(methylamino)pentanoic acid, 6-(methylamino)hexanoic acid, 4-hydroxypiperidine-3-carboxylic acid, 4-hydroxypiperidine-2-carboxylic acid, 2-hydroxypiperidine-3-carboxylic acid, 5-hydroxypiperidine-3-carboxylic acid, 6-hydroxypiperidine-3-carboxylic acid, 5,5-difluoropiperidine-3-carbonitrile, (*R*)-5,5-difluoropiperidine-3-carbonitrile, (*S*)-5,5-difluoropiperidine-3-carbonitrile, 5,5-difluoropiperidine-2-carbonitrile, (*R*)-5,5-difluoropiperidine-2-carbonitrile, (*S*)-5,5-difluoropiperidine-2-carbonitrile, 5,5-difluoropiperidine-4-carbonitrile, (*R*)-5,5-difluoropiperidine-4-carbonitrile, (*S*)-5,5-difluoropiperidine-4-carbonitrile, 5,5-difluoropiperidine-6-carbonitrile, (*R*)-5,5-difluoropiperidine-6-carbonitrile, (*S*)-5,5-difluoropiperidine-6-carbonitrile, 2,2-difluoropiperidine-3-carbonitrile, (*R*)-2,2-difluoropiperidine-3-

carbonitrile, (S)-2,2-difluoropiperidine-3-carbonitrile, 4,4-difluoropiperidine-3-carbonitrile, (R)-4,4-difluoropiperidine-3-carbonitrile, (S)-4,4-difluoropiperidine-3-carbonitrile, 6,6-difluoropiperidine-3-carbonitrile, (R)-6,6-difluoropiperidine-3-carbonitrile, (S)-6,6-difluoropiperidine-3-carbonitrile, 3,3-difluoro-5-(1*H*-tetrazol-5-yl)piperidin-1-yl, (R)-3,3-difluoro-5-(1*H*-tetrazol-5-yl)piperidin-1-yl, (S)-3,3-difluoro-5-(1*H*-tetrazol-5-yl)piperidin-1-yl, 3,3-difluoro-2-(1*H*-tetrazol-5-yl)piperidin-1-yl, (R)-3,3-difluoro-2-(1*H*-tetrazol-5-yl)piperidin-1-yl, (S)-3,3-difluoro-2-(1*H*-tetrazol-5-yl)piperidin-1-yl, 3,3-difluoro-4-(1*H*-tetrazol-5-yl)piperidin-1-yl, (R)-3,3-difluoro-4-(1*H*-tetrazol-5-yl)piperidin-1-yl, (S)-3,3-difluoro-4-(1*H*-tetrazol-5-yl)piperidin-1-yl, 3,3-difluoro-6-(1*H*-tetrazol-5-yl)piperidin-1-yl, (R)-3,3-difluoro-6-(1*H*-tetrazol-5-yl)piperidin-1-yl, (S)-3,3-difluoro-6-(1*H*-tetrazol-5-yl)piperidin-1-yl, 2,2-difluoro-5-(1*H*-tetrazol-5-yl)piperidin-1-yl, (R)-2,2-difluoro-5-(1*H*-tetrazol-5-yl)piperidin-1-yl, (S)-2,2-difluoro-5-(1*H*-tetrazol-5-yl)piperidin-1-yl, 4,4-difluoro-5-(1*H*-tetrazol-5-yl)piperidin-1-yl, (R)-4,4-difluoro-5-(1*H*-tetrazol-5-yl)piperidin-1-yl, (S)-4,4-difluoro-5-(1*H*-tetrazol-5-yl)piperidin-1-yl, 6,6-difluoro-5-(1*H*-tetrazol-5-yl)piperidin-1-yl, (R)-6,6-difluoro-5-(1*H*-tetrazol-5-yl)piperidin-1-yl, (S)-6,6-difluoro-5-(1*H*-tetrazol-5-yl)piperidin-1-yl, 5-azaspiro[2.5]octane-1-carboxylic acid, 1-(piperidin-3-yl)cyclopropane-1-carboxylic acid, 1-(piperidin-2-yl)cyclopropane-1-carboxylic acid, 1-(piperidin-4-yl)cyclopropane-1-carboxylic acid, N-(2-(1*H*-tetrazol-5-yl)ethyl), N-(3-(1*H*-tetrazol-5-yl)propyl), N-(4-(1*H*-tetrazol-5-yl)butyl), N-(5-(1*H*-tetrazol-5-yl)pentyl), N-(6-(1*H*-tetrazol-5-yl)hexanyl), N-methyl-2-(1*H*-tetrazol-5-yl)ethyl-amine, 2-cyano-2-(piperidin-3-yl)acetic acid, 2-cyano-2-(piperidin-2-yl)acetic acid, 2-cyano-2-(piperidin-4-yl)acetic acid, N-(1*H*-tetrazol-5-yl)piperidine-3-carboxamide, (R)-N-(1*H*-tetrazol-5-yl)piperidine-3-carboxamide, (S)-N-(1*H*-tetrazol-5-yl)piperidine-3-carboxamide, N-(1*H*-tetrazol-5-yl)piperidine-2-carboxamide, (R)-N-(1*H*-tetrazol-5-yl)piperidine-2-carboxamide, (S)-N-(1*H*-tetrazol-5-yl)piperidine-2-carboxamide, N-(1*H*-tetrazol-5-yl)piperidine-4-carboxamide, (R)-N-(1*H*-tetrazol-5-yl)piperidine-4-carboxamide, (S)-N-(1*H*-tetrazol-5-yl)piperidine-4-carboxamide, 2-(piperidin-3-yl)acetamide, (R)-2-(piperidin-3-yl)acetamide, (S)-2-(piperidin-3-yl)acetamide, 2-(piperidin-2-yl)acetamide, (R)-2-(piperidin-2-yl)acetamide, (S)-2-(piperidin-2-yl)acetamide, 2-(piperidin-4-yl)acetamide, (R)-2-(piperidin-4-yl)acetamide, (S)-2-(piperidin-4-yl)acetamide, 3-(methoxymethyl)piperidin-1-yl, (R)-3-(methoxymethyl)piperidin-1-yl, (S)-3-(methoxymethyl)piperidin-1-yl, 2-(methoxymethyl)piperidin-1-yl, (R)-2-(methoxymethyl)piperidin-1-yl, (S)-2-(methoxymethyl)piperidin-1-yl, 4-(methoxymethyl)piperidin-1-yl, (R)-4-(methoxymethyl)piperidin-1-yl, (S)-4-(methoxymethyl)piperidin-1-yl, 6-ethylpiperidine-3-carboxylic acid, 6-ethylpiperidine-2-carboxylic acid, 6-ethylpiperidine-4-carboxylic acid, 6-ethylpiperidine-5-carboxylic acid, 2-ethylpiperidine-3-carboxylic acid, 4-ethylpiperidine-3-carboxylic acid, 5-ethylpiperidine-3-carboxylic acid, 2-(6-methylpiperidin-3-yl)acetonitrile, 2-(5-methylpiperidin-3-yl)acetonitrile, 2-(4-methylpiperidin-3-yl)acetonitrile, 2-(2-methylpiperidin-3-yl)acetonitrile, 2-(6-methylpiperidin-2-yl)acetonitrile, 2-(6-methylpiperidin-4-yl)acetonitrile, 2-(6-methylpiperidin-5-yl)acetonitrile, 2-(piperidin-3-yl)-2-(1*H*-tetrazol-5-yl)acetonitrile, (R)-2-((R)-piperidin-3-yl)-2-(1*H*-tetrazol-5-yl)acetonitrile, (S)-2-((R)-piperidin-3-yl)-2-(1*H*-tetrazol-5-yl)acetonitrile, (R)-2-((S)-piperidin-3-yl)-2-(1*H*-tetrazol-5-yl)acetonitrile, (S)-2-((S)-piperidin-3-yl)-2-(1*H*-tetrazol-5-yl)acetonitrile, 3-(1*H*-1,2,3-triazol-5-yl)piperidin-1-yl, (R)-3-(1*H*-1,2,3-triazol-5-yl)piperidin-1-yl, (S)-3-(1*H*-1,2,3-triazol-5-yl)piperidin-1-yl, 2-(1*H*-1,2,3-triazol-5-yl)piperidin-1-yl, (R)-2-(1*H*-1,2,3-triazol-5-yl)piperidin-1-yl, (S)-2-(1*H*-1,2,3-triazol-5-yl)piperidin-1-yl, 4-(1*H*-1,2,3-triazol-5-yl)piperidin-1-yl, (R)-4-(1*H*-1,2,3-triazol-5-yl)piperidin-1-yl, (S)-4-(1*H*-1,2,3-triazol-5-yl)piperidin-1-yl, 3-(4*H*-1,2,4-triazol-3-yl)piperidin-1-yl, (R)-3-(4*H*-1,2,4-triazol-3-yl)piperidin-1-yl, (S)-3-(4*H*-1,2,4-triazol-3-yl)piperidin-1-yl, 2-(4*H*-1,2,4-triazol-3-yl)piperidin-1-yl, (R)-2-(4*H*-1,2,4-

triazol-3-yl)piperidin-1-yl, (S)-2-(4*H*-1,2,4-triazol-3-yl)piperidin-1-yl, 4-(4*H*-1,2,4-triazol-3-yl)piperidin-1-yl, (R)-4-(4*H*-1,2,4-triazol-3-yl)piperidin-1-yl and (S)-4-(4*H*-1,2,4-triazol-3-yl)piperidin-1-yl.

R²⁰ may represent optionally substituted alkyl. R²⁰ may be C₁-C₃-alkyl optionally substituted with halogen, hydroxyl, or cyano;

R¹⁸ may represent hydrogen, alkyl or cycloalkyl. R¹⁸ may represent hydrogen, optionally C₃-C₇-cycloalkyl-substituted C₁-C₄-alkyl, C₃-C₇-cycloalkyl or a 4 to 6 membered heterocyclic ring having 1 to three hetero atoms selected from N, O and S. R¹⁸ may represent hydrogen or methyl.

Q² may represent a direct bond, alkyl, cycloalkyl, alkylcycloalkyl or cycloalkylalkyl. Q² may represent a direct bond, C₁-C₄-alkyl, C₃-C₇-cycloalkyl, C₁-C₄-alkyl-C₃-C₇-cycloalkyl or C₃-C₇-cycloalkyl-C₁-C₄-alkyl. Q² may represent a direct bond, C₁-C₄-alkyl, C₃-C₇-cycloalkyl-, C₁-C₄-alkyl-C₃-C₇-cycloalkyl- or C₃-C₇-cycloalkyl-C₁-C₄-alkyl-. Q² may represent methyl, ethyl, propyl, butyl, pentyl or hexyl.

R³ may represent hydrogen, amino, alkyl, alkylthio, haloalkyl, nitro, alkylamino, dialkylamino, acyl or cyano;

R³ may represent hydrogen, amino, methyl, ethyl, propyl, C₁-C₃-alkylthio, halo- C₁-C₃-alkyl, nitro, C₁-C₃-alkylamino, di-C₁-C₃-alkylamino, C₁-C₃-acyl or cyano;

R^{4a} and R^{4c} independently of each other may represent hydrogen, amino, alkyl, alkoxy, alkylthio, halogen, haloalkyl, nitro, alkylamino, dialkylamino, acyl or cyano;

R^{4a} and R^{4c} independently of each other may represent hydrogen, amino, methyl, ethyl, propyl, C₁-C₃-alkoxy, C₁-C₃-alkylthio, halogen, halo- C₁-C₃-alkyl, nitro, C₁-C₃-alkylamino, di-C₁-C₃-alkylamino, C₁-C₃-acyl or cyano;

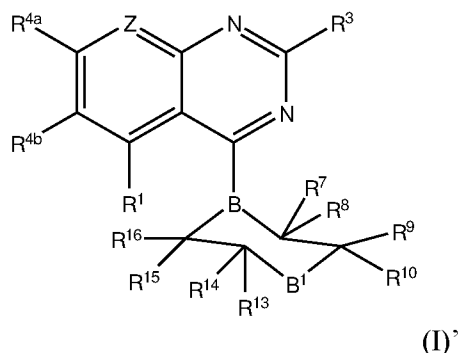
R^{4b} may represent hydrogen, amino, alkyl, alkoxy, alkylthio, halogen, haloalkyl, nitro, alkylamino, dialkylamino, or acyl;

R^{4b} may represent hydrogen, amino, methyl, ethyl, propyl, C₁-C₃-alkoxy, C₁-C₃-alkylthio, halogen, halo- C₁-C₃-alkyl, nitro, C₁-C₃-alkylamino, di-C₁-C₃-alkylamino or C₁-C₃-acyl;

R³ may represent hydrogen, methyl or amino.

R^{4a}, R^{4b} and R^{4c} independently of each other may represent hydrogen, methyl, methoxy or fluorine.

The compound may have the following formula (I) as represented by formula (I)'



wherein R^1 , R^3 , R^{4a} , R^{4b} and Z are as defined above and

B^1 may represent O, S, NR^{21} , CH_2CHR^{11} , $C=O$ or $CR^{11}R^{12}$;

B may represent N, CH or CR^{17} , preferably N;

R^7 , R^8 , R^9 , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} independently from another may represent hydrogen, $-COOH$, C_1-C_3 -alkyl- $-COOH$, fluorine, chlorine, hydroxyl ($-OH$), C_1-C_3 -alkyl-O- C_1-C_3 -alkyl-, C_1-C_3 -alkyl- $N(C_1-C_3$ -alkyl) $_2$, C_1-C_3 -alkyl- $-OH$, or C_1-C_4 -alkyl; and

R^{10} may represent hydrogen, cyano, halogen, C_1-C_3 -alkyl-cyano, halo- C_1-C_3 -alkyl-cyano, halo- C_1-C_3 -alkyl-, $-NHCOO-C_1-C_3$ -alkyl-, $-COOH$, $-COCOOH$, $-CH(OH)-COOH$, $=CH-COOH$, C_3-C_8 -cycloalkyl- $-COOH$, $-NHSO_2-C_1-C_3$ -alkyl-, $-SO_2H$, $-SO_3H$, C_1-C_6 -alkyl- $-COOH$, halo- C_1-C_6 -alkyl- $-COOH$, halo- C_1-C_6 -alkyl- $-COOH$, C_2-C_6 -alkenyl- $-COOH$, C_2-C_6 -alkinyl- $-COOH$, C_1-C_6 -alkyl- $-OH$, C_2-C_6 -alkenyl- $-OH$ -, C_1-C_6 -alkyl- $-SH$, C_2-C_6 -alkenyl- $-SH$, $-C(O)-NH-OH$, C_1-C_6 -alkinyl- $-COOH$, tetrazolyl, triazolyl, imidazolyl, oxadiazolonyl, oxadiazolyl, C_1-C_3 -alkyl-tetrazolyl, C_1-C_3 -alkyl-triazolyl, C_1-C_3 -alkyl-imidazolyl, C_1-C_3 -alkyl-oxadiazolonyl, C_1-C_3 -alkyl-oxadiazolyl, halo- C_1-C_3 -alkyl-tetrazolyl, halo- C_1-C_3 -alkyl-triazolyl, halo- C_1-C_3 -alkyl-imidazolyl, halo- C_1-C_3 -alkyl-oxadiazolonyl, halo- C_1-C_3 -alkyl-oxadiazolyl, C_1-C_6 -alkyl-CN, halo- C_1-C_6 -alkyl-CN, C_3-C_8 -cycloalkyl-CN, halo- C_1-C_6 -alkyl-CN, C_2-C_6 -alkenyl-CN, C_2-C_6 -alkinyl-CN, C_3-C_6 -cycloalkyl-tetrazolyl, C_3-C_6 -cycloalkyl-triazolyl, C_3-C_6 -cycloalkyl-imidazolyl, C_3-C_6 -cycloalkylalkyl-oxadiazolonyl, C_3-C_6 -cycloalkyl-oxadiazolyl, $-CO-NH$ -tetrazolyl, $-CO-NH$ -triazolyl, $-CO-NH$ -imidazolyl, $-CO-NH$ -oxadiazolonyl, $-CO-NH$ -oxadiazolyl, cyano- C_1-C_3 -alkyl-tetrazolyl, cyano- C_1-C_3 -alkyl-triazolyl, cyano- C_1-C_3 -alkyl-imidazolyl, cyano- C_1-C_3 -alkyl-oxadiazolonyl, cyano- C_1-C_3 -alkyl-oxadiazolyl, heterocyclyl substituted C_1-C_3 -alkyl-tetrazolyl, heterocyclyl substituted C_1-C_3 -alkyl-triazolyl, heterocyclyl substituted C_1-C_3 -alkyl-imidazolyl, heterocyclyl substituted C_1-C_3 -alkyl-oxadiazolonyl, heterocyclyl substituted C_1-C_3 -alkyl-oxadiazolyl, heterocyclyl substituted C_1-C_3 -alkyl-cyano wherein the heterocyclyl substituent can be selected from a 4 to 6 membered heterocyclic ring having 1 to three hetero atoms selected from N, O and S;

R^{10} may be selected from the group consisting of $-COOH$, hydroxyl ($-OH$), tetrazolyl, cyano, 2-methylpropanoic acid, propanoic acid, acetic acid, 2-oxoacetic acid, 2-hydroxyacetic acid, 1,1,1-trifluoroethyl, trifluoromethyl, methanol, formohydrazide, 1,3,4-oxadiazol-2(3*H*)-one, *N*-(methylsulfonyl)formamide, sulfonic acid, *N*-hydroxyformamide, 5-methyl-1*H*-tetrazole, fluorine, acetonitrile, cyclopropane-carboxylic acid, 2-cyanoacetic acid, *N*-(1*H*-tetrazol-5-yl)formamide, acetamide, methoxymethyl,

or R⁹ and R¹⁰ together may form a C₃-C₆-cycloalkyl-COOH group together with the ring to which they are bonded or form a pyrazol group which is optionally substituted by C₁-C₃-alkyl, COOH, cyano or C₃-C₆-cycloalkyl;

or R¹¹ and R¹² together may represent a -O-CH₂-CH₂-O- spirocyclic moiety;

or two substituents of R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶ and R¹⁷ may form a C₁-C₃-alkyl bridge which may be substituted with -COOH, wherein C₁-C₃-alkyl bridge may comprise of C₁-C₃-alkyl group;

R²¹ may represent hydrogen or alkyl.

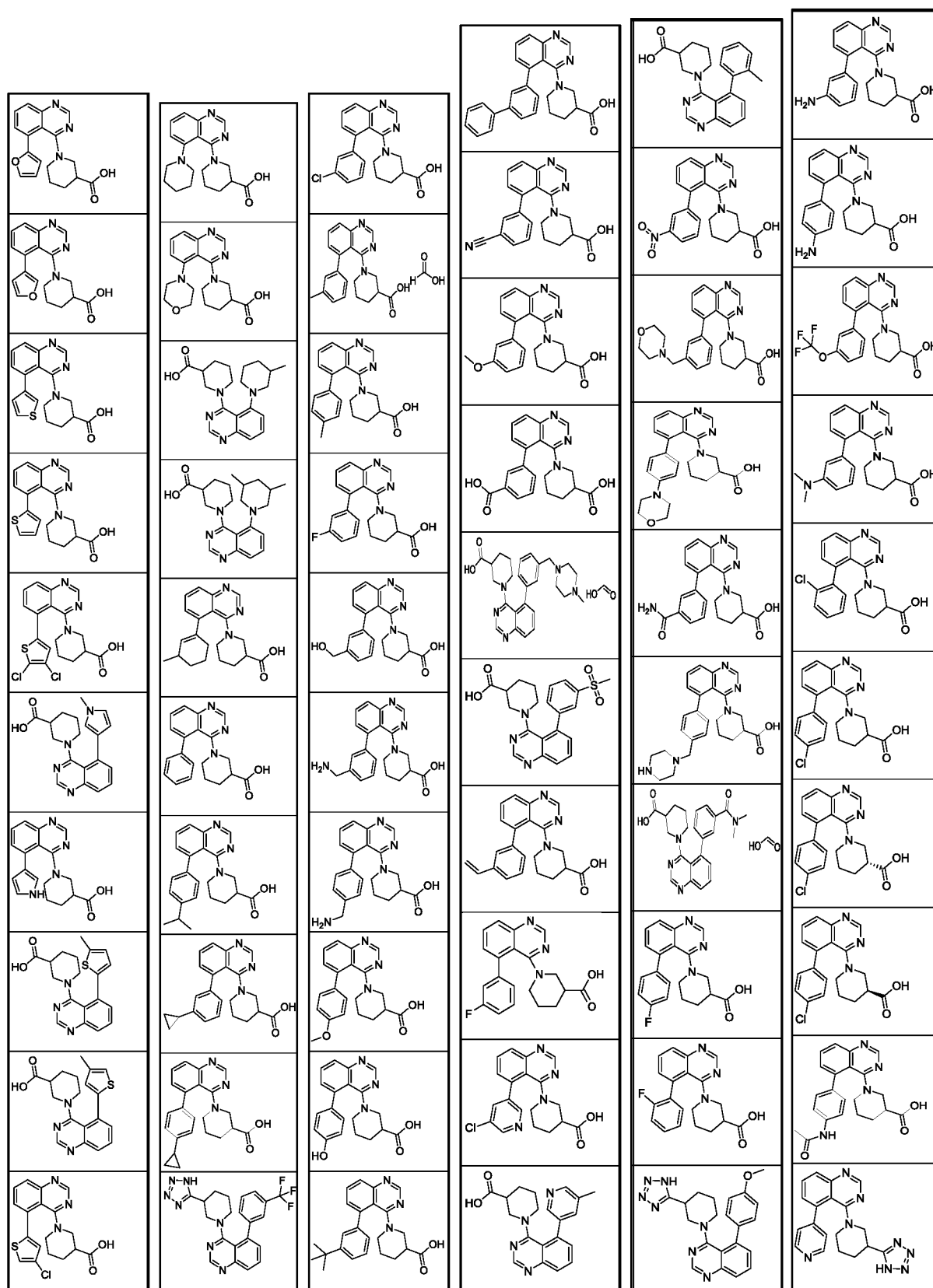
Where R⁹ and R¹⁰ are bonded together, they may form a cyclopropyl-COOH group.

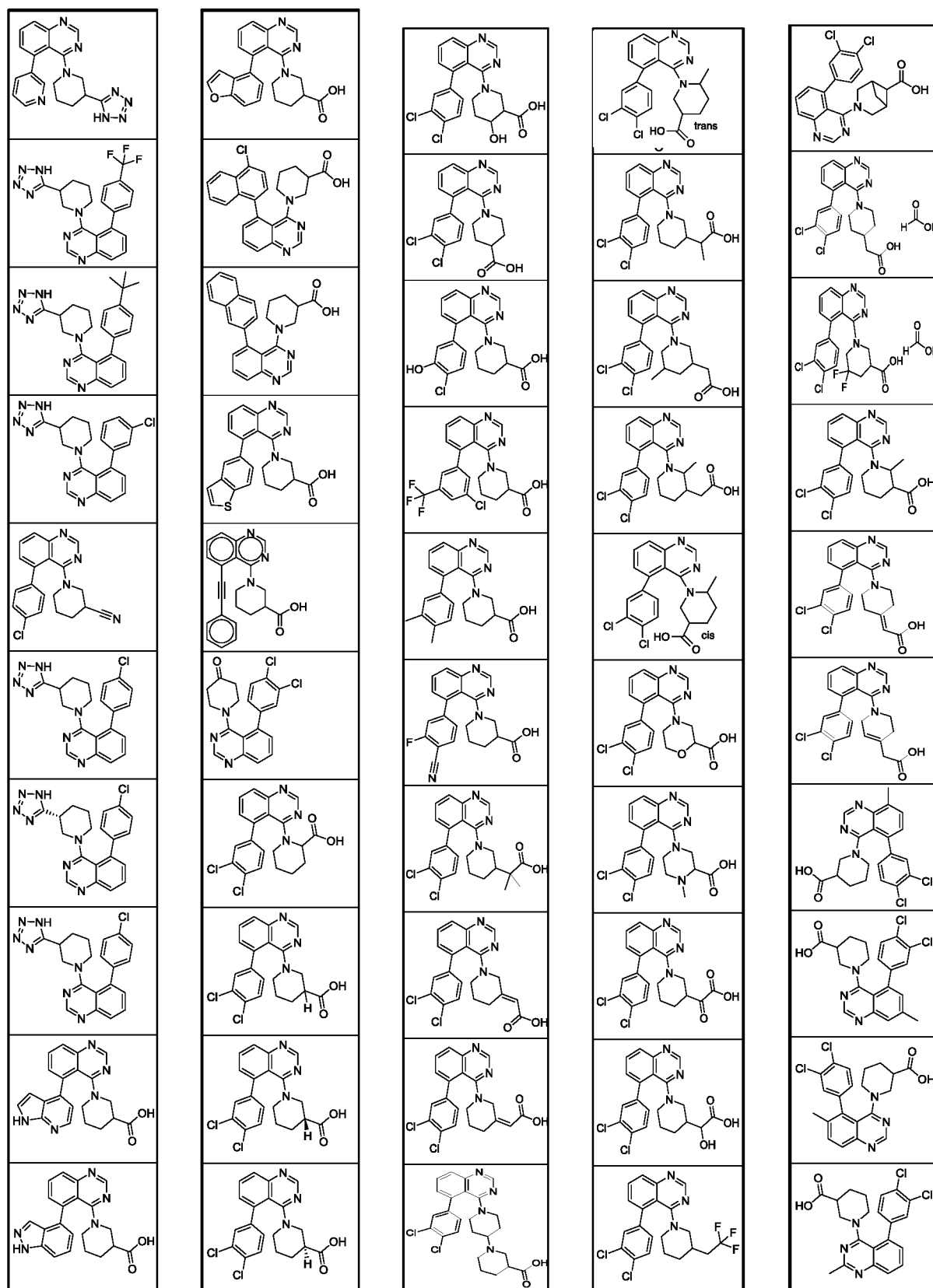
Where R¹¹ and R¹² are bonded together, they may represent a 1,3-dioxolane group.

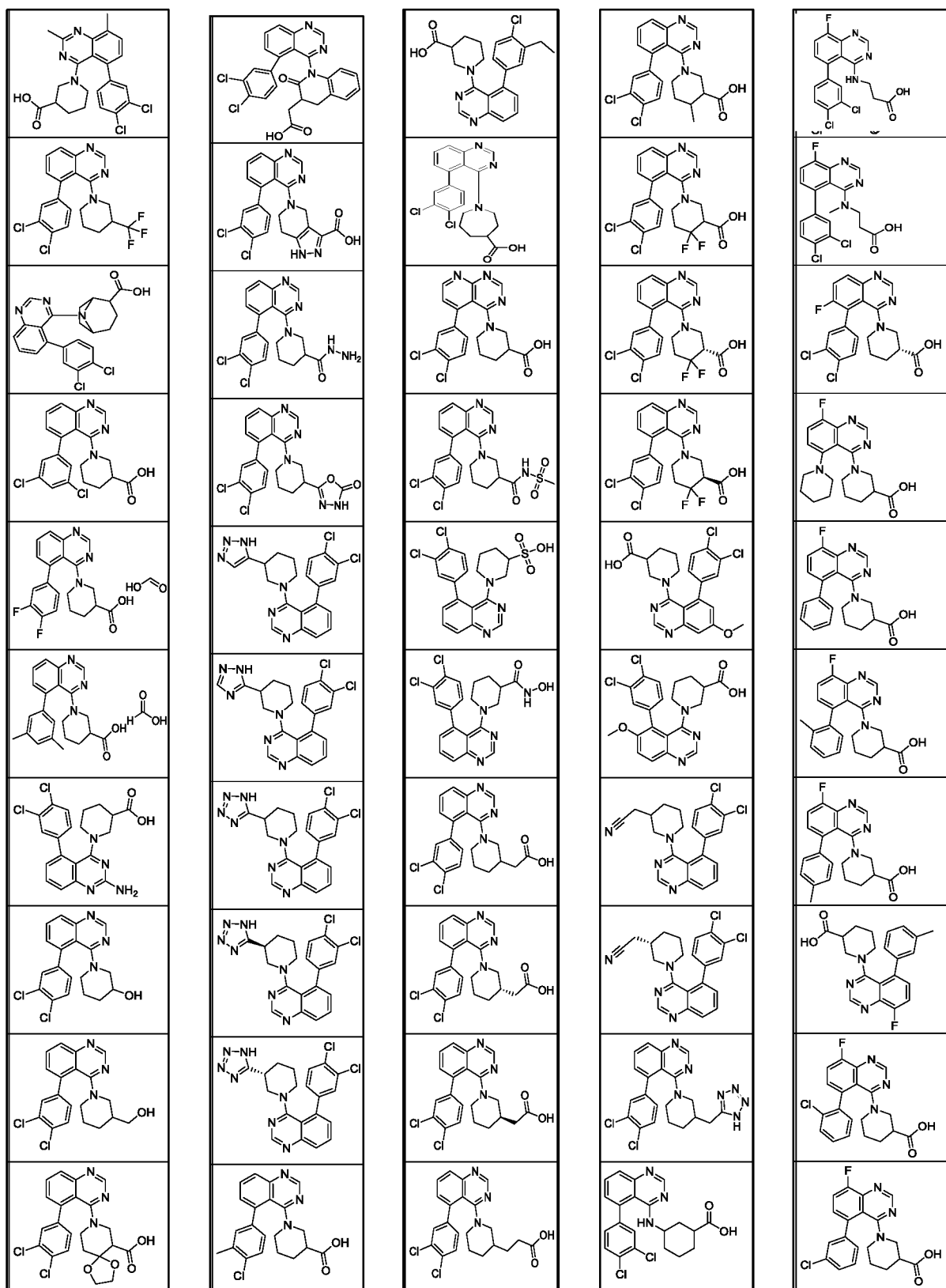
Where B¹ is CHR¹¹, R¹¹ may represent piperidine-3-carboxylic acid.

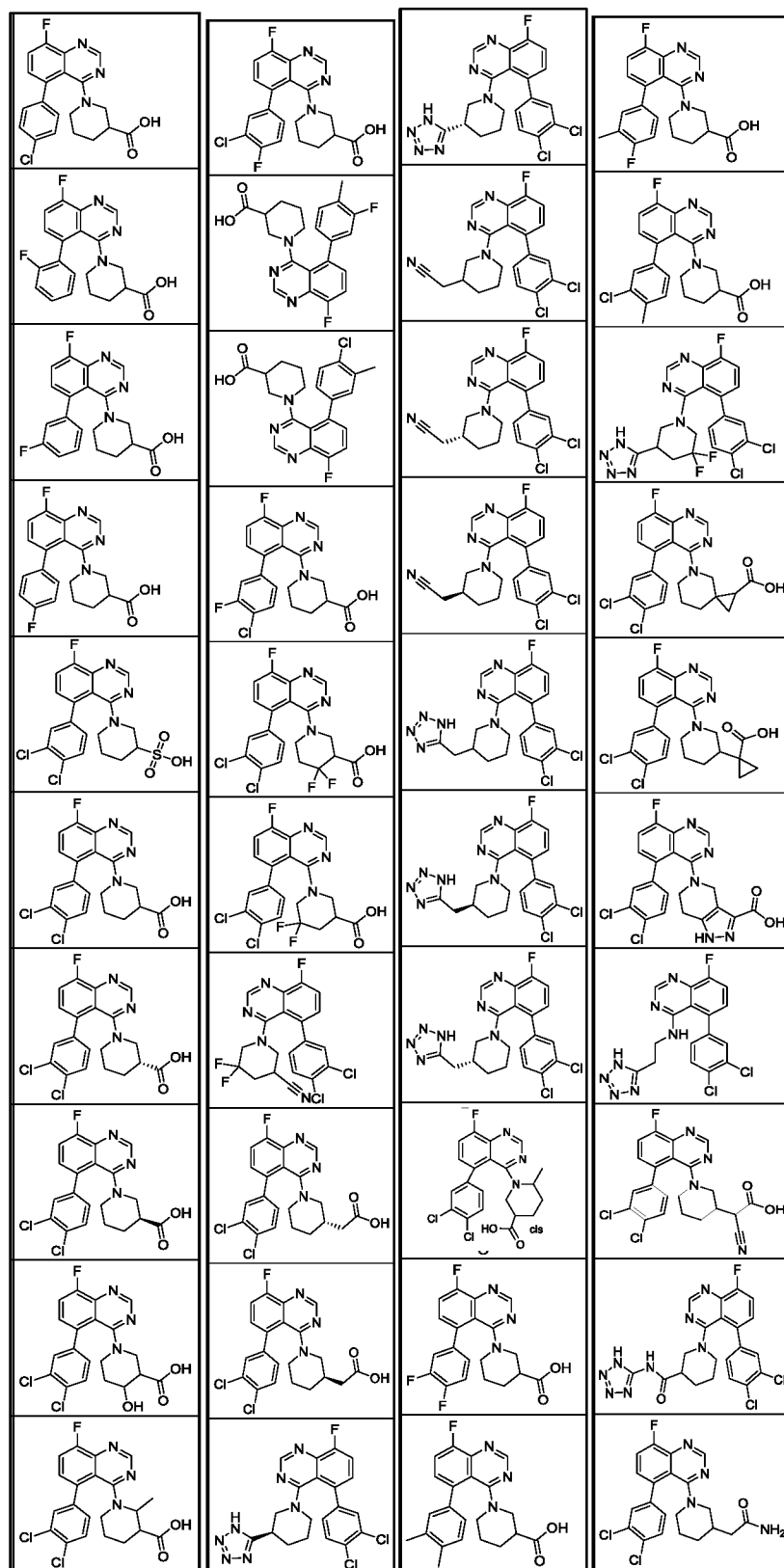
R²¹ may represent hydrogen or C₁₋₆ alkyl. R²¹ may represent hydrogen, methyl, ethyl, propyl or butyl.

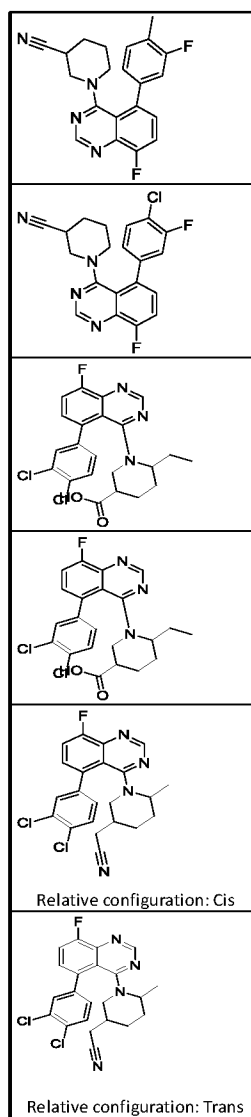
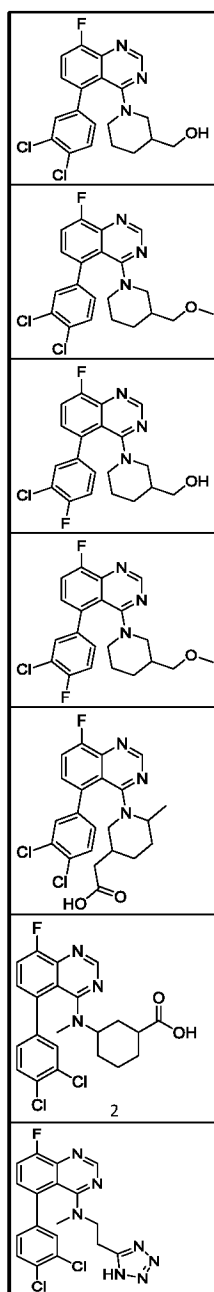
The compound may be selected from group (A) consisting of:



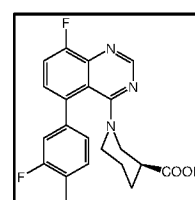
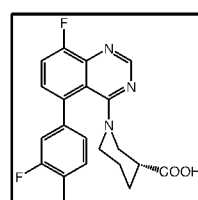
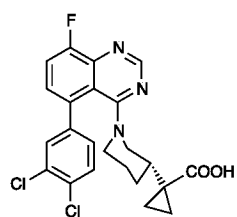
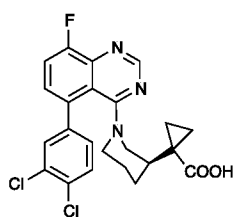
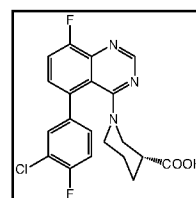
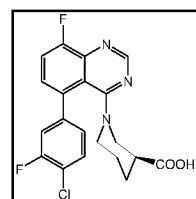
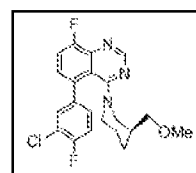
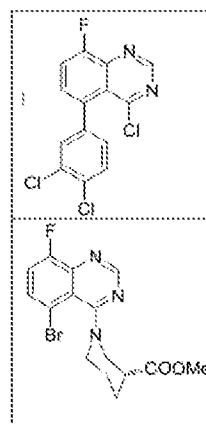
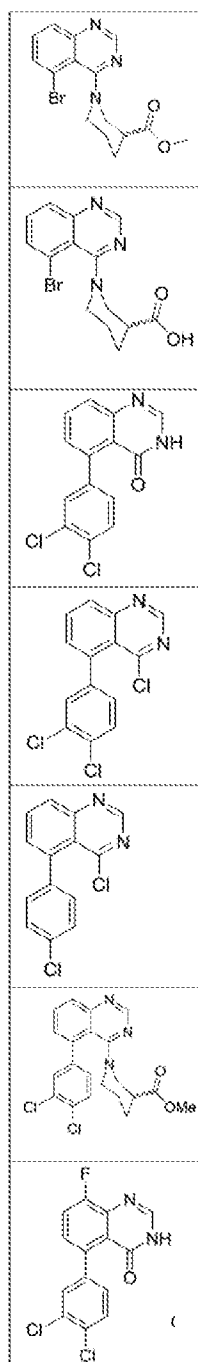


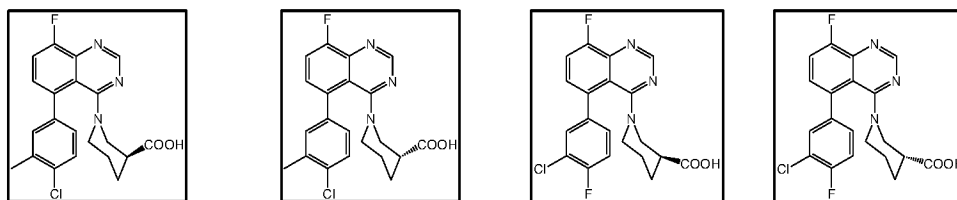




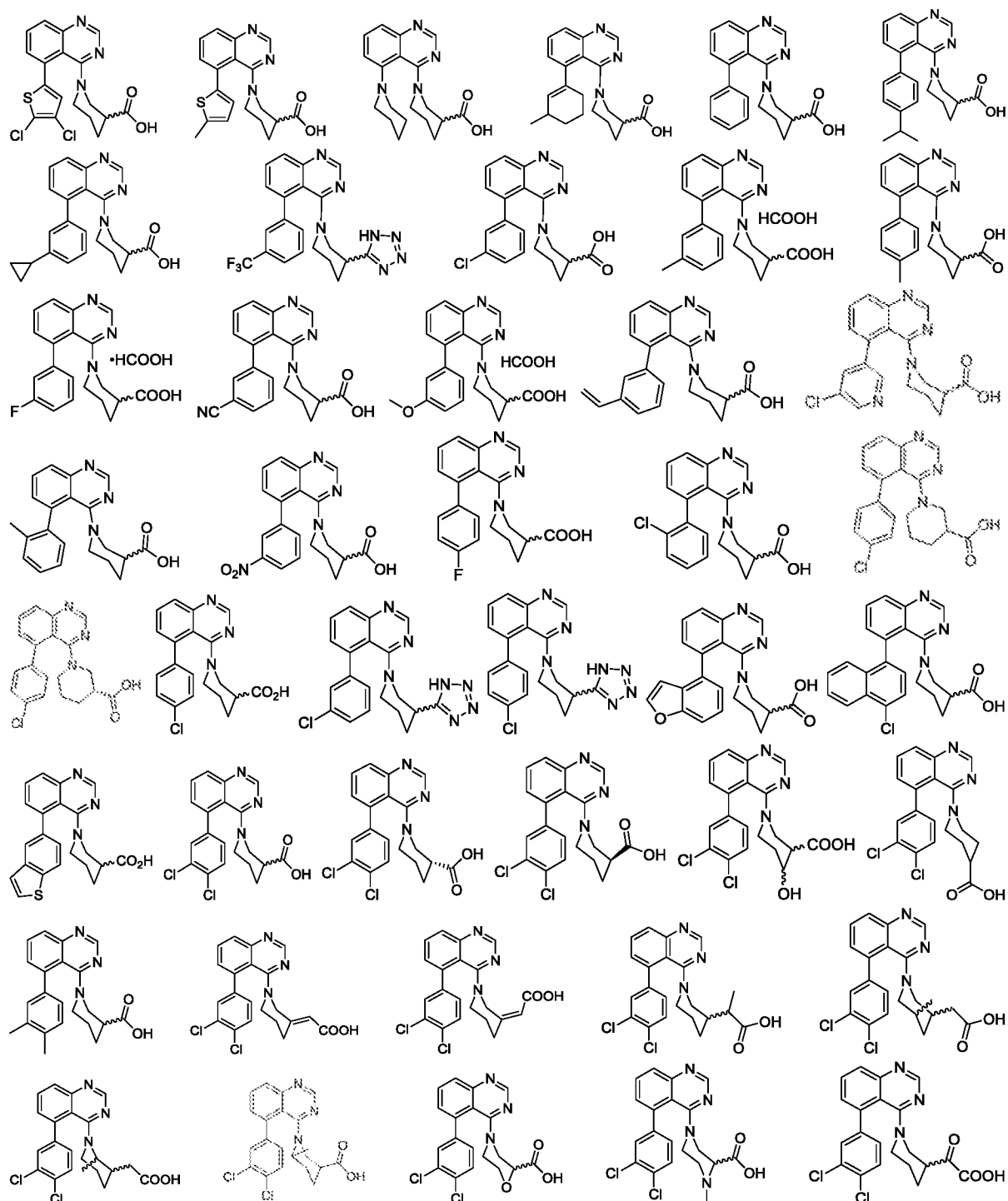


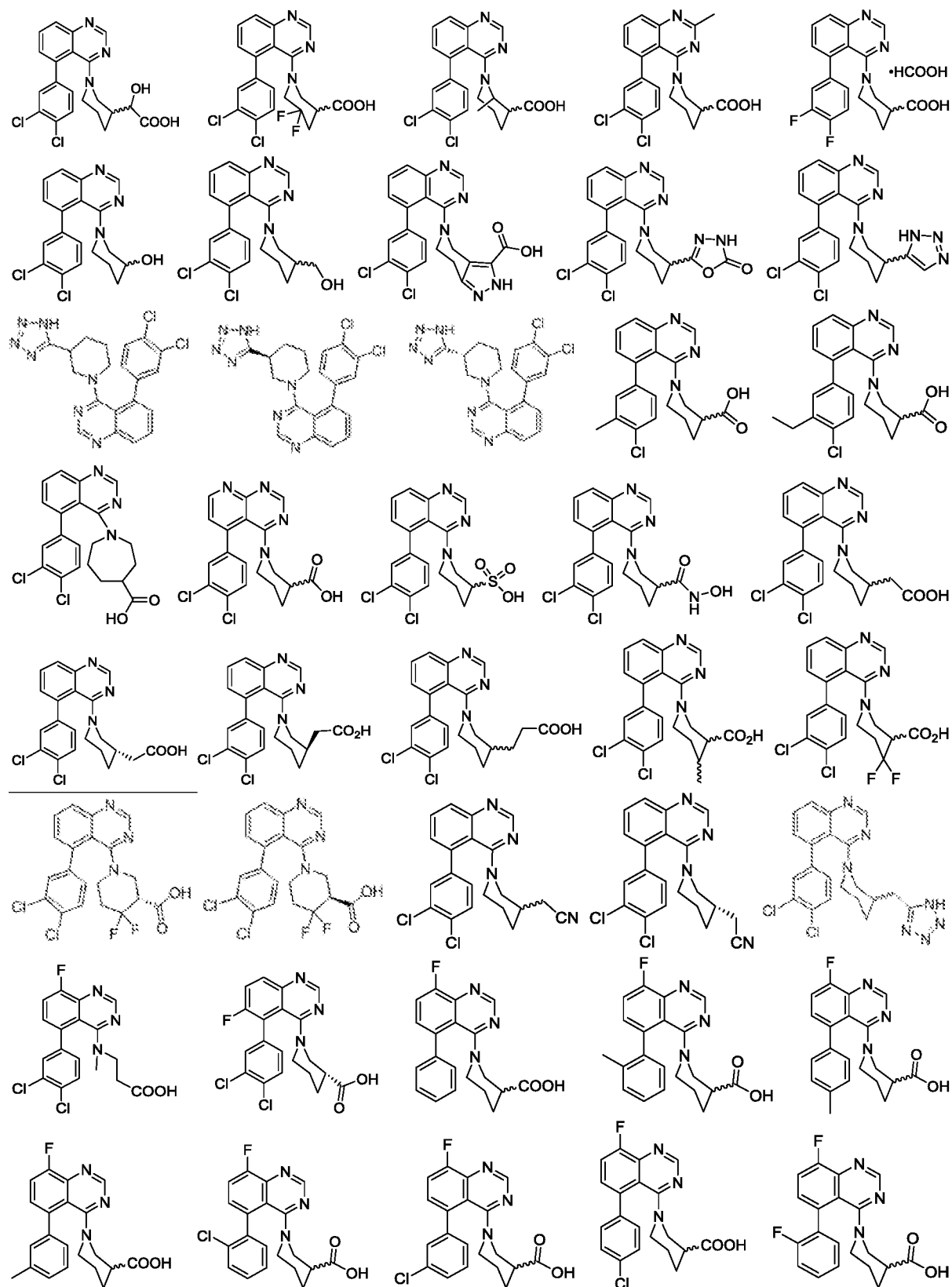
Relative configuration: Trans

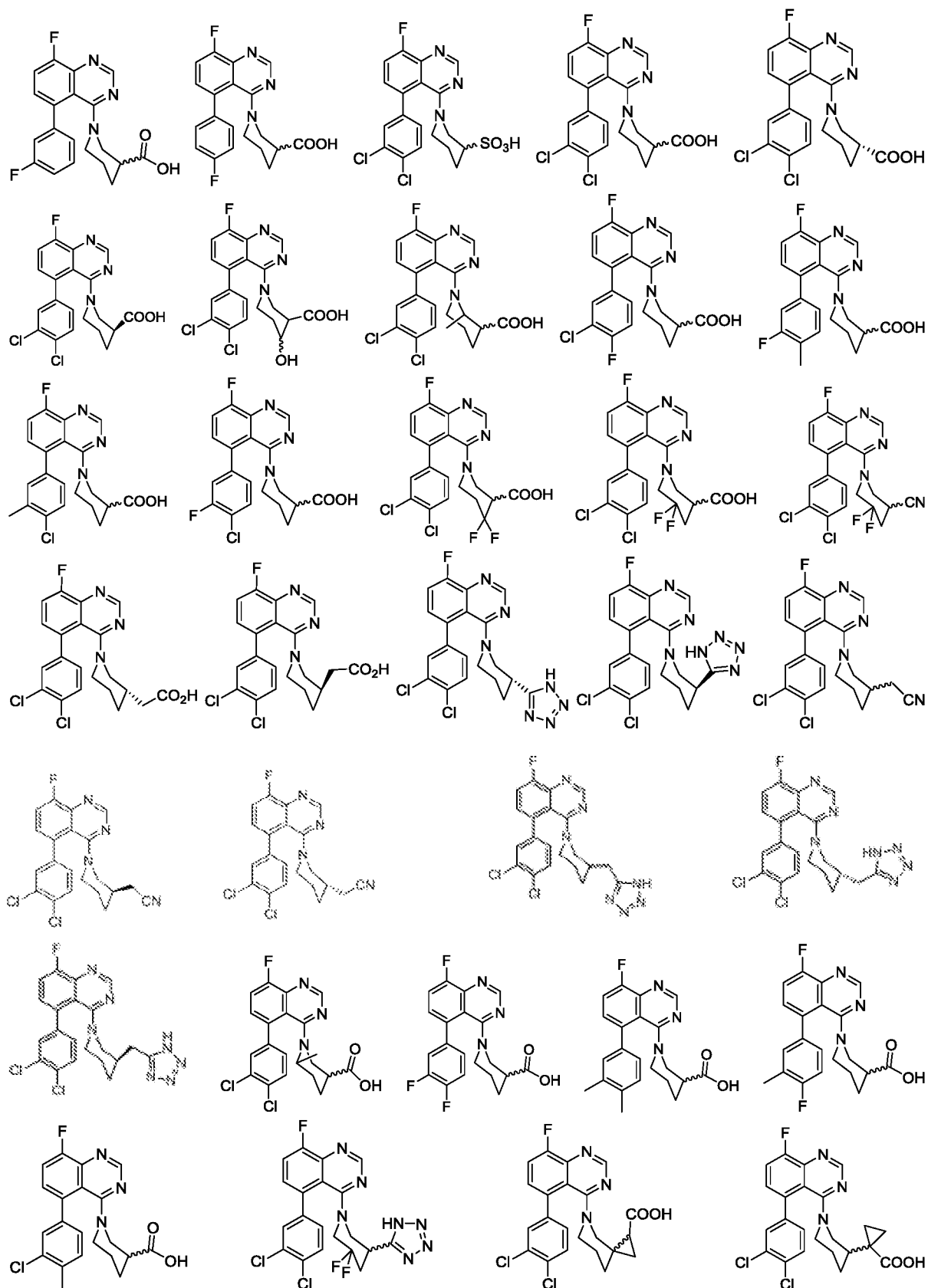


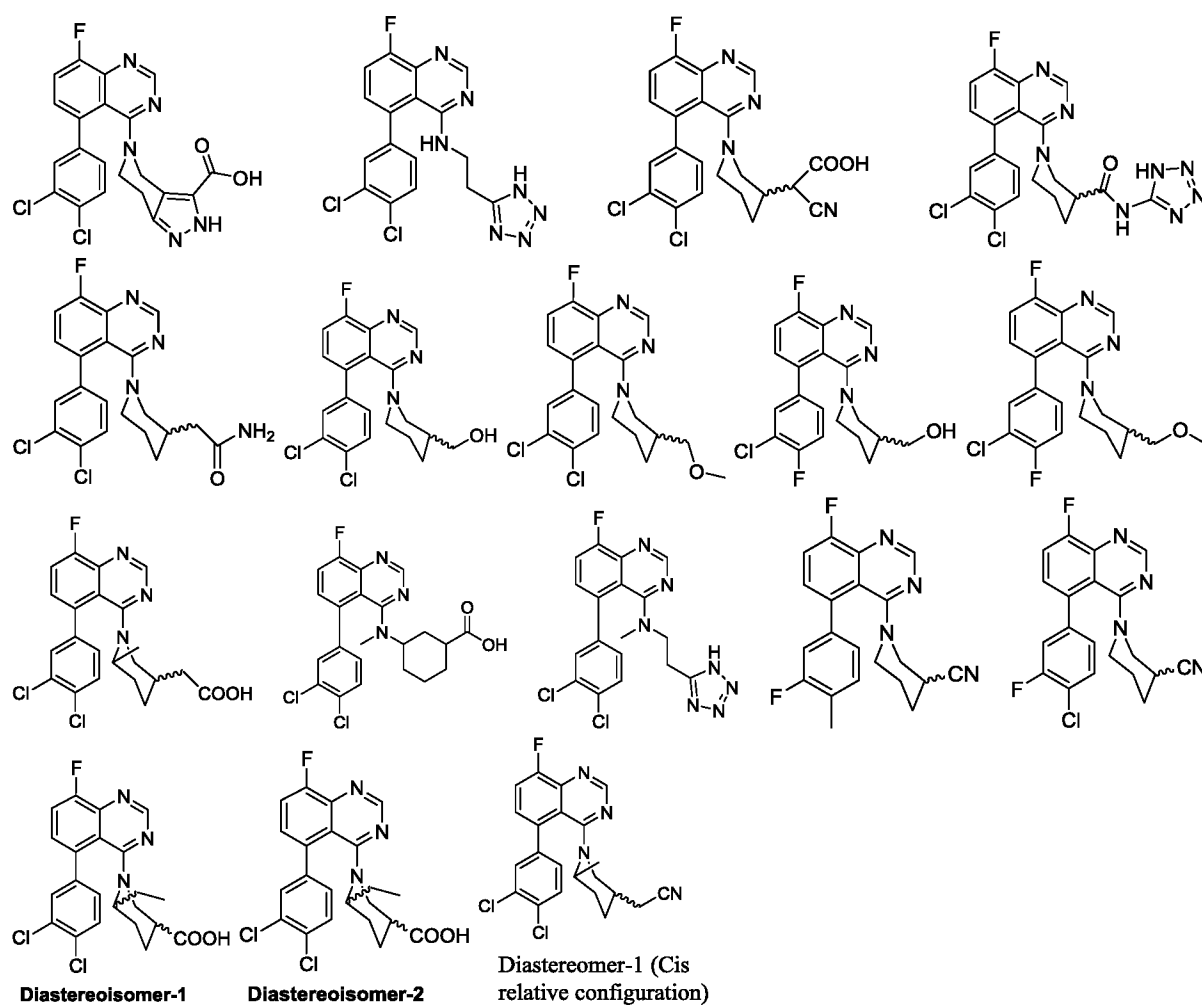


The compound may be selected from group (B) consisting of:



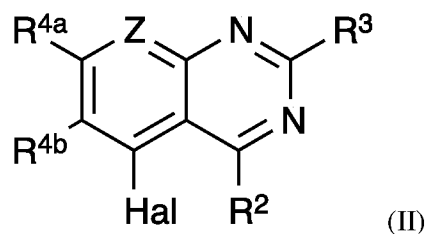






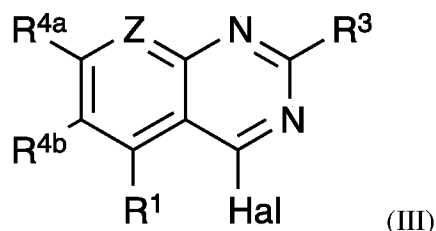
There is provided a process for making a compound of formula (I) as defined above comprising the step of reacting

(a) a compound of formula (II),



wherein R^2 , R^3 , R^{4a} , R^{4b} and Z are as defined above and Hal represents halogen, preferably chlorine,

or a compound of formula (III),



wherein R^1 , R^3 , R^{4a} , R^{4b} and Z are as defined above and Hal represents halogen, preferably chlorine, in an organic solvent in the presence of a base and optionally L-proline with an amine of formula (IV)



or (IV)' respectively,



wherein R^1 and R^2 are as defined above;

The reaction step may be described as disclosed above.

The reaction may be carried out in a solvent. The solvent may be selected from the group consisting of *N,N*-dimethylformamide, dimethyl sulfoxide, 1,4-dioxane, dichloromethane or methylenechloride, tetrahydrofuran (THF), ethyl acetate, acetone or acetonitrile.

The base may be inorganic or organic base. The inorganic base may be selected from the group consisting of potassium carbonate, potassium phosphate tribasic or cesium carbonate.

The reaction temperature may be in a range of about 20 °C to about 50 °C, 20 °C to about 25 °C, 20 °C to about 30 °C, 20 °C to about 35 °C, 20 °C to about 40 °C, 20 °C to about 45 °C, 25 °C to about 50 °C, 30 °C to about 50 °C, 35 °C to about 50 °C, 40 °C to about 50 °C or 45 °C to about 50 °C.

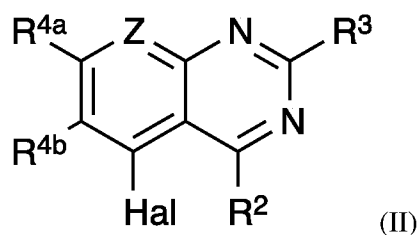
The reaction time may vary between about 5 minutes to about 60 minutes. It may vary in a range of about 5 minutes to about 60 minutes, about 10 minutes to about 60 minutes, about 15 minutes to about 60 minutes, about 20 minutes to about 60 minutes, about 25 minutes to about 60 minutes, about 30 minutes to about 60 minutes, about 35 minutes to about 60 minutes, about 40 minutes to about 60 minutes, about 45 minutes to about 60 minutes, about 50 minutes to about 60 minutes, about 55 minutes to about 60 minutes, about 5 minutes to about 10 minutes, about 5 minutes to about 15 minutes, about 5 minutes to about 20 minutes, about 5 minutes to about 25 minutes, about 5 minutes to about 30 minutes, about 5 minutes to about 35 minutes, about 5 minutes to about 40 minutes, about 5 minutes to about 45 minutes, about 5 minutes to about 50 minutes or about 5 minutes to about 55 minutes.

After the reaction is complete, that reaction solution may be extracted with a polar aprotic solvent. The polar aprotic solvent may be selected from dichloromethane or methylenechloride, tetrahydrofuran (THF), ethyl acetate, or acetonitrile.

The combined reaction solution may be dried over a drying agent, filtered and concentrated under pressure. The extraction step may be carried out at least once twice, three times, four times or up to five times. The drying agent may be selected from the group consisting of anhydrous sodium sulfate, magnesium sulfate, calcium chloride or calcium sulphate. The combined reaction solution may be concentrated under reduced pressure. The reaction residue (reaction crude product) may be purified.

There is also provided a process for making a compound of formula (I) as defined above, comprising the step of reacting

(b) a compound of formula (II),



wherein R^2 , R^3 , R^{4a} , R^{4b} and Z are as defined above and Hal represents halogen, preferably bromine,

in an organic solvent or organic solvent/water mixture in the presence of a base and a palladium catalyst with a boronic acid of formula (V),



wherein R^1 is as defined above;

The reaction step may be described as disclosed above.

The reaction may be carried out in an organic solvent and/or aqueous solution. The organic solvent may be selected from the group consisting of *N,N*-dimethylformamide, dimethyl sulfoxide, 1,4-dioxane, dichloromethane or methylenechloride, toluene, tetrahydrofuran (THF), ethyl acetate, acetone or acetonitrile. The organic solvent may be a high-boiling solvent. The aqueous solution may be water or deionized water.

The base may be inorganic or organic base. The inorganic base may be selected from the group consisting of potassium phosphate tribasic or cesium carbonate.

The palladium catalyst may be tetrakis(triphenylphosphine)palladium(0), palladium(II) acetate or Bis(triphenylphosphine)palladium(II) dichloride.

The reaction temperature may be in a range of about 100 °C to about 300 °C, about 150 °C to about 300 °C, about 200 °C to about 300 °C, about 250 °C to about 300 °C, about 100 °C to about 150 °C,

about 100 °C to about 200 °C, about 100 °C to about 250 °C, about 150 °C to about 200 °C, about 200 °C to about 300 °C, or about 250 °C to about 300 °C, e.g. at about 100 °C, at about 110 °C, at about 120 °C, at about 180 °C, at about 200 °C.

The reaction may take place under heating in a sealed tube. The reaction may take place in a reflux apparatus. The reaction or the reactor may be heated by an oil bath or a sand bath. The reaction may take place under inert gas. The inert gas may be argon or nitrogen. The reaction or the reactor may be heated using microwave irradiation.

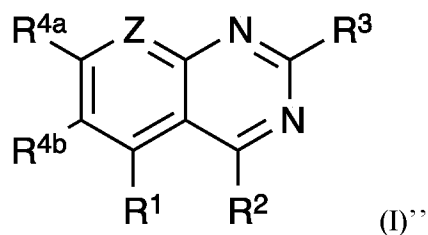
The reaction time may vary between 30 minutes to 12 hours. It may vary in a range of about 30 minutes to about 6 hours, about 1 hour to about 6 hours, about 1.5 hours to about 6 hours, about 2 hours to about 6 hours, about 2.5 hours to about 6 hours, about 3 hours to about 6 hours, about 3.5 hours to about 6 hours, about 4 hours to about 6 hours, about 5 hours to about 6 hours, about 30 minutes to about 5 hours, about 30 minutes to about 4 hours, about 30 minutes to about 3 hours, about 30 minutes to about 2 hours, about 30 minutes to about 1 hour, about 6 hours to about 12 hours, about 7 hours to about 12 hours, about 8 hours to about 12 hours, about 9 hours to about 12 hours, about 10 hours to about 12 hours, about 11 hours to about 12 hours, about 6 hours to about 7 hours, about 6 hours to about 8 hours, about 6 hours to about 9 hours, about 6 hours to about 10 hours, about 6 hours to about 11 hours, e.g. it may be about 30 minutes, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, or about 6 hours.

After the reaction is complete, that reaction solution may be acidified with acid, extracted with water and a polar aprotic solvent. The acid may be inorganic acid or organic acid. The acid may be diluted hydrochloric acid. The polar aprotic solvent may be selected from dichloromethane or methylenechloride, tetrahydrofuran (THF), ethyl acetate, or acetonitrile.

The combined reaction solution may be dried over a drying agent, filtered and concentrated under pressure. The extraction step may be carried out at least once or up to five times. The drying agent may be selected from the group consisting of anhydrous sodium sulfate, magnesium sulfate, calcium chloride or calcium sulphate. The combined reaction solution may be concentrated under reduced pressure. The reaction residue (reaction crude product) may be purified.

There is also provided a process for making a compound of formula (I) as defined above, comprising the step of converting

(c) a compound of formula (I)',



R^1 , R^2 , R^3 , R^{4a} , R^{4b} and Z are as defined above and wherein R^2 carries a $-\text{COO}-\text{C}_1-\text{C}_3\text{-alkyl}$ or $-\text{SO}_2-\text{O}-\text{C}_1-\text{C}_3\text{-alkyl}$ ester group,

in an organic solvent or organic solvent/water mixture in the presence of a base into an acid group carrying compound.

The reaction step may be described as disclosed above.

The reaction may be carried out in an organic solvent and/or organic solvent/water mixture. The organic solvent may be selected from the group consisting of tetrahydrofuran (THF), *N,N*-dimethylformamide, dimethyl sulfoxide, 1,4-dioxane, dichloromethane or methylenechloride, ethyl acetate, acetone or acetonitrile. The non-organic solvent may be water or deionized water. The organic solvent/water mixture may comprise of polar aprotic solvent, polar protic solvent and water. The polar protic solvent may be selected from the group consisting of methanol, ethanol, propanol, butanol or acetic acid.

The base may be an inorganic or organic base. The inorganic base may be selected from the group consisting of lithium hydroxide, sodium hydroxide, potassium hydroxide or calcium carbonate.

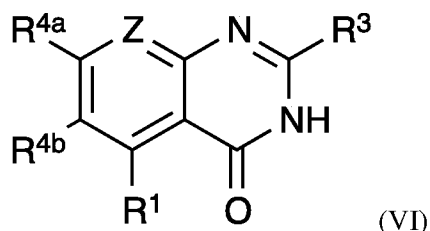
The reaction temperature may be in a range of about 20 °C to about 50 °C, 20 °C to about 25 °C, 20 °C to about 30 °C, 20 °C to about 35 °C, 20 °C to about 40 °C, 20 °C to about 45 °C, 25 °C to about 50 °C, 30 °C to about 50 °C, 35 °C to about 50 °C, 40 °C to about 50 °C or 45 °C to about 50 °C.

The reaction time may vary in a range of about 1 hour to about 12 hours, about 1 hour to about 2 hours, about 1 hour to about 3 hours, about 1 hour to about 4 hours, about 1 hour to about 5 hours, about 1 hour to about 6 hours, about 1 hour to about 7 hours, about 1 hour to about 8 hours, about 1 hour to about 9 hours, about 1 hour to about 10 hours, about 1 hour to about 11 hours, about 2 hours to about 12 hours, about 3 hours to about 12 hours, about 4 hours to about 12 hours, about 5 hours to about 12 hours, about 6 hours to about 12 hours, about 7 hours to about 12 hours, about 8 hours to about 12 hours, about 9 hours to about 12 hours, about 10 hours to about 12 hours or about 11 hours to about 12 hours, e.g. it may be about about 6 hours, about 8 hours, about 10 hours or about 12 hours.

After the reaction is complete, the reaction solution may be diluted, extracted with a polar aprotic solvent and acidified with acid. The acid may be inorganic acid or organic acid. The acid may be diluted hydrochloric acid. The polar aprotic solvent may be selected from dichloromethane or methylenechloride, tetrahydrofuran (THF), ethyl acetate, or acetonitrile. The extraction step may be carried out at least once or up to five times. The combined reaction solution may be dried over a drying agent, filtered and concentrated under pressure. The drying agent may be selected from the group consisting of anhydrous sodium sulfate, magnesium sulfate, calcium chloride or calcium sulphate. The combined reaction solution may be concentrated under reduced pressure. The reaction residue (reaction crude product) may be purified.

There is also provided a process for making a compound of formula (I) as defined above, comprising the step of reacting

(d) a compound of formula (VI),



R^1 , R^3 , R^{4a} , R^{4b} and Z are defined as mentioned above,

in the presence of a dehydrating agent, preferably phosphoryl chloride, with an amine of formula (IV),

R^2 -H (IV),

herein R^2 is as defined above,

The reaction step may be described as disclosed above.

The reaction may be carried out in a solvent. The organic solvent may be a high-boiling solvent. The organic solvent may be selected from the group consisting of *N,N*-dimethylformamide, dimethyl sulfoxide, 1,4-dioxane, dichloromethane or methylenechloride, toluene, tetrahydrofuran (THF), ethyl acetate, acetone or acetonitrile.

The reaction temperature may be in a range of about 100 °C to about 300 °C, about 150 °C to about 300 °C, about 200 °C to about 300 °C, about 250 °C to about 300 °C, about 100 °C to about 150 °C, about 100 °C to about 200 °C, about 100 °C to about 250 °C, about 150 °C to about 200 °C, about 200 °C to about 300 °C, or about 250 °C to about 300 °C, e.g. at about 100 °C, at about 110 °C, at about 120 °C, at about 180 °C, at about 200 °C.

The reaction may take place under heating in a sealed tube. The reaction may take place in a reflux apparatus. The reaction or the reactor may be heated by an oil bath or a sand bath. The reaction may take place under inert gas. The inert gas may be argon or nitrogen. The reaction or the reactor may be heated using microwave irradiation.

The reaction time may vary between 30 minutes to 6 hours. It may vary in a range of about 30 minutes to 6 hours, about 1 hour to 6 hours, about 1.5 hours to 6 hours, about 2 hours to 6 hours, about 2.5 hours to 6 hours, about 3 hours to 6 hours, about 3.5 hours to 6 hours, about 4 hours to 6 hours, about 5 hours to 6 hours, about 30 minutes to 5 hours, about 30 minutes to 4 hours, about 30 minutes to 3 hours, about 30 minutes to 2 hours, about 30 minutes to 1 hour, e.g. it may be about 30 minutes, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours or about 6 hours.

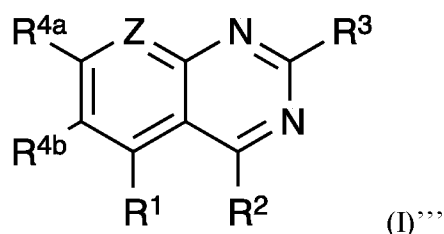
After the reaction is complete, the reaction solution may be cooled to room temperature, diluted in polar aprotic solvent, and poured into cold water. The reaction solution pH may be adjusted to pH 6 to 7 with a base. The base may be inorganic or organic base. The inorganic base may be diluted sodium hydroxide.

The combined reaction solution may be dried over a drying agent, filtered and concentrated under pressure. The combined reaction solution may be concentrated under reduced pressure. The drying

agent may be selected from the group consisting of anhydrous sodium sulfate, magnesium sulfate, calcium chloride or calcium sulphate. The reaction residue (reaction crude product) may be purified.

There is also provided a process for making a compound of formula (I) as defined above, comprising the step of reacting

(e) a compound of the formula (I)'''



wherein R^1 , R^2 , R^3 , R^{4a} , R^{4b} and Z are as defined above and wherein R^2 is carrying a cyano group,

in an organic solvent optionally in the presence of an amine with a triazide, preferably an alkali metal triazide,

and in all alternatives (a) to (e) the reaction product is isolated.

The reaction step may be described as disclosed above.

The reaction may be carried out in a solvent. The organic solvent may be a high-boiling solvent. The organic solvent may be selected from the group consisting of toluene, *N,N*-dimethylformamide, dimethyl sulfoxide, 1,4-dioxane, dichloromethane or methylenechloride, tetrahydrofuran (THF), ethyl acetate, acetone or acetonitrile. The alkali metal triazide may be sodium azide. The amine may be selected from the group consisting of triethylamine, trimethylamine, pyridine or diisopropylethylamine.

The reaction temperature may be in a range of about 100 °C to about 300 °C, about 150 °C to about 300 °C, about 200 °C to about 300 °C, about 250 °C to about 300 °C, about 100 °C to about 150 °C, about 100 °C to about 200 °C, about 100 °C to about 250 °C, about 150 °C to about 200 °C, about 200 °C to about 300 °C, or about 250 °C to about 300 °C, e.g. at about 100 °C, at about 110 °C, at about 120 °C, at about 180 °C, at about 200 °C.

The reaction may take place under heating in a sealed tube. The reaction may take place in a reflux apparatus. The reaction or the reactor may be heated by an oil bath or a sand bath. The reaction may take place under inert gas. The inert gas may be argon or nitrogen. The reaction or the reactor may be heated using microwave irradiation.

The reaction time may vary in a range of about 10 hours to about 18 hours, about 10 hours to about 11 hours, about 10 hours to about 12 hours, about 10 hours to about 13 hours, about 10 hours to about 14 hours, about 10 hours to about 15 hours, about 10 hours to about 16 hours, about 10 hours to about 17

hours, about 11 hours to about 18 hours, about 12 hours to about 18 hours, about 13 hours to about 18 hours, about 14 hours to about 18 hours or about 15 hours to about 18 hours, about 16 hours to about 18 hours, about 17 hours to about 18 hours e.g. it may be about about 10 hours, about 12 hours, about 14 hours, about 16 hours or 18 hours.

After the reaction is complete, the reaction solution may be cooled to room temperature and filtered. The reaction solution was concentrated under reduced pressure to afford a residue (crude reaction product) that may be purified.

The compounds as defined above may be made according to the general processes as disclosed above or according to the general principles of the working examples.

The compound may be a modulator that modulates, inhibits or disrupts the glycine metabolism pathway. The compounds may modulate, inhibit or disrupt an enzyme that is involved in the glycine metabolism pathway, such as glycine decarboxylase. By modulating, inhibiting or disrupting the function or structure of the glycine decarboxylase, the glycine decarboxylase may not be able to bind to its target substrate, which is glycine. In this manner, the expression of glycine may be upregulated, leading to increased production of the glycine. Due to the modulation, inhibition or disruption of glycine decarboxylase, this may affect the biosynthesis of serine (which is based on the metabolism of glycine), leading to an underexpression of serine as the glycine is not decarboxylated by the glycine decarboxylase. The compound may also be a modulator of a kinase, a protease and a G-protein-coupled receptor.

The compounds may inhibit glycine metabolism pathways. Where the glycine metabolism pathway may affect the metabolism pathway of serine thus, the serine metabolism pathway may also be modulated by the compounds directly or indirectly. Hence, in this manner, the compounds may be deemed to be modulators, inhibitors or disruptors of both the glycine and serine metabolism pathways.

A compound of formula (I) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof may be for use as a medicament.

A compound of group (B) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof may be for use as a medicament.

A compound of formula (I) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof may be for use in the treatment of diseases, disorders and conditions associated with glycine metabolism. There is also provided a compound of formula (I) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof that may be for use in the treatment of diseases, disorders and conditions associated with glycine and serine metabolism.

A compound of group (B) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof may be for use in the treatment of diseases, disorders and conditions associated with glycine metabolism. There is also provided a compound of group (B) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof that may be for use in the treatment of diseases, disorders and conditions associated with glycine and serine metabolism.

A compound of formula (I) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof may be for use in the treatment of diseases, disorders and conditions which are selected from cancer, inflammation, Alzheimer's disease, metabolic disorders, neurological disorders and central nervous system disorders.

A compound of group (B) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof may be for use in the treatment of diseases, disorders and conditions which are selected from cancer, inflammation, Alzheimer's disease, metabolic disorders, neurological disorders and central nervous system disorders.

Use of a compound of formula (I) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof may be in the manufacture of a medicament for the treatment of a disease, disorder or condition associated with glycine metabolism. There is also provided use of a compound of formula (I) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof may be in the manufacture of a medicament for the treatment of a disease, disorder or condition associated with glycine and serine metabolism.

Use of a compound of group (B) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof may be in the manufacture of a medicament for the treatment of a disease, disorder or condition associated with glycine metabolism. There is also provided use of a compound of group (B) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof may be in the manufacture of a medicament for the treatment of a disease, disorder or condition associated with glycine and serine metabolism.

A method of treating a disease, disorder or condition associated with glycine metabolism in a subject in need of such treatment, may comprise administering to said subject a compound of formula (I) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof. There is also provided a method of treating a disease, disorder or condition associated with glycine and serine metabolism in a subject in need of such treatment, may comprise administering to said subject a compound of formula (I) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof.

A method of treating a disease, disorder or condition associated with glycine metabolism in a subject in need of such treatment, may comprise administering to said subject a compound of group (B) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof. There is also provided a method of treating a disease, disorder or condition associated with glycine and serine metabolism in a subject in need of such treatment, may comprise administering to said subject a compound of group (B) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof.

The disease, disorder and condition may be cancer, inflammation, Alzheimer's disease, metabolic disorders, neurological disorders and central nervous system disorders

The disease, disorder and condition may be a new group of neurometabolic diseases comprising γ -aminobutyric acid (GABA) transaminase (GT) disorder, succinic semialdehyde dehydrogenase (SSD)

disorder, 3-phosphoglycerate dehydrogenase (PGDH) disorder, pyrroline-5-carboxylate synthase (P5CS) disorder, proline oxidase disorder, pyrroline-5-carboxylate (P5CDH) dehydrogenase disorder, prolidase disorder, hydroxyproline oxidase disorder, sarcosine dehydrogenase disorder, dimethylglycine dehydrogenase disorder or neurometabolic disorder due to serine overexpression or hyperactivity. The disease, disorder and condition may be a glycine decarboxylase overexpression or hyperactivity or glycine cleavage system (GCS) overexpression or hyperactivity (nonketotic hyperglycinemia).

The clinical symptoms of the disorders of this new group of neurometabolic diseases may comprise of axial hypotonia and generalized convulsions, a wide range of neurological abnormalities, mainly psychomotor retardation, hypotonia, ataxia, hyporeflexia, hyperexcitability, convulsions, aggressive behavior, hyperkinesis, spastic tetraparesis, choreoathetosis and nystagmus, coma, hypotonia, seizures, hypoventilation and apnea requiring artificial ventilation, severe mental retardation, severe myoclonic and generalized seizure disorder, pronounced axial hypotonia, spastic quadriplegia, corpus callosum, cortical malformations, hydrocephalus with posterior fossa cystic malformation, progressive neurodegeneration, joint laxity, skin hyperelasticity, bilateral subcapsular cataracts, hyperprolinemia, hyperammonemia, hypooornithinemia, hypocitrullinemia, hypoargininemia, leg ulceration, mild mental retardation, frequent infections, unique face, sarcosinemia, iminoglycinuria, congenital microcephaly, glycine encephalopathy, seizures and severe psychomotor retardation in the central nervous system. Depression may also be associated with glycine metabolism disorder.

The glycine metabolism disorder may be associated with the glycine cleavage system (GCS) or the glycine decarboxylase complex (GDC), for instance, T-protein, P-protein, L-protein, and H-protein, in particular, P-protein. If there is a mutation in the genetic code of any of the proteins such as deletions or missense mutation, this may result in an unregulated production of glycine. Hence, the metabolism of a diseased organ or a body part, under certain circumstances may be altered to consume serine and/or glycine to survive and sustain the disease. The enzymes implicated in this "new" utilisation of glycine and/or serine could be upregulated, overexpressed (or amplified) to efficiently fulfilled this new role. Inhibition of any enzyme of this disease-driven metabolism, such as glycine decarboxylase may be a way to control the disease. The compounds in the present disclosure may be for use in the treatment of diseases, disorders and conditions associated with glycine metabolism. The compounds in the present disclosure may be for use in the treatment of diseases, disorders and conditions associated with glycine decarboxylase metabolism.

The compounds in the present disclosure may specifically modify the activity of glycine decarboxylase. The compounds in the present disclosure may specifically inhibit the activity of glycine decarboxylase.

The serine metabolism disorder may be associated with the serine synthesis pathway. The compounds in the present disclosure may be for use in the treatment of diseases, disorders and conditions associated with serine metabolism.

The compounds in the present disclosure may be for use in the treatment of diseases, disorders and conditions associated with glycine decarboxylase metabolism that may directly or indirectly affect serine metabolism.

The disease, disorder and condition may be any cancer that is associated with glycine metabolism and/or overexpression or hyperactivity. The disease, disorder and condition may be any cancer that is associated with defective glycine decarboxylase activity. The cancer may be lymphoma, cutaneous T-cell lymphoma, follicular lymphoma, or Hodgkin lymphoma, cervical cancer, ovarian cancer, breast cancer, lung cancer (Small cell lung cancer, non small cell lung cancer, prostate cancer, colorectal cancer, gastric cancer, pancreatic cancer, sarcoma, hepatocellular carcinoma, leukemia or myeloma, retinal angiogenic disease, liver fibrosis, non-small cell lung cancer, glioma, brain cancer, brain tumors, carcinoid tumor, islet cell tumors, pancreatic neuroendocrine tumors, thyroid cancer, germ cell tumors, kidney fibrosis, or myelofibrosis.

The disease, disorder and condition may be any inflammation that is associated with glycine metabolism and/or overexpression or hyperactivity. The disease, disorder and condition may be any inflammation that is associated with defective glycine decarboxylase activity. The term “inflammation” refers to those conditions that are characterized by signs of pain, heat, redness, swelling, and/or loss of function (which can be partial or complete, temporary or permanent). Inflammation takes on many forms and includes, but is not limited to, acute, adhesive, atrophic, focal, fibrosing, simple, specific, subacute, suppurative, toxic, traumatic, and/or ulcerative inflammation.

The disease, disorder and condition may be any metabolic disorder that is associated with glycine metabolism and/or overexpression or hyperactivity. The disease, disorder and condition may be any metabolic disorder that is associated with defective glycine decarboxylase activity.

The disease, disorder and condition may be any neurological disorder that is associated with glycine metabolism and/or overexpression or hyperactivity. The disease, disorder and condition may be any neurological disorder that is associated with defective glycine decarboxylase activity.

The disease, disorder and condition may be any central nervous system disorder that is associated with glycine metabolism and/or overexpression or hyperactivity. The disease, disorder and condition may be any central nervous system disorder that is associated with defective glycine decarboxylase activity.

The disease, disorder and condition may be of any cancer, inflammation, metabolic disorder, neurological disorder or central nervous disorder that is associated with glycine and serine metabolism.

The compound may be administered with an additional therapeutic agent, wherein said medicament may be administered in combination or alteration with the additional therapeutic agent.

A pharmaceutical composition may comprise a compound of formula (I) as defined above or pharmaceutically acceptable salts, hydrates and solvates thereof and a pharmaceutically acceptable excipient.

A pharmaceutical composition may comprise a compound of group (B) as defined above or pharmaceutically acceptable salts, hydrates and solvates thereof and a pharmaceutically acceptable excipient.

A pharmaceutical composition may comprise a compound of formula (I) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof and a pharmaceutically acceptable excipient for treatment of a disease, disorder or condition associated with glycine metabolism.

A pharmaceutical composition may comprise a compound of group (B) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof and a pharmaceutically acceptable excipient for treatment of a disease, disorder or condition associated with glycine metabolism.

A compound of formula (I) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof may be for use in the treatment of diseases, disorders and conditions associated with glycine and/or serine metabolism.

A compound of group (B) as defined above or pharmaceutically acceptable salts, hydrates or solvates thereof may be for use in the treatment of diseases, disorders and conditions associated with glycine and/or serine metabolism.

The compound may be administered alone or in the form of a pharmaceutical composition in combination with a pharmaceutically acceptable carrier, diluent or excipient. The compounds, while effective themselves, may be typically formulated and administered in the form of their pharmaceutically acceptable salts as these forms are typically more stable, more easily crystallized and have increased solubility.

The compound may, however, typically be used in the form of pharmaceutical compositions which are formulated depending on the desired mode of administration.

A pharmaceutical composition may comprise a compound as disclosed above, or a pharmaceutically acceptable form or prodrug thereof, and a pharmaceutically acceptable excipient. The compositions may be prepared in manners well known in the art.

The amount of compound in the compositions may be such that it is effective to measurably treat the disease, disorder or condition associated with glycine metabolism. The amount of compound in the compositions may be such that it is effective to measurably treat the disease, disorder or condition associated with glycine and serine metabolism. The amount of compound in the compositions may be such that it is effective to measurably treat the disease, disorder or condition associated with serine metabolism. The composition may be formulated for administration to a patient in need of such composition.

In using the compounds, they may be administered in any form or mode which may make the compound bioavailable. One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the particular characteristics of the compound selected, the condition to be treated, the stage of the condition to be treated and other relevant circumstances.

The pharmaceutically acceptable excipient may be a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of

this disclosure may include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol or wool fat.

Compositions as defined above may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this disclosure may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

Pharmaceutically acceptable compositions as defined above may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

Pharmaceutical compositions for parenteral injection may comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper

fluidity may be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of micro-organisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminium monostearate and gelatin.

If desired, and for more effective distribution, the compounds may be incorporated into slow release or targeted delivery systems such as polymer matrices, liposomes, and microspheres.

The injectable formulations may be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Alternatively, pharmaceutically acceptable compositions as defined above may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

Pharmaceutically acceptable compositions as defined above may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations may be readily prepared for each of these areas or organs.

Topical application for the lower intestinal tract may be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

For topical applications, the pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of compounds as defined above may include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutically acceptable compositions may be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers may include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetaryl alcohol, 2 octyldodecanol, benzyl alcohol and water.

For ophthalmic use, the pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum.

Pharmaceutically acceptable compositions as defined above may also be administered by nasal aerosol or inhalation. Such compositions may be prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

Most preferably, pharmaceutically acceptable compositions as defined above may be formulated for oral administration. Such formulations may be administered with or without food. In some embodiments, pharmaceutically acceptable compositions as defined above may be administered without food. In other embodiments, pharmaceutically acceptable compositions as defined above may be administered with food.

The amount of compound that may be combined with the carrier materials to produce a composition in a single dosage form may vary depending upon the host treated, the particular mode of administration. Preferably, the compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present disclosure in the composition will also depend upon the particular compound in the composition.

Examples

Non-limiting examples of the disclosure will be further described in greater detail by reference to specific Examples, which should not be construed as in any way limiting the scope of the invention.

List of abbreviations used

ACN: acetonitrile
AcOEt: ethyl acetate
AcOH: acetic acid
AUC: area under the curve
Brine: saturated aqueous solution of NaCl
bs: broad signal (broad peak) ¹H NMR
cat.: catalyst
d: day(s)
DBU: 1,8-Diazabicycloundec-7-ene
DCM: dichloromethane
DIPEA: diisopropylethylamine
DMF: *N,N*-dimethylformamide
DMSO: dimethylsulfoxide
DMSO-*d*₆: per-deuterated dimethylsulfoxide
dppf: 1,1'- Bis(diphenylphosphino) ferrocene

EDCI: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide)
Ether: diethylether
EtOH: ethanol
h: hour(s)
HATU: 2-(1*H*-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate
Methanaminium
HBTU: O-Benzotriazole-*N,N,N',N'*-tetramethyl-uronium-hexafluoro-phosphate
HOBt: *N*-Hydroxybenzotriazole
HPLC: high pressure liquid chromatography
IPA: Iso-propanol (2-propanol)
L: litre(s)
LC-MS: Liquid chromatography–mass spectrometry
Me: methyl
MeOH: methanol
min: minute(s)
m.p.: melting point
MS: mass spectrometry
NBS: *N*-Bromosuccinimide
Et₃N: triethylamine
NIS: *N*-iodosuccinimide
NMM: *N*-methylmorpholine
NMR: Nuclear Magnetic Resonance
Pd(dppf)Cl₂: [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
Pet ether: petroleum ether
PyBOP: Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
TBAF: Tetra-butyl-ammonium iodide
TEA: triethylamine
THF: tetrahydrofuran
TFA: trifluoroacetic acid
TLC: thin layer chromatography
TMS: trimethylsilyl

Compounds according to the invention, for example, starting materials, intermediates or products, are prepared as described herein or by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature.

Compounds useful according to the invention may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, for example those described by Larock, R.C., *Comprehensive Organic Transformations*, VCH publishers, (1989), which is hereby incorporated by reference in its entirety.

Materials and Methods

Acetic acid, dithiothreitol and Glycine were obtained from Sigma (St. Louis, Missouri, United States), DMSO was purchased from Merck Millipore (Bayswater, Victoria, Australia), and 1M TRIS buffer was acquired from 1st BASE (Selangor, Malaysia). All reagents and solvents were commercial grade and were used as received unless noted otherwise. GLDC and lipoylated protein were produced in-house according to in-house standard operating procedures. Low density volume microplates (LP-0200) were purchased from Labcyte (San Jose, California, United States), and 384-well polypropylene assay plates (781280) were obtained from Greiner Bio-one (Kremsmünster, Austria). General experimental conditions for Chemisry: Flash chromatography was performed on a Teledyne,

Isco RF200 is the model, using prepacked silica gel columns. Proton magnetic resonance spectra were recorded on an FT-NMR spectrometer Varian 400 MHz Mercury Plus, Bruker ARX400 MHz. LC MS analyses were performed on a Agilent 1200 series or RapidFire360 series with PDA detector and Ion Trap Mass detector; Waters Acquity UPLC with PDA, ELSD and Quattro micro mass detector; Waters Acquity UPLC with PDA and 3100 mass detector; Agilent 1100 and 1200 series with PDA detector and Single Quadrupole Mass detector; Shimadzu 2020 with PDA detector and Single Quadrupole Mass detector. Reverse phase HPLC analyses were performed on a Waters Alliance HPLC system with a PDA detector, Waters Acquity UPLC system with a PDA detector; Varian prostar system with PDA detector. The following columns were used: Waters Acquity BEH;C18;100x2.1mm, 1.7 μ ; Waters X-Bridge;C18;250x4.6mm, 5 μ ; Waters X-Bridge C8;250x4.6mm, 5 μ ; Waters X-Bridge; C18;100x4.6mm, 3.5 μ ; Phenomenex Luna, C18, 100x4.6 mm, 5 μ ; Phenomenex Luna, C18, 250x4.6 mm, 5 μ . Purifications by preparative HPLC were performed on a Waters 2545 Binary Gradient prep system with 2767 Auto sampler, Gilson GX-281 with UV detector, Shimadzu Prominence UFLC with diode array; Shimadzu Prominence with UV detector; Varian Prostar with PDA detector.

Example 1

GLDC biochemical assay

Half maximal inhibitory concentrations (IC_{50}) of each compound against glycine decarboxylase activity were determined biochemically using mass spectrometry. A ten point three-fold serial dilution was performed with a Bravo liquid handler (Agilent) from 2.8 mM of each test compound solution dissolved in 100% DMSO in a low volume plate. 0.75 μ L aliquots of the dilution series were then transferred into an assay plate in duplicate. The biochemical assay was performed by pre-incubating GLDC (0.2 μ M) with pre-dispensed compounds in assay wells at room temperature for 25 minutes. Lipoylated H-protein substrate and glycine (15 μ M and 600 μ M respectively) were subsequently added and incubated for 20 minutes at room temperature. The assay was conducted in a final reaction volume of 30 μ L in 10 mM Tris, pH 7.5, then stopped with 4% v/v of acetic acid and 0.5 mM DTT. Each reaction was analysed with a 6520 Accurate Mass Quadrupole-TOF mass spectrometer.

Data handling and analysis

GLDC activity was measured as a percentage of product formed using area measured by peak integration of substrate and product peaks (H-protein and H_{am}-protein respectively) using the following equation:

$$\% \text{ product formed} = \left[\frac{\text{Area under curve of Product peak}}{\text{Area under curve of (Product + Substrate)peak}} \right] \times 100\%$$

Acquired ion chromatograms for each assay plate were extracted, integrated and exported as text files using the MassHunter analysis software (Agilent), then processed using an in-house developed script to generate data files ready for import into ActivityBase (ID Business Solutions Ltd, Surrey, UK). Processed data was further analysed as percentage inhibition data points, which were then plotted and

fitted to generate dose response curves and derive IC₅₀ values for each test compound against GLDC activity within ActivityBase,

Example 2

General Procedures

General Procedure A

To a solution of a 4-chloroquinazoline derivative in DMSO (2 mL/mmol) was added the amine (1 eq), copper iodide (0.1 eq), L-proline (0.6 eq) and potassium carbonate (2 eq). The reaction mixture was stirred at room temperature for 15 minutes, was then acidified with 1N HCl (1.5 mL/mol), diluted with water (2 mL/mmol) and extracted with dichloromethane (3X). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was then diluted with DCM and washed with brine (3 X). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue (reaction crude product) was purified as described.

General Procedure B

To a solution of a 5-bromoquinazolin-4-yl (carboxylic acid or carboxylic ester) derivative (175 mg, 0.48 mmol) in a mixture of DMF or 1,4-dioxane (4 mL/mmol) and water (1 mL/mmol) was added the boronic acid (1.5 to 2 eq), Pd(PPh₃)₄ (0.1 eq) and potassium phosphate tribasic or Cs₂CO₄ (2 eq). The reaction mixture was either heated under nitrogen in an oil bath at 110 °C overnight or in a microwave apparatus at 120 °C for 2 hours, was then acidified with 1N HCl (2 eq), diluted with water (4 mL/mmol) and extracted with dichloromethane (2 X). The combined organic layers were then washed with brine (2 X), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue (reaction crude product) was purified as described.

General Procedure C

To a solution of carboxylic ester (160 mg, 0.37 mmol) in a mixture of either THF (4 mL/mmol) and water (1.3 mL/mmol) or MeOH (2.7 mL/mmol), dioxane (2.7 mL/mmol), and water (2.7 mL/mmol) was added LiOH (2 eq). The reaction mixture was stirred at room temperature overnight, was diluted with water and extracted with dichloromethane (2 X mL). The aqueous layer was acidified with 1N HCl and extracted with dichloromethane (3 X). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a residue (reaction crude product) that was purified as described.

General Procedure D

To a solution of quinazolin-4(3H)-one derivative (200 mg, 0.69 mmol) in POCl₃ (5 mL/mmol) was added the amine (3 eq). The reaction mixture was heated at 120 °C for 5 hours, was cooled to room temperature. The reaction mixture was then diluted in dichloromethane and poured into cold water. The resulting solution pH was adjusted to 6-7 with 1N NaOH. The organic layer was dried over

anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford a residue (reaction crude product) that was purified as described.

General Procedure E

To a solution of *5-bromoquinazolin derivative* (100 mg, 0.30 mmol) in a mixture of 1,4-dioxane (6.7 mL/mmol) and water (1.3 mL/mmol) was added *the boronic acid* (1.5-2.0 eq), Pd(dppf)Cl₂.CH₂Cl₂ (0.1 eq) and cesium carbonate (2 eq) or K₃PO₄ (2 eq). The reaction mixture was heated at 90 °C overnight under nitrogen, was then quenched with 1N HCl, filtered through celite and concentrated under reduced pressure. The residue was then diluted with water and extracted with dichloromethane (3 X). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a residue (reaction crude product) that was purified as described.

General Procedure F

To a solution of nitrile derivative (150 mg, ~0.301 mmol) in toluene were added NaN₃ (17 eq) and TEA.HCl (10 eq). The reaction mixture was heated at 110 °C for 16 hours and was filtered. The filtrate was concentrated under reduced pressure to afford a residue (reaction crude product) that was purified as described.

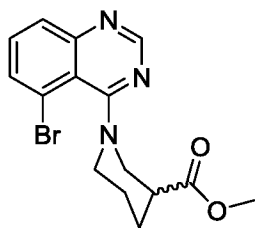
General Procedure G

A solution of 4-chloroquinazoline derivative and TEA or DIPEA (3 eq) in THF or DMF was heated at 80 °C for 10 hours or at 120 °C in a microwave reactor for 30 minutes. The reaction mixture was either concentrated to a smaller volume and purified or was diluted with water and extracted with ethyl acetate (2 X). The extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford a residue (reaction crude product) that was purified as described.

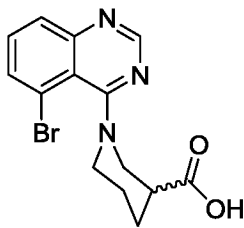
Example 3

The following list represents the exemplified compounds of this disclosure, together with the biological activity data.

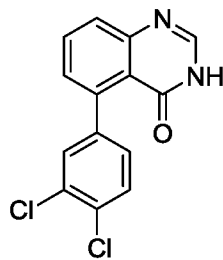
Intermediate List



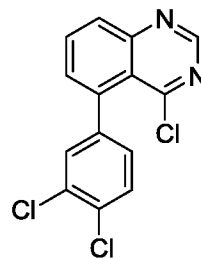
Intermediate 1



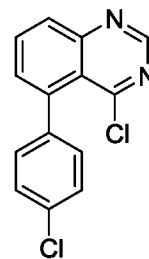
Intermediate 2



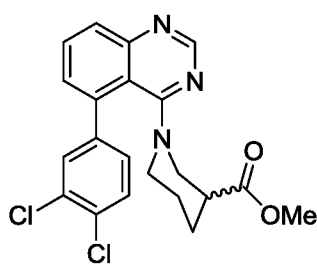
Intermediate 3



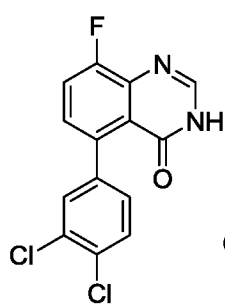
Intermediate 4



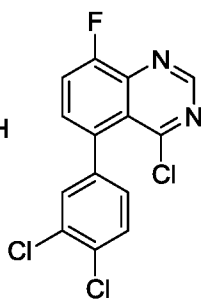
Intermediate 5



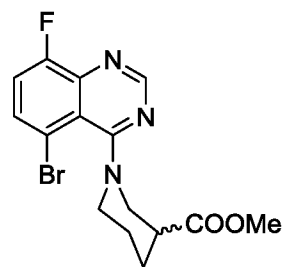
Intermediate 6



Intermediate 7



Intermediate 8



Intermediate 9

Compound List

Example	Structure	Example	Structure	Example	Structure	Example	Structure
001		011		021		031	
002		012		022		032	
003		013		023		033	
004		014		024		034	
005		015		025		035	
006		016		026		036	
007		017		027		037	
008		018		028		038	
009		019		029		039	
010		020		030		040	

Example	Structure	Example	Structure	Example	Structure	Example	Structure
041		051		061		071	
042		052		062		072	
043		053		063		073	
044		054		064		074	
045		055		065		075	
046		056		066		076	
047		057		067		077	
048		058		068		078	
049		059		069		079	
050		060		070		080	

Example	Structure	Example	Structure	Example	Structure	Example	Structure
081		091		101		111	
082		092		102		112	
083		093		103		113	
084		094		104		114	
085		095		105		115	
086		096		106		116	
087		097		107		117	
088		098		108		118	
089		099		109		119	
090		100		110		120	

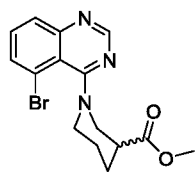
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122		132		142		152	
123		133		143		153	
124		134		144		154	
125		135		145		155	
126		136		146		156	
127		137		147		157	
128		138		148		158	
129		139		149		159	
130		140		150		160	

Example	Structure	Example	Structure	Example	Structure	Example	Structure
161		171		181		191	
162		172		182		192	
163		173		183		193	
164		174		184		194	
165		175		185		195	
166		176		186		196	
167		177		187		197	
168		178		188		198	
169		179		189		199	
170		180		190		200	

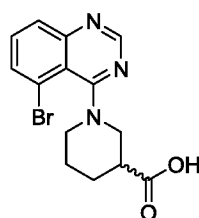
Example	Structure	Example	Structure
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202		209	
203		210	
204		211	
205		212	
206		213	
207			

Example	Structure	Example	Structure	Example	Structure
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215		221		227	
216		222		228	
217		223		229	
218		224		230	
219		225			

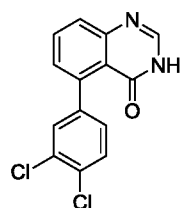
Example 4

Characterization data**Intermediate 1: Methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate**

To a solution of 5-bromo-4-chloroquinazoline (6.8 g, 28.09 mmol) in THF (175 mL) were added methyl piperidine-3-carboxylate (5.2 mL, 36.52 mmol) and TEA (11.8 mL, 84.29 mmol) at rt. The reaction mixture was heated at 80 °C for 3 hours and was diluted with water, extracted with ethyl acetate. The combined organic phase was dried over Na₂SO₄, filtered and concentrated. The crude compound was purified by column chromatography (silica gel, eluent Pet ether/EtOAc 80/20) to afford methyl-1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (7 g, 77%, AUC-HPLC 95%) as a pale yellow gummy solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.63–8.58 (m, 1H), 7.80 (q, *J* = 10.4 Hz, 1H), 7.68 (dd, *J* = 7.2 Hz, 16.2 Hz, 1H), 7.54–7.47 (m, 1H), 4.40 (d, *J* = 13.2 Hz, 1H), 4.13–4.09 (m, 1H), 3.93 (d, *J* = 3.2 Hz, 1H), 3.56 (s, 3H), 3.52–3.39 (m, 1H), 3.17–3.12 (m, 1H), 2.17–2.04 (m, 1H), 1.97–1.90 (m, 1H), 1.80–1.69 (m, 2H); MS (ESI) *m/z*: 350.16 [C₁₅H₁₆BrN₃O₂ + H]⁺.

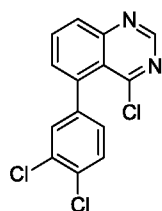
Intermediate 2: 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid

A solution of methyl-1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (1.7 g, 4.85 mmol), LiOH·H₂O (400 mg, 9.71 mmol) in THF:H₂O (40 mL) was stirred at rt for 4 hours. The reaction mixture was concentrated to a smaller volume and acidified with aq. KHSO₄ solution to pH-5. The precipitate was isolated by filtration and dried to afford 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (1.36 g, 85%, AUC HPLC 97.75%) as a white solid. mp. 219–227 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.52 (d, *J* = 14.0 Hz, 1H), 7.81–7.73 (m, 2H), 7.66–7.61 (m, 1H), 4.22 (d, *J* = 14 Hz, 1H), 4.01–3.91 (m, 1H), 3.67–3.64 (m, 1H), 3.47–3.36 (m, 1H), 3.10–3.04 (m, 1H), 2.40 (bs, 1H), 2.01–1.66 (m, 3H); MS (ESI) *m/z*: 336.20 [C₁₅H₁₆BrN₃O₂ + H]⁺.

Intermediate 3: 5-(3,4-dichlorophenyl)quinazolin-4(3H)-one

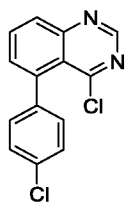
To a solution of 5-bromoquinazolin-4(3*H*)-one (10 g, 44.64 mmol), 3,4-dichlorophenylboronic acid (15.26 g, 80.35 mmol) and potassium phosphate (18.92 g, 89.28 mmol) in a mixture of 1,4 Dioxane (400 mL) and water (50 mL) was added Pd(dppf)Cl₂.DCM (2.91 g, 3.57 mmol) under argon and the reaction mixture was heated at 100 °C for 16 hours. The reaction mixture was concentrated under reduced pressure. The residue was diluted with water (100 mL), extracted with ethyl acetate. The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude was triturated with DCM and the solid was isolated by filtration and dried to afford 5-(3,4-dichlorophenyl)quinazolin-4(3*H*)-one (9.5 g 73.13%, LC-MS 96.86%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 12.10 (bs, 1H), 8.06 (s, 1H), 7.87 (t, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.58–7.53 (m, 2H), 7.26 (d, *J* = 6.4 Hz, 2H); MS (ESI) *m/z*: 291.21 [C₁₄H₈Cl₂N₂O+H]⁺.

Intermediate 4: 4-chloro-5-(3,4-dichlorophenyl)quinazoline:



A solution of 5-(3,4-dichlorophenyl)quinazolin-4(3*H*)-one (4 g, 13.74 mmol) in SOCl₂ (50 mL) and a catalytic amount of DMF (0.5 mL) was heated to 80 °C for 6 hours. The reaction mixture was concentrated under reduced pressure and dissolved in DCM. The organic phase was washed with an aqueous solution of NaHCO₃, dried over Na₂SO₄ filtered and concentrated. The crude compound was purified by silica gel column (silica gel, eluant Pet ether/EtOAc 90:10) to afford 4-chloro-5-(3,4-dichlorophenyl)quinazoline (3.6 g, 85%, LC-MS 94.86) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 9.05 (s, 1H), 8.15 (d, *J* = 7.6 Hz, 1H), 7.95 (t, *J* = 7.6 Hz, 1H), 7.57–7.51 (m, 3H), 7.18 (dd, *J* = 1.2 Hz, 7.6 Hz, 1H); MS (ESI) *m/z*: 309.09 [C₁₄H₇Cl₃N₂+H]⁺.

Intermediate 5: 4-chloro-5-(4-chlorophenyl)quinazoline



Step 1: 5-(4-chlorophenyl)quinazolin-4(3*H*)-one

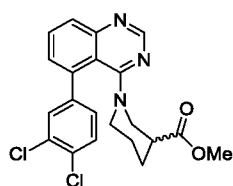
To a solution of 5-bromoquinazolin-4(3*H*)-one (3 g, 13.39 mmol) in 1, 4-dioxane (30 mL) and water (10 mL) was added 4-chlorophenylboronic acid (110 mg, 0.7250 mmol), K₃PO₄ (5.6 g, 26.78 mmol) and Pd(dppf)₂Cl₂.DCM complex (1.0 g, 1.339 mmol). The reaction mixture was heated to 100 °C for 16 hours, was diluted with water (50 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts was washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The crude product was purified by column chromatography (silica gel, DCM/MeOH 98/2) to afford 5-(4-chlorophenyl)quinazolin-4(3*H*)-one (2.5 g, 72%, LC-MS 96%). ¹H

NMR (400 MHz, DMSO- d_6) δ (ppm): 12.01 (s, 1H), 8.06 (d, $J = 3.6$ Hz, 1H), 7.79 (t, $J = 8.0$ Hz, 1H), 7.68 (d, $J = 8.0$ Hz, 1H), 7.39 (d, $J = 8.4$ Hz, 2H), 7.27 (m, 3H); MS (ESI) m/z : 257.35 [$C_{14}H_9ClN_2O+H$] $^+$.

Step 2: 4-chloro-5-(4-chlorophenyl)quinazoline

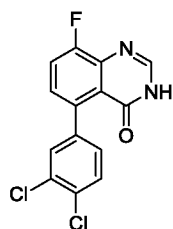
To a solution of 5-(4-chlorophenyl)quinazolin-4(3H)-one (1.6 g, 5.85 mmol) in $SOCl_2$ (18 mL) was added a catalytic amount of DMF and the mixture was heated to 85 °C for 3 hours. The reaction mixture was concentrated under reduced pressure and treated with ice-water. The precipitate was isolated by filtration, washed with *n*-pentane and dried to afford 4-chloro-5-(4-chlorophenyl)quinazoline (1.6 g, LC-MS 70%) as a yellow solid.

Intermediate 6: Methyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxylate

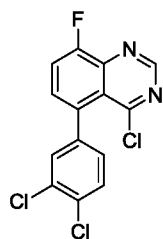


To a solution of 4-chloro-5-(3,4-dichlorophenyl)quinazoline (400 mg, 1.302 mmol) in THF (30 mL) were added methyl piperidine-3-carboxylate (370 mg, 2.605 mmol) and TEA (0.54 mL, 3.908 mmol) and the mixture was stirred at 80 °C for 10 hours. The reaction mixture was diluted with water and extracted with ethyl acetate (2 x 20 mL). The combined organic phase was dried over Na_2SO_4 , filtered and concentrated. The crude compound was purified by column chromatography (silica gel, eluent pet-ether/EtOAc 80/20) to afford methyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxylate (500 mg, 92%, LC-MS 85%) as an off-white solid. MS (ESI) m/z : 416.18 [$C_{21}H_{19}Cl_2N_3O_2+H$] $^+$.

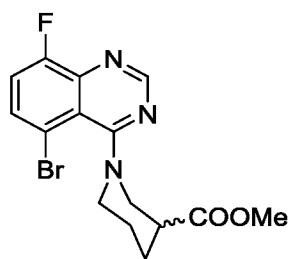
Intermediate 7: 5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4(3H)-one



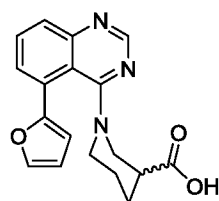
To a solution of 5-bromo-8-fluoroquinazolin-4(3H)-one (2.5 g, 10.37 mmol), 3,4-dichlorophenylboronic acid (3.54 g, 18.67 mmol) and potassium phosphate (4.39 g, 20.74 mmol) in 1,4-dioxane (130 mL) and water (20 mL) was added $Pd(dppf)Cl_2 \cdot DCM$ (507 mg, 0.62 mmol) under argon. The reaction mixture was heated at 100 °C for 16 hours and was diluted with water. The aqueous phase was extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 , filtered and concentrated under the reduced pressure. The crude compound was triturated with DCM and the solid was isolated by filtration and dried to afford 5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4(3H)-one, (2.5 g, 78%, LC-MS 77%) as an off-white solid. MS (ESI) m/z : 309.13 [$C_{14}H_7Cl_2FN_2O+H$] $^+$.

Intermediate 8: 4-chloro-5-(3,4-dichlorophenyl)-8-fluoro-3,4-dihydroquinazoline

A solution of 5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4(3*H*)-one (1.5 g, 4.13 mmol) in SOCl_2 (15 mL) in presence of a catalytic amount of DMF (0.2 mL) was heated at 80 °C for 4 hours. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in DCM. The organic phase was washed with an aqueous solution of NaHCO_3 , dried over Na_2SO_4 , filtered and concentrated to afford 4-chloro-5-(3,4-dichlorophenyl)-8-fluoro-3,4-dihydroquinazoline, Intermediate 8, (1.2 g, 92%, LC-MS 88%) as yellow solid. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 9.01 (s, 1H), 7.69 (t, J = 8.4 Hz, 1H), 7.52 (t, J = 8.4 Hz, 1H), 7.44 (d, J = 1.6 Hz, 2H), 7.11–7.15 (m, 1H); MS (ESI) m/z : 329.16 $[\text{C}_{14}\text{H}_8\text{Cl}_3\text{FN}_2 + \text{H}]^+$.

Intermediate 9: Methyl 1-(5-bromo-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate

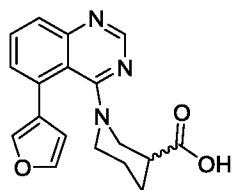
To a solution of 5-bromo-4-chloro-8-fluoroquinazoline (1.39 g, 5.35 mmol) in THF (2.0 mL) was added methyl piperidine-2-carboxylate (1.15 g, 8.03 mmol) and TEA (1.5 mL, 10.70 mmol). The resulting mixture was heated at 75 °C for 5 hours and was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent Hexane/Ethyl acetate 100:0 to 50:50) to afford methyl 1-(5-bromo-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (1.96 g, 99.9%) as a viscous oil. ^1H NMR (400 MHz, $\text{MeOD}-d_4$) δ (ppm): 8.70-8.31 (m, 1H), 7.70 (s, 1H), 7.61-7.32 (m, 1H), 4.66-3.83 (m, 2H), 3.81-3.22 (m, 5H), 2.92-2.54 (m, 1H), 2.21-1.13 (m, 4H); MS (ESI) m/z : 368.0 $[\text{C}_{15}\text{H}_{15}\text{BrFN}_3\text{O}_2 + \text{H}]^+$.

Compound 1: 1-(5-(furan-2-yl)quinazolin-4-yl)piperidine-3-carboxylic acid

Step 1: The title compound was prepared in a similar fashion as described in general procedure B starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (100 mg, 0.29 mmol) and 2-(furan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (112.54 mg, 0.58 mmol). The reaction crude product was purified by column chromatography (silica gel, 100% DCM, DCM/Methanol 95:5 to DCM/MeOH/AcOH 95:4.5:0.5) to afford methyl 1-(5-(furan-2-yl)quinazolin-4-yl)piperidine-3-carboxylate (38.16 mg, 0.11 mmol, 39 %) as yellow thick oil. MS (ESI) m/z 338.10 [$C_{19}H_{19}N_3O_3 + H$]⁺.

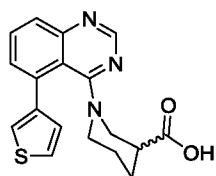
Step 2: The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(furan-2-yl)quinazolin-4-yl)piperidine-3-carboxylate (35 mg, 0.10 mmol). The crude product was purified by preparative HPLC to afford 1-(5-(furan-2-yl)quinazolin-4-yl)piperidine-3-carboxylic acid (0.77 mg, 2.38 μ mol, AUC HPLC 97.64 %) as off-white solid; 8.48 (bs, 1H), 7.80 (2d, J = 8.0, 7.6 Hz, 1H), 7.70 (bs, 1H), 7.64 (d, J = 7.6 Hz, 1H),), 7.60 (d, J = 7.2 Hz, 1H), 7.58-7.53 (m, 1H), 7.16 (bs, 1H), 4.45-4.30 & 4.00-3.85 (2m, 1H), 3.80-3.60 (m, 1H), 3.10-3.00 (m, 1H), 2.80-2.60 & 2.50-2.30 (2m, 1H), 2.05-1.85 (m, 1H), 1.80-1.60 (m, 2H), 1.59-1.20 (m, 2H); MS (ESI) m/z 324.10 [$C_{18}H_{17}N_3O_3 + H$]⁺.

Compound 2: 1-(5-(furan-3-yl)quinazolin-4-yl)piperidine-3-carboxylic acid



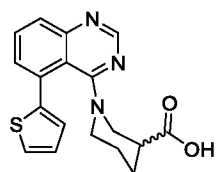
Step 1: The title compound was prepared in a similar fashion as described in general procedure B starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (100 mg, 0.29 mmol) and furan-3-ylboronic acid (64.89 mg, 0.58 mmol). The crude product was purified by preparative HPLC to afford methyl 1-(5-(furan-3-yl)quinazolin-4-yl)piperidine-3-carboxylate (37 mg, 0.11 mmol, 37.8 %) as a thick oil; MS (ESI) m/z 338.10 [$C_{19}H_{19}N_3O_3 + H$]⁺.

Step 2: The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(furan-3-yl)quinazolin-4-yl)piperidine-3-carboxylate (37 mg, 0.11 mmol). The reaction crude product was purified by preparative HPLC to afford 1-(5-(furan-3-yl)quinazolin-4-yl)piperidine-3-carboxylic acid (3.56 mg, 0.011 mmol, 10 %, AUC HPLC 99.08 %) as off-white solid; ¹H NMR (400 MHz, MeOD) δ (ppm): 8.50 (s, 1H), 7.81 (2d, J = 7.6, 7.2 Hz, 2H), 7.69 (bs, 1H), 7.63 (s, 1H), 7.58 (d, J = 7.2 Hz, 1H),), 6.60 (d, J = 18.0 Hz, 1H), 4.45-4.30 & 4.00-3.85 (2m, 1H), 3.80-3.60 (m, 1H), 3.10-3.00 (m, 1H), 2.80-2.60 & 2.50-2.30 (2m, 1H), 2.05-1.85 (m, 1H), 1.80-1.60 (m, 2H), 1.59-1.20 (m, 2H); MS (ESI) m/z 324.10 [$C_{18}H_{17}N_3O_3 + H$]⁺.

Compound 3: 1-(5-(thiophen-3-yl)quinazolin-4-yl)piperidine-3-carboxylic acid

Step 1: The title compound was prepared in a similar fashion as described in general procedure A starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (100 mg, 0.29 mmol) and thiophen-3-ylboronic acid (74.21 mg, 0.58 mmol). The reaction crude product was purified using column chromatography (silica gel, eluent 100% DCM, DCM/Methanol 95:5 to DCM:MeOH/AcOH 95:4.5:0.5) to afford methyl 1-(5-(thiophen-3-yl)quinazolin-4-yl)piperidine-3-carboxylate (86.7 mg, 0.25 mmol, 84.6 %) as thick gel; MS (ESI) m/z 354.10 [$C_{19}H_{19}N_3O_2S + H$] $^+$.

Step 2: The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(thiophen-3-yl)quinazolin-4-yl)piperidine-3-carboxylate (85 mg, 0.24 mmol). The reaction crude product was purified by preparative HPLC to afford 1-(5-(thiophen-3-yl)quinazolin-4-yl)piperidine-3-carboxylic acid (8.45 mg, 0.025 mmol, 10.4 %, AUC HPLC 99.54 %) as a white solid; ^1H NMR (400 MHz, MeOD) δ (ppm): 8.50 (bs, 1H), 7.83 (2d, $J = 8.0$, 7.6 Hz, 1H), 7.70 (d, $J = 8.0$ Hz, 1H), 7.63 (d, $J = 7.2$ Hz, 1H), 7.60-7.50 (m, 2H), 7.21 (bs, 1H), 4.45-4.30 & 4.00-3.85 (2m, 1H), 3.80-3.60 (m, 1H), 3.10-2.75 (m, 1H), 2.50-2.30 (m, 1H), 2.00-1.80 (m, 1H), 1.79-1.60 (m, 1H), 1.59-1.45 (m, 1H), 1.44-1.20 (m, 1H), 1.19-1.00 (m, 1H); MS (ESI) m/z 340.10 [$C_{18}H_{17}N_3O_2S + H$] $^+$.

Compound 4: 1-(5-(thiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylic acid**Step 1: methyl 1-(5-(thiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylate**

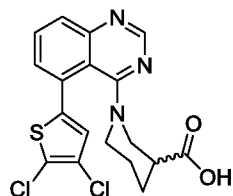
The title compound was prepared in a similar fashion as described in general procedure B starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (100 mg, 0.29 mmol) and thiophen-2-ylboronic acid (74.22 mg, 0.58 mmol). The residue was purified by flash column chromatography (silica gel, eluent 100 % DCM, DCM/MeOH 95:5 to DCM: MeOH/AcOH 95:5) to afford methyl 1-(5-(thiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylate (17.13 mg, 0.048 mmol, 16.7 %) as thick oil; MS (ESI) m/z 354.10 [$C_{19}H_{19}N_3O_2S + H$] $^+$.

Step 2: 1-(5-(thiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(thiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylate (15 mg, 0.042 mmol). The reaction crude product was purified by preparative HPLC to afford 1-(5-(thiophen-2-yl)quinazolin-4-

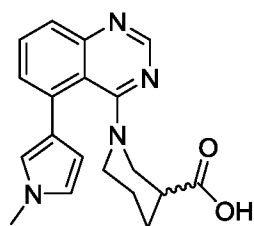
yl)piperidine-3-carboxylic acid (1.36 mg, 4.00 μ mol, 9.5 %, AUC HPLC 98.07 %) as off-white solid; ^1H NMR (400 MHz, MeOD) δ (ppm): 8.47 (bs, 1H), 7.79 (2d, J = 8.0, 7.6 Hz, 1H), 7.72 (bs, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.62 (d, J = 7.2 Hz, 1H), 7.58-7.53 (m, 2H), 7.16 (bs, 1H), 4.05-3.70 (m, 1H), 3.05-2.70 (m, 1H), 2.60-2.20 (m, 1H), 2.10-1.70 (m, 2H), 1.69-1.40 (m, 3H), 1.20-1.00 (m, 1H); MS (ESI) m/z 340.10 [$\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_2\text{S} + \text{H}$] $^+$.

Compound 5: 1-(5-(4,5-dichlorothiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylic acid

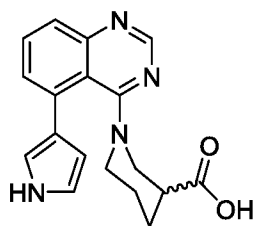


The title compound was prepared in a similar fashion as described in general procedure E using (4,5-dichlorothiophen-2-yl)boronic acid (200 mg, 1.02 mmol). The residue was purified by preparative HPLC to afford 1-(5-(4,5-dichlorothiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylic acid (1.02 mg, 2.50 μ mol, AUC HPLC 96.66 %) as off-white solid; ^1H NMR (400 MHz, MeOD- d_4) δ (ppm): 8.51 (d, J = 17.4 Hz, 1H), 7.81 (s, 2H), 7.62-7.60 (m, 1H), 7.11 (d, J = 17.4 Hz, 1H), 4.50-4.40, 4.10-4.00 & 3.80-3.70 (3m, 1H), 3.10-2.80 (m, 1H), 2.70-2.60 & 2.40-2.30 (2m, 1H), 2.05-1.90 (m, 1H), 1.80-1.50 (m, 2H), 1.40-1.15 (m, 2H), 1.00-0.80 (m, 1H); MS (ESI) m/z 408.00 [$\text{C}_{18}\text{H}_{15}\text{Cl}_2\text{N}_3\text{O}_2\text{S} + \text{H}$] $^+$.

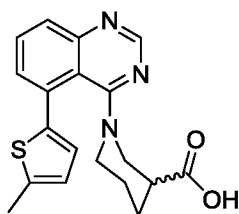
Compound 6: 1-(5-(1-methyl-1H-pyrrol-3-yl)quinazolin-4-yl)piperidine-3-carboxylic acid



The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole (124.25 mg, 0.60 mmol). The residue was by preparative HPLC to afford 1-(5-(1-methyl-1H-pyrrol-3-yl)quinazolin-4-yl)piperidine-3-carboxylic acid (8.1 mg, 0.024 mmol, 8.03 %, AUC HPLC 99.67 %) as white solid. ^1H NMR (400 MHz, MeOD) δ (ppm): 8.46 (s, 2H), 7.82-7.77 (m, 1H), 7.76-7.69 (m, 2H), 7.61 (td, J = 8.0, 3.2 Hz, 2H), 4.55-4.40 (m, 1H), 4.20-4.00 (m, 1H), 3.80-3.60 (m, 1H), 3.55-3.40 (m, 2H), 2.90-2.80 & 2.75-2.50 (2m, 1H), 2.20-2.05 (m, 2H), 1.90-1.70 (m, 3H), 1.50-1.20 (m, 1H); MS (ESI) m/z 337.10 [$\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}_2 + \text{H}$] $^+$.

Compound 7: 1-(5-(1H-pyrrol-3-yl)quinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure B starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (196 mg, 0.56 mmol) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole (216.22 mg, 1.12 mmol). The residue was purified by preparative HPLC to afford 1-(5-(1H-pyrrol-3-yl)quinazolin-4-yl)piperidine-3-carboxylic acid (16.7 mg, 0.052 mmol, AUC HPLC 97.61 %) as yellow solid. ^1H NMR (400 MHz, MeOD) δ (ppm): 8.42 (s, 1H), 7.85-7.75 (m, 1H), 7.65-7.55 (m, 1H), 7.49 (d, $J = 7.6$ Hz, 1H), 7.01 (s, 1H), 6.88 (s, 1H), 6.24 (d, $J = 11.2$ Hz, 1H), 3.90-3.70 (m, 1H), 3.55-3.40 & 3.25-3.15 (2m, 1H), 2.90-2.75 (m, 1H), 2.65-2.50 & 2.40-2.25 (2m, 1H), 2.00-1.75 (m, 2H), 1.70-1.45 (m, 2H), 1.40-1.15 (m, 1H); MS (ESI) m/z 323.10 [$\text{C}_{18}\text{H}_{18}\text{N}_4\text{O}_2 + \text{H}$] $^+$.

Compound 8: 1-(5-(5-methylthiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylic acid**Step 1: Preparation of methyl 1-(5-(5-methylthiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylate:**

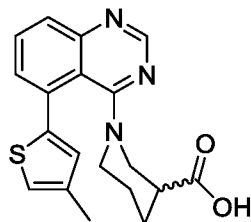
The title compound was prepared in a similar fashion as described in general procedure E starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (200 mg, 0.57 mmol) and 4,4,5,5-tetramethyl-2-(5-methylthiophen-2-yl)-1,3,2-dioxaborolane (0.3 mL, 1.14 mmol). The crude was purified by column chromatography (silica gel, eluent pet-ether/EtOAc 60:40) to afford methyl 1-(5-(5-methylthiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylate (200 mg 95%, LC-MS 90%) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.62 (bs, 1H), 7.77 (bs, 1H), 7.67 (t, $J = 7.2$ Hz, 1H), 7.48 (d, $J = 7.2$ Hz, 1H), 6.84 (bs, 1H), 6.74 (s, 1H), 3.86-3.78 (m, 2H), 3.68-3.60 (m, 3H), 3.49 (s, 1H), 2.84 (q, $J = 12.0$ Hz, 2H), 2.54 (s, 4H), 2.04-1.90 (m, 2H), 1.70 (s, 1H); MS (ESI) m/z : 368.49 [$\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_2\text{S} + \text{H}$] $^+$.

Step 2: Preparation of 1-(5-(5-methylthiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylic acid:

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(5-methylthiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylate (200 mg, 0.54 mmol). The reaction mixture was concentrated to half the volume and acidified with aq. KHSO_4 to pH 5. The precipitate was isolated by filtration and dried to afford 1-(5-(5-methylthiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylic acid (125 mg, 65%, AUC-HPLC 99.50 %) as a green solid,

m.p: 107-116 °C; ^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.43 (bs, 1H), 7.76 (t, $J = 7.6$ Hz, 1H), 7.66 (bs, 1H), 7.58–7.56 (m, 1H), 6.92 (bs, 1H), 6.82 (bs, 1H), 4.01–3.85 (m, 1H), 3.13–3.12 (m, 1H), 2.99–2.87 (m, 1H), 2.59–2.54 (m, 3H), 2.31 (bs, 1H), 1.96 (s, 1H), 1.80 (bs, 1H), 1.64–1.51 (m, 2H), 1.28–1.19 (m, 1H); MS (ESI) m/z : 354.16 $[\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_2\text{S}+\text{H}]^+$.

Compound 9: 1-(5-(4-methylthiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylic acid



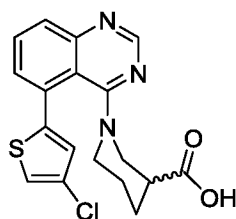
Step 1: Preparation of methyl 1-(5-(4-methylthiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylate

The title compound was prepared in a similar fashion as described in general procedure E starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (250 mg, 0.684 mmol) and 4-methylthiophen-2-ylboronic acid (106 mg, 0.753 mmol). The residue was purified by column chromatography (silica gel, eluent DCM/MeOH 99/1) to afford methyl 1-(5-(4-methylthiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylate (150 mg, 57%, LC-MS 94%) as a pale brown gummy solid. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.52–8.70 (m, 1H), 7.77–7.82 (m, 2H), 7.62–7.70 (m, 1H), 7.50–7.55 (m, 1H), 6.80–6.89 (m, 2H), 3.85–4.0 (m, 2H), 3.50–3.52 (m, 3H), 2.70–2.91 (m, 2H), 2.49–2.51 (m, 1H), 2.30 (s, 3H), 1.89–2.01 (m, 1H), 1.7121.80 (m, 1H), 1.40–1.51 (m, 1H); MS (ESI) m/z : 368.43 $[\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_2\text{S}+\text{H}]^+$.

Step 2: Preparation of 1-(5-(4-methylthiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(4-methylthiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylate (150 mg, 0.408 mmol). The reaction mixture was concentrated to half the volume and acidified with aq. KHSO_4 solution to pH 5. The precipitate was isolated by filtration and dried to afford 1-(5-(4-methylthiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylic acid (30 mg, 21%, AUC-HPLC 97%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 8.50–8.45 (m, 1H), 7.81–7.74 (m, 2H), 7.58 (d, $J = 6.0$ Hz, 1H), 7.23 (s, 1H), 7.00–6.94 (m, 1H), 3.85–3.67 (m, 2H), 2.88–2.71 (m, 2H), 2.26 (m, 3H), 1.80–1.78 (m, 1H), 1.67–1.23 (m, 3H), 0.99–0.85 (m, 1H); MS (ESI) m/z : 354.159 $[\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_2\text{S}+\text{H}]^+$.

Compound 10: 1-(5-(4-chlorothiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylic acid

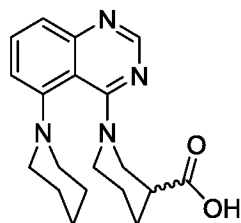


Step 1: Preparation of methyl 1-(5-(4-chlorothiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylate:

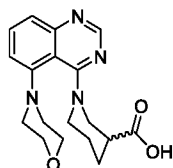
The title compound was prepared in a similar fashion as described in general procedure E starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (150 mg, 0.42 mmol) and 4-chlorothiophen-2-ylboronic acid (209 mg, 0.85 mmol). The crude product was purified by column chromatography (silica gel, eluent pet-ether/EtOAc 80:20) to afford methyl 1-(5-(4-chlorothiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylate (160 mg, 96%, LC-MS 68%) as a white solid. MS (ESI) m/z : 388.36 $[\text{C}_{19}\text{H}_{18}\text{ClN}_3\text{O}_2\text{S}+\text{H}]^+$.

Step 2: Preparation of 1-(5-(4-chlorothiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(4-chlorothiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylate (160 mg, ~0.27 mmol). The crude compound was purified by preparative HPLC to afford 1-(5-(4-chlorothiophen-2-yl)quinazolin-4-yl)piperidine-3-carboxylic acid (20 mg, 19%, AUC-HPLC 98.09%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 8.58–8.51 (m, 1H), 7.80–7.72 (m, 3H), 7.60 (d, $J = 6.0$ Hz, 1H), 7.20 (d, $J = 12.8$ Hz, 1H), 3.85–3.67 (m, 2H), 2.82–2.67 (m, 1H), 2.32–2.21 (m, 1H), 1.83 (d, $J = 10.0$ Hz, 1H), 1.67–1.55 (m, 1H), 1.37–1.31 (m, 1H), 1.23–1.11 (m, 1H), 0.87 (bs, 1H); MS (ESI) m/z : 374.15 $[\text{C}_{18}\text{H}_{16}\text{ClN}_3\text{O}_2\text{S}+\text{H}]^+$.

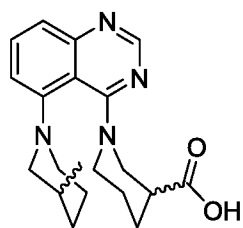
Compound 11: 1-(5-(piperidin-1-yl)quinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure A starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (100 mg, 0.29 mmol) and piperidine (0.23 mL, 2.29 mmol). The residue was purified by preparative HPLC to afford 1-(5-(piperidin-1-yl)quinazolin-4-yl)piperidine-3-carboxylic acid (4.01 mg, 0.01 mmol, AUC HPLC 96.66 %) as yellow solid. ^1H NMR (400 MHz, MeOD) δ (ppm): 8.39 (bs, 1H), 7.71 (s, 1H), 7.20 (m, 2H), 4.20–4.00 (m, 1H), 3.80–3.60 (m, 2H), 3.20–2.90 (m, 1H), 2.89–2.75 (m, 1H), 2.60–2.40 (m, 1H), 2.15–2.00 (m, 1H), 1.99–1.60 (m, 10H), 1.50–1.40 (m, 1H), 0.89 (t, $J = 6.8$ Hz, 1H); MS (ESI) m/z 341.20 $[\text{C}_{19}\text{H}_{24}\text{N}_4\text{O}_2+\text{H}]^+$.

Compound 12: 1-(5-morpholinoquinazolin-4-yl)piperidine-3-carboxylic acid

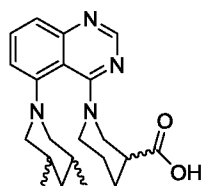
The title compound was prepared in a similar fashion as described in general procedure A starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and morpholine (0.21 mL, 2.38 mmol). The residue was purified by preparative HPLC to afford 1-(5-morpholinoquinazolin-4-yl)piperidine-3-carboxylic acid (1.73 mg, 5.05 μ mol, AUC HPLC 97.51 %) as yellow solid. ^1H NMR (400 MHz, MeOD) δ (ppm): 8.40 (bs, 1H), 7.74 (t, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.16 (bs, 1H), 4.12 (t, J = 6.4 Hz, 1H), 4.00-3.80 (m, 4H), 3.70-3.60 (m, 1H), 3.20-3.10 (m, 2H), 2.90-2.60 (m, 2H), 2.15-2.00 (m, 1H), 1.90-1.65 (m, 2H), 1.45-1.20 (m, 3H), 0.89 (t, J = 7.0 Hz, 1H); MS (ESI) m/z 343.10 [$\text{C}_{18}\text{H}_{22}\text{N}_4\text{O}_3 + \text{H}$] $^+$.

Compound 13: 1-(5-(3-methylpiperidin-1-yl)quinazolin-4-yl)piperidine-3-carboxylic acid



The title compound was prepared in a similar fashion as described in general procedure A starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (100 mg, 0.29 mmol) and 3-methylpiperidine (0.28 mL, 2.32 mmol). The residue was purified by preparative HPLC to afford 1-(5-(3-methylpiperidin-1-yl)quinazolin-4-yl)piperidine-3-carboxylic acid (0.66 mg, 1.86 μ mol, AUC HPLC 99.81%) as yellow solid; ^1H NMR (400 MHz, MeOD) δ (ppm): 8.49 (bs, 1H), 7.70 (s, 1H), 7.25-7.10 (m, 2H), 3.80-3.50 (m, 2H), 3.20-2.90 (m, 2H), 2.89-2.50 (m, 2H), 2.20-2.00 (m, 1H), 1.95-1.55 (m, 10H), 1.40-1.30 (m, 1H), 0.40-0.38 (m, 3H); MS (ESI) m/z 355.20 [$\text{C}_{20}\text{H}_{26}\text{N}_4\text{O}_2 + \text{H}$] $^+$.

Compound 14: 1-(5-(3,5-dimethylpiperidin-1-yl)quinazolin-4-yl)piperidine-3-carboxylic acid



Step 1: *N*-(2-cyano-3-fluorophenyl)pivalamide:

To a solution of 2-amino-6-fluorobenzonitrile (5 g, 36.76 mmol) in dichloromethane (50 mL) was added *tert*-butyl hypochlorite (8.823 g, 73.52 mmol) and TEA (7.95 mL) at 0 $^{\circ}\text{C}$ and the reaction mixture was stirred at rt for 16 hours. The reaction mixture was diluted with water and extracted with dichloromethane (2 x 100 mL). The extracts were dried over Na_2SO_4 , concentrated to afford *N*-(2-cyano-3-fluorophenyl)pivalamide (7 g, LC-MS 71%) as an off-white solid. MS (ESI) m/z : 220.24 [$\text{C}_{12}\text{H}_{13}\text{FN}_2\text{O} + \text{H}$] $^+$.

Step 2: *N*-(2-cyano-3-(3,5-dimethylpiperidin-1-yl)phenyl) pivalamide:

A solution of *N*-(2-cyano-3-fluorophenyl)pivalamide (1.5 g, 6.81 mmol, 3,5-dimethylpiperidine (1.15 g, 10.22 mmol) and potassium carbonate (2.78 g, 20.45 mmol) in DMF (15 mL) was heated at 120 $^{\circ}\text{C}$

for 24 hours. The reaction mixture was poured into water and extracted with ethyl acetate (2 x 50 mL). The extracts were dried over Na₂SO₄, filtered and concentrated. The crude compound was purified by column chromatography (silica gel, eluent pet-ether/EtOAc 5:95) to afford *N*-(2-cyano-3-(3,5-dimethylpiperidin-1-yl)phenyl)pivalamide (800 mg, 37%, LC-MS 98%); MS (ESI) *m/z*: 313.44 [C₁₉H₂₇N₃O+H]⁺.

Step 3: *2-amino-6-(3,5-dimethylpiperidin-1-yl) benzonitrile*:

A solution of *N*-(2-cyano-3-(3,5-dimethylpiperidin-1-yl)phenyl) pivalamide (0.8 g, 2.55 mmol) and 2M KOH in ethanol (10 mL) was heated at 100 °C for 16 hours. The reaction mixture was diluted with water and extracted with ethyl acetate (2 x 50 mL). The extracts were dried over Na₂SO₄, filtered and concentrated. The crude compound was purified by column chromatography (silica gel, eluent pet-ether/EtOAc 95/5) to afford 2-amino-6-(3,5-dimethylpiperidin-1-yl)benzonitrile (320 mg, 59%, LC-MS 99%) as a liquid. MS (ESI) *m/z*: 229.32 [C₁₄H₁₉N₃+H]⁺.

Step 4: *5-(3,5-dimethylpiperidin-1-yl)quinazolin-4(3H)-one*:

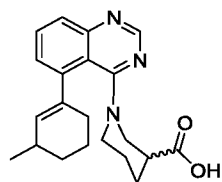
A solution of 2-amino-6-(3,5-dimethylpiperidin-1-yl) benzonitrile (0.3 g, 1.31 mmol) in formic acid (3 mL) was heated at 120 °C for 16 hours and was concentrated to a smaller volume. The residue was diluted with water, basified with aq.NaHCO₃ solution and washed with ethyl acetate. The aqueous solution was neutralised with aq.KHSO₄ solution, extracted with 10% methanol in DCM (2 x 20 mL). The extracts were dried over Na₂SO₄, filtered and concentrated to afford 5-(3,5-dimethylpiperidin-1-yl)quinazolin-4(3H)-one (190 mg, LC-MS 40%) as a colourless liquid. MS (ESI) *m/z*: 257.33 [C₁₅H₁₉N₃O +H]⁺.

Step 5: *methyl 1-(5-(3,5-dimethylpiperidin-1-yl)quinazolin-4-yl)piperidine-3-carboxylate*:

To a solution of 5-(3,5-dimethylpiperidin-1-yl)quinazolin-4(3H)-one (190 mg, 0.498 mmol) in ACN (3 mL) were added PyBOP (388 mg, 0.748 mmol), DBU (151 mg, 0.997 mmol) and methyl piperidine-3-carboxylate (142 mg, 0.997 mmol) and the mixture was stirred at rt for 16 hours. The reaction mixture was then diluted with water and extracted with ethyl acetate (2 x 50 mL). The extracts were dried over Na₂SO₄, filtered and concentrated to dryness under reduced pressure to afford methyl 1-(5-(3,5-dimethylpiperidin-1-yl)quinazolin-4-yl)piperidine-3-carboxylate (102 mg, LC-MS 80%) as a yellow liquid. MS (ESI) *m/z*: 382.50 [C₂₂H₃₀N₄O₂+H]⁺.

Step 6: *1-(5-(3,5-dimethylpiperidin-1-yl)quinazolin-4-yl)piperidine-3-carboxylic acid*

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(3,5-dimethylpiperidin-1-yl)quinazolin-4-yl)piperidine-3-carboxylate (100 mg, ~0.208 mmol). The crude compound was purified by preparative HPLC to afford 1-(5-(3,5-dimethylpiperidin-1-yl)quinazolin-4-yl)piperidine-3-carboxylic acid (39 mg, 51%, AUC-HPLC 98.71%) as a yellow solid mp: 241 °C-252 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.38 (s, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 6.97 (s, 1H), 3.25-2.80 (m, 6H), 2.28-1.68 (m, 7H), 1.66-1.55 (m, 2H), 1.05-0.75 (m, 7H), 0.64-0.59 (m, 1H); MS (ESI) *m/z*: 368.47 [C₂₁H₂₈N₄O₂+H]⁺.

Compound 15: 1-(5-(3-methylcyclohex-1-enyl)quinazolin-4-yl)piperidine-3-carboxylic acid**Step 1: Preparation of 5-(3-methylcyclohex-1-enyl)quinazolin-4(3H)-one:**

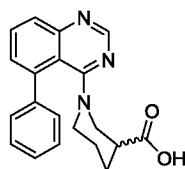
The title compound was prepared in a similar fashion as described in general procedure E starting from 5-bromoquinazolin-4(3H)-one (500 mg, 1.43 mmol) and 4,4,5,5-tetramethyl-2-(3-methylcyclohex-1-enyl)-1,3,2-dioxaborolane (636 mg, 2.86 mmol). The crude product was purified by column chromatography (silica gel, Hexane/EtOAc 50:50) to afford 5-(3-methylcyclohex-1-enyl)quinazolin-4(3H)-one (200 mg, LC-MS 91%) as a pale yellow semi solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.35–10.05 (m, 1H), 7.96 (s, 1H), 7.75–7.55 (m, 2H), 7.25–7.15 (m, 1H), 2.27 (s, 3H), 2.05–1.85 (m, 4H), 1.12–0.95 (m, 3H); MS (ESI) m/z : 241.38 [$\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}+\text{H}$] $^+$.

Step 2: Preparation of 3-methyl 1-(5-(3-methylcyclohex-1-enyl)quinazolin-4-yl)piperidine-3-carboxylate :

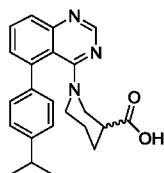
To a solution of 5-(3-methylcyclohex-1-enyl)quinazolin-4(3H)-one (270 mg, 1.12 mmol) in acetonitrile were added PyBOP (1.17 gm, 2.25 mmol) and DBU (340 mg, 2.25 mmol). The reaction mixture was stirred for 30 minutes prior to the addition of methyl piperidine-3-carboxylate (321 mg, 2.25 mmol). The reaction mixture was stirred for 16 hours at room temperature and was concentrated under reduced pressure. The residue was diluted with water and extracted with dichloromethane (2 x 20 mL). The organic phase was dried over Na_2SO_4 , filtered and concentrated. The crude was purified by column chromatography (silica gel, dichloromethane/methanol 50:50) to afford 3-methyl 1-(5-(3-methylcyclohex-1-enyl)quinazolin-4-yl)piperidine-3-carboxylate (100 mg, 24%, LC-MS 67%) as an off white solid. MS (ESI) m/z : 366.48 [$\text{C}_{22}\text{H}_{27}\text{N}_3\text{O}_2+\text{H}$] $^+$.

Step 3: Preparation of 3-1-(5-(3-methylcyclohex-1-enyl)quinazolin-4-yl)piperidine-3-carboxylic acid:

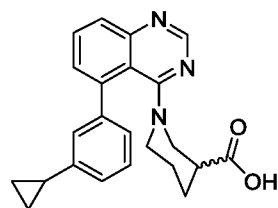
The title compound was prepared in a similar fashion as described in general procedure C starting from 3-methyl 1-(5-(3-methylcyclohex-1-enyl)quinazolin-4-yl)piperidine-3-carboxylate (100 mg, 0.27 mmol). The crude compound was purified by preparative HPLC to afford 3-1-(5-(3-methylcyclohex-1-enyl)quinazolin-4-yl)piperidine-3-carboxylic acid (12 mg, 12%, AUC-HPLC 67 % + 29%) as an off-white solid. mp: 143–156 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ (ppm): 12.30 (bs, 1H); 8.60–8.40 (bs, 1H), 7.80–7.55 (m, 2H), 7.42–7.25 (m, 1H), 5.91–5.55 (m, 1H), 4.29–3.70 (m, 2H), 3.10–2.90 (m, 2H), 2.45–2.35 (m, 1H), 2.32–2.22 (m, 2H), 2.05–1.50 (m, 7H), 1.23 (s, 2H), 1.10–0.95 (m, 3H); MS (ESI) m/z : 352.36 [$\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_2+\text{H}$] $^+$.

Compound 16: 1-(5-phenylquinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and phenylboronic acid (73.15 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford 1-(5-phenylquinazolin-4-yl)piperidine-3-carboxylic acid (39.75 mg, 0.12 mmol, 39.7 %, AUC HPLC 99.80 %) as white solid. ¹H NMR (400 MHz, MeOD) δ (ppm): 8.53 (bs, 1H), 7.85 (2d, J = 8.0, 7.6 Hz, 1H), 7.75 (d, J = 6.8 Hz, 1H), 7.57 (d, J = 6.4 Hz, 1H), 7.50-7.40 (m, 5H), 3.90-3.60 (m, 2H), 3.10-2.90 (m, 1H), 2.89-2.60 (m, 1H), 2.40-2.20 (m, 1H), 1.90-1.70 (m, 1H), 1.60-1.30 (m, 2H), 1.00-0.80 (m, 1H); MS (ESI) m/z 334.10 [$C_{20}H_{19}N_3O_2 + H$]⁺.

Compound 17: 1-(5-(4-isopropylphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid

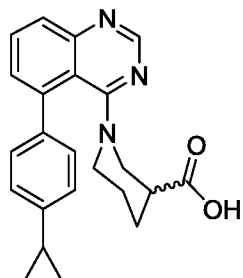
The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (4-isopropylphenyl)boronic acid (98.40 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford 1-(5-(4-isopropylphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (20 mg, 0.053 mmol, 17.8 %, AUC HPLC 99.15 %) as off-white solid. ¹H NMR (400 MHz, DMSO) δ (ppm): 8.56 (s, 1H), 7.82 (2d, J = 8.4, 7.2 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 6.8 Hz, 1H), 7.38-7.29 (m, 4H), 3.85-3.55 (m, 7H), 3.05-2.90 (m, 4H), 2.75-2.55 (m, 4H), 1.75-1.60 (m, 1H), ; MS (ESI) m/z 376.55 [$C_{23}H_{25}N_3O_2 + H$]⁺.

Compound 18: 1-(5-(3-cyclopropylphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (3-cyclopropylphenyl)boronic acid (97.2 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford 1-(5-(3-cyclopropylphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (26.9 mg, 0.072 mmol, 24.0 %, AUC HPLC 99.81%) as white solid. ¹H NMR (400 MHz, MeOD) δ (ppm): 8.53

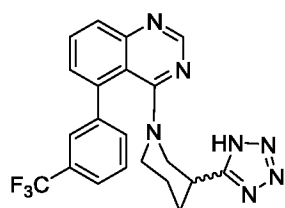
(bs, 1H), 7.84 (2d, $J = 8.4, 7.2$ Hz, 1H), 7.74 (d, $J = 7.2$ Hz, 1H), 7.56 (d, $J = 7.2$ Hz, 1H), 7.35 (t, $J = 7.2$ Hz, 1H), 7.25-7.05 (m, 3H), 4.00-3.60 (m, 1H), 3.00-2.70 (m, 1H), 2.50-2.10 (m, 1H), 2.00-1.95 (m, 1H), 1.95-1.70 (m, 1H), 1.60-1.50 (m, 1H), 1.49-1.15 (m, 3H), 1.05-0.95 (m, 2H), 0.94-0.80 (m, 1H), 0.79-0.65 (m, 2H); MS (ESI) m/z 374.10 [$C_{23}H_{23}N_3O_2 + H$] $^+$.

Compound 19: 1-(5-(4-cyclopropylphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (4-cyclopropylphenyl)boronic acid (97.19 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford 1-(5-(4-cyclopropylphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (16.54 mg, 0.044 mmol, 14.76 %, AUC HPLC 99.17 %) as off-white solid. ^1H NMR (400 MHz, DMSO) δ (ppm): 8.57 (s, 1H), 7.81 (d, $J = 6.4$ Hz, 1H), 7.75 (d, $J = 7.6$ Hz, 1H), 7.48 (d, $J = 6.4$ Hz, 1H), 7.28 (bs, 2H), 7.16 (d, $J = 7.2$ Hz, 2H), 2.30-2.10 (m, 2H), 2.05-1.95 (m, 2H), 1.75-1.60 (m, 1H), 1.45-1.30 (m, 1H), 1.25-1.10 (m, 2H), 1.00 (dd, $J = 8.4, 2.0$ Hz, 3H), 0.80-0.50 (m, 3H); MS (ESI) m/z 374.10 [$C_{23}H_{23}N_3O_2 + H$] $^+$.

Compound 20: 4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(3-(trifluoromethyl)phenyl)quinazoline



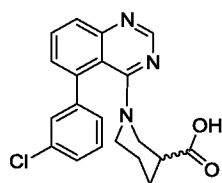
Step 1: Preparation of 1-(5-(3-(trifluoromethyl)phenyl)quinazolin-4-yl)piperidine-3-carbonitrile:

The title compound was prepared in a similar fashion as described in general procedure E starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carbonitrile (250 mg, 0.788 mmol) and 3-(trifluoromethyl)phenylboronic acid (298 mg, 1.577 mmol). The crude product was purified by column chromatography (silica gel, eluent DCM/MeOH 96:4) to afford 1-(5-(3-(trifluoromethyl)phenyl)quinazolin-4-yl)piperidine-3-carbonitrile (280 mg, 93%, LC-MS 82%) as a viscous liquid. MS (ESI) m/z : 383.91 [$C_{21}H_{17}F_3N_4 + H$] $^+$.

Step 2: Preparation of 4-(3-(1*H*-tetrazol-5-yl)piperidin-1-yl)-5-(3-(trifluoromethyl)phenyl)quinazoline:

The title compound was prepared in a similar fashion as described in general procedure F starting from 1-(5-(3-(trifluoromethyl)phenyl)quinazolin-4-yl)piperidine-3-carbonitrile (300 mg, 0.785 mmol). The crude product was purified by preparative HPLC to afford 4-(3-(1*H*-tetrazol-5-yl)piperidin-1-yl)-5-(3-(trifluoromethyl)phenyl)quinazoline (70 mg, 21%, AUC-HPLC 95.43%) as an off-white solid. mp: 204–214 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 16.10 (bs, 1H), 8.70–8.66 (m, 1H), 7.90–7.60 (m, 7H), 3.95 (bs, 1H), 3.69 (bs, 1H), 3.14 (bs, 1H), 2.82–2.67 (m, 2H), 1.92 (bs, 1H), 1.55 (bs, 1H), 1.34–1.23 (m, 1H), 0.56 (bs, 1H); MS (ESI) *m/z*: 426.33 [C₂₁H₁₈F₃N₇+H]⁺.

Compound 21: 3-(5-(3-chlorophenyl)quinazolin-4-yl)cyclohexanecarboxylic acid



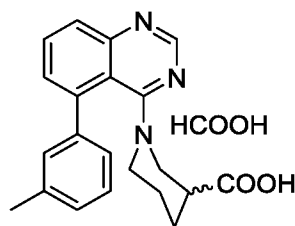
Step 1: Preparation of methyl 3-(5-(3-chlorophenyl)quinazolin-4-yl)cyclohexanecarboxylate:

The title compound was prepared in a similar fashion as described in general procedure E starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (250 mg, 0.71 mmol) and 3-chlorophenylboronic acid (222 mg, 1.42 mmol). The filtrate was concentrated under reduced pressure to afford methyl 3-(5-(3-chlorophenyl)quinazolin-4-yl)cyclohexanecarboxylate (150 mg, 55%, LC-MS 78%); (ESI) *m/z*: 382.82 [C₂₁H₂₀ClN₃O₂+1]⁺. The crude product was used without further purification in the next step without further purification.

Step 2: Preparation of 3-(5-(3-chlorophenyl)quinazolin-4-yl)cyclohexanecarboxylic acid

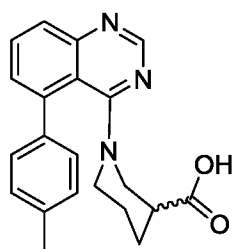
The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 3-(5-(3-chlorophenyl)quinazolin-4-yl)cyclohexanecarboxylate (282 mg, 0.73 mmol). The crude compound was purified by preparative HPLC to afford 3-(5-(3-chlorophenyl)quinazolin-4-yl)cyclohexanecarboxylic acid (60 mg, 22%, AUC-HPLC 95.05%) as an off-white solid. m.p 218–226 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.61–8.52 (m, 1H), 7.85 (d, *J* = 9.6 Hz, 2H), 7.55–7.45 (m, 5H), 3.76 (s, 1H), 2.70 (s, 2H), 2.18 (br.s, 1H), 1.70 (bs, 2H), 1.46 (bs, 1H), 1.23 (bs, 1H), 0.84 (s, 1H); MS (ESI) *m/z*: 368.10 [C₂₀H₁₈ClN₃O₂+1]⁺.

Compound 22: 1-(5-(*m*-tolyl)quinazolin-4-yl)piperidine-3-carboxylic acid



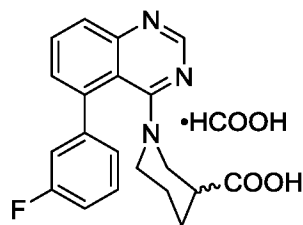
The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and *m*-tolylboronic acid (61 mg, 0.45 mmol). The residue was purified by preparative HPLC (C18, eluent CH₃CN/H₂O/HCOOH 0.01%) to afford 1-(5-(*m*-tolyl)quinazolin-4-yl)piperidine-3-carboxylic acid (31 mg, 30%, AUC HPLC 98.31%) as white solid; ¹H NMR (300 MHz, MeOD-*d*₄) δ (ppm): 8.57 (s, 1H), 8.31 (bs, 1H), 7.92 (t, *J* = 7.2 Hz, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.64 (d, *J* = 7.0 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 7.4 Hz, 2H), 7.22 (bs, 1H), 4.49-3.43 (m, 2H), 3.10-2.53 (m, 1H), 2.51-2.20 (m, 4H), 2.01-1.54 (m, 2H), 1.53-0.91 (m, 3H); MS (ESI) *m/z* 348.50 [C₂₁H₂₁N₃O₂ + H]⁺.

Compound 23: 1-(5-(*p*-tolyl)quinazolin-4-yl)piperidine-3-carboxylic acid



To a solution of 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (200 mg, 0.595 mmol) and *p*-tolylboronic acid (162 mg, 1.190 mmol) in a mixture of ethanol (10 mL), toluene (10 mL) and water (4 mL) were added potassium phosphate (252 mg, 1.190 mmol) and Pd(PPh₃)₄ (55 mg, 0.047 mmol) under argon. The reaction mixture was heated at 100 °C for 16 hours and was concentrated to dryness under reduced pressure. The residue was purified by preparative HPLC to afford 1-(5-(*p*-tolyl)quinazolin-4-yl)piperidine-3-carboxylic acid (15 mg, AUC-HPLC 97.19%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.56–8.42 (m, 2H), 7.78–7.74 (m, 2H), 7.45 (d, *J* = 6.8 Hz, 1H), 7.30–7.26 (m, 3H), 3.82–3.58 (m, 2H), 3.20–2.90 (m, 2H), 2.37 (s, 3H), 2.01 (bs, 1H), 1.74–1.66 (m, 1H), 1.23–1.14 (m, 3H), MS (ESI) *m/z*: 348.27 [C₂₁H₂₁N₃O₂ + H]⁺.

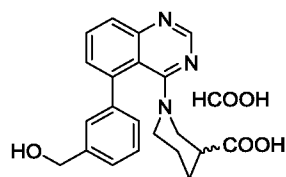
Compound 24: 1-(5-(3-fluorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (3-fluorophenyl)boronic acid (63 mg, 0.45 mmol). The residue was purified by preparative HPLC (C18, eluent CH₃CN/H₂O/HCOOH 0.01%) to afford 1-(5-(3-fluorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (22 mg, 21%, AUC HPLC 99.14%) as white solid; ¹H NMR (300 MHz, MeOD-*d*₄) δ (ppm): 8.59 (s, 1H), 8.20 (bs, 1H), 7.93 (t, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.65 (d, *J* = 7.3

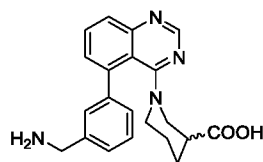
Hz, 1H), 7.58-7.47 (m, 1H), 7.42-7.14 (m, 3H), 4.47-3.07 (m, 3H), 2.85-2.29 (m, 1H), 1.98-1.72 (m, 1H), 1.71-0.94 (m, 4H); MS (ESI) m/z 352.50 [$C_{20}H_{18}FN_3O_2 + H$]⁺.

Compound 25: 1-(5-(3-(hydroxymethyl)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



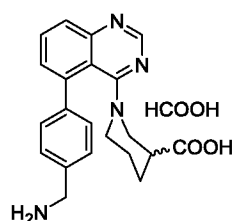
The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (3-(hydroxymethyl)phenyl)boronic acid (68 mg, 0.45 mmol). The residue was purified by preparative HPLC (C18, eluent $CH_3CN/H_2O/HCOOH$ 0.01%) to afford 1-(5-(3-(hydroxymethyl)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (15 mg, 14%, AUC HPLC 97.12%) as white solid; ^1H NMR (300 MHz, $MeOD-d_4$) δ (ppm): 8.55 (s, 1H), 8.22 (bs, 1H), 7.90 (t, $J = 7.8$ Hz, 1H), 7.74 (d, $J = 7.8$ Hz, 1H), 7.63 (d, $J = 6.4$ Hz, 1H), 7.51-7.41 (m, 3H), 7.37 (bs, 1H), 4.69 (s, 2H), 4.46-3.43 (m, 2H), 3.28-2.92 (m, 1H), 2.80-2.18 (m, 1H), 1.97-1.52 (m, 2H), 1.51-0.90 (m, 3H); MS (ESI) m/z 364.55 [$C_{21}H_{21}N_3O_3 + H$]⁺.

Compound 26: 1-(5-(3-(aminomethyl)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



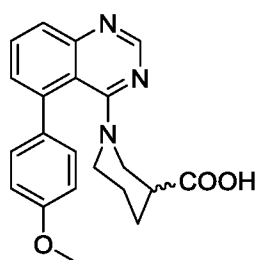
The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (3-(aminomethyl)phenyl)boronic acid (68 mg, 0.45 mmol). The residue was purified by preparative HPLC (C18, eluent $CH_3CN/H_2O/HCOOH$ 0.01%) to afford 1-(5-(3-(aminomethyl)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (25 mg, 23%, AUC HPLC 99.66%) as white solid; ^1H NMR (300 MHz, $MeOD-d_4$) δ (ppm): 8.59 (s, 1H), 8.15 (s, 1H), 7.94 (t, $J = 7.8$ Hz, 1H), 7.87-7.74 (m, 1H), 7.66 (d, $J = 7.2$ Hz, 1H), 7.63-7.31 (m, 3H), 4.24 (s, 2H), 4.16-3.39 (m, 2H), 3.20-2.27 (m, 2H), 1.95-1.60 (m, 2H), 1.59-0.73 (m, 3H); MS (ESI) m/z 363.10 [$C_{21}H_{22}N_4O_2 + H$]⁺.

Compound 27: 1-(5-(4-(aminomethyl)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (4-(aminomethyl)phenyl)boronic acid (68 mg, 0.45 mmol). The residue was purified by preparative HPLC (C18, eluent CH₃CN/H₂O/HCOOH 0.01%) to afford 1-(5-(4-(aminomethyl)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (72 mg, 66%, AUC HPLC 97.97%) as white solid; ¹H NMR (300 MHz, MeOD-*d*₄) δ (ppm): 8.60 (s, 1H), 8.08 (s, 1H), 7.96 (t, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.71-7.65 (m, 1H), 7.64-7.52 (m, 4H), 4.39-3.52 (m, 4H), 3.25-1.83 (m, 3H), 1.81-0.84 (m, 4H); MS (ESI) *m/z* 363.20 [C₂₁H₂₂N₄O₂ + H]⁺.

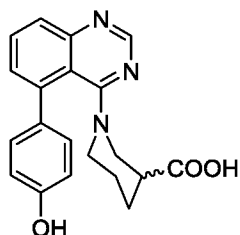
Compound 28: 1-(5-(4-methoxyphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



Step 1: Preparation of 1-(5-(4-methoxyphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid:

To a solution of 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (200 mg, 0.595 mmol) and 4-methoxyphenylboronic acid (180 mg, 1.190 mmol) in ethanol (10 mL), toluene (10 mL) and water (4 mL) was added potassium phosphate (252 mg, 1.190 mmol) and Pd(PPh₃)₄ (68 mg, 0.059 mmol) under argon. The reaction mixture was heated at 100 °C for 16 hours and was concentrated to dryness under reduced pressure. The residue was purified by preparative HPLC to afford 1-(5-(4-methoxyphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (30 mg, 14%, AUC-HPLC 99.29%) as a pale yellow solid, mp: 198-208 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.57–8.51 (m, 1H), 7.80–7.72 (m, 2H), 7.45 (d, *J* = 6.8 Hz, 1H), 7.35 (bs, 2H), 7.0 (d, *J* = 8.0 Hz, 2H), 3.81 (s, 3H), 3.63 (bs, 2H), 2.67–2.55 (s, 2H), 2.25–2.07 (m, 1H), 1.70 (bs, 1H), 1.39–1.11 (m, 3H); MS (ESI) *m/z*: 364.31 [C₂₁H₂₁N₃O₃ + H]⁺.

Compound 29: 1-(5-(4-hydroxyphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



Step 1: Preparation of methyl 1-(5-(4-hydroxyphenyl)quinazolin-4-yl)piperidine-3-carboxylate

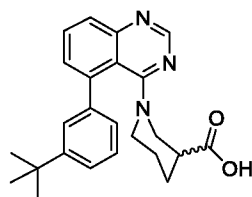
The title compound was prepared in a similar fashion as described in general procedure E starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (250 mg, 0.71 mmol) and 4-

hydroxyphenylboronic acid (197 mg, 1.42 mmol). After an aqueous work-up, the filtrate was concentrated under reduced pressure to afford methyl 1-(5-(4-hydroxyphenyl)quinazolin-4-yl)piperidine-3-carboxylate (200 mg, 77%, LC-MS 70%); (ESI) m/z : 364.50 [$C_{21}H_{21}N_3O_3+2$]⁺.

Step 2: Preparation of 1-(5-(4-hydroxyphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid

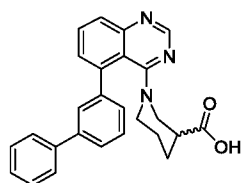
The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 3-(5-(4-hydroxyphenyl)quinazolin-4-yl)cyclohexanecarboxylate (150 mg, 0.41 mmol). The crude compound was purified by preparative HPLC to afford 1-(5-(4-hydroxyphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (12 mg, 8.3%, AUC-HPLC 99.19%) as a pale yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 9.61 (bs, 1H), 8.55 (s, 1H), 7.73 (d, J = 6.8 Hz, 2H), 7.42 (d, J = 6.8 Hz, 1H), 7.21 (bs, 1H), 6.83 (d, J = 8.4 Hz, 2H), 6.57 (bs, 1H), 3.67 (bs, 2H), 3.00 (bs, 1H), 2.67–2.54 (m, 1H), 2.30–2.00 (m, 1H), 1.82–1.60 (m, 1H), 1.39–1.23 (m, 3H); MS (ESI) m/z : 350.28 [$C_{20}H_{19}N_3O_3+2$]⁺.

Compound 30: 1-(5-(3-(*tert*-butyl)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (3-(*tert*-butyl)phenyl)boronic acid (106.80 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford 1-(5-(3-(*tert*-butyl)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (36.41 mg, 0.093 mmol, 31.2 %, AUC HPLC 99.42 %) as white solid. ¹H NMR (400 MHz, MeOD) δ (ppm): 8.53 (bs, 1H), 7.85 (2d, J = 8.4, 7.2 Hz, 1H), 7.74 (d, J = 6.4 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.28 (bs, 1H), 4.00–3.60 (m, 1H), 2.95–2.70 (m, 1H), 2.50–2.00 (m, 1H), 1.95–1.60 (m, 1H), 1.37 (s, 13H), 1.00–0.75 (m, 1H); MS (ESI) m/z 390.20 [$C_{24}H_{27}N_3O_2+H$]⁺.

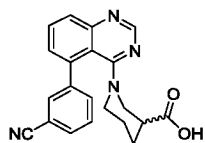
Compound 31: 1-(5-([1,1'-biphenyl]-3-yl)quinazolin-4-yl)piperidine-3-carboxylic acid



The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and [1,1'-biphenyl]-3-ylboronic acid (118.8 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford 1-(5-([1,1'-biphenyl]-3-yl)quinazolin-4-yl)piperidine-3-carboxylic acid (69.16 mg, 0.17 mmol, 56.2 %, AUC HPLC 98.19 %) as white solid. ¹H NMR (400 MHz, MeOD) δ (ppm): 8.57 (bs, 1H), 7.89 (dt, J = 7.8, 3.3 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.68–7.63 (m, 3H),

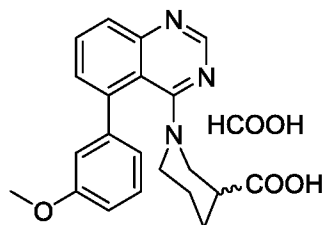
7.58 (bs, 2H), 7.45 (t, $J = 7.6$ Hz, 2H), 7.36 (d, $J = 7.6$ Hz, 1H), 4.00-3.60 (m, 2H), 3.05-2.70 (m, 1H), 2.40-2.20 (m, 1H), 2.00-1.70 (m, 1H), 1.60-1.20 (m, 3H), 1.10-0.80 (m, 1H); MS (ESI) m/z 410.20 $[\text{C}_{26}\text{H}_{23}\text{N}_3\text{O}_2 + \text{H}]^+$.

Compound 32: 1-(5-(3-cyanophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



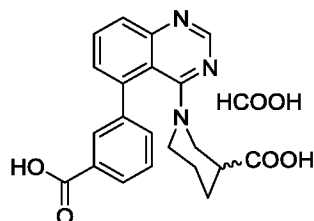
The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (3-cyanophenyl)boronic acid (88.16 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford 1-(5-(3-cyanophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (3.52 mg, 9.82 μmol , AUC HPLC 99.71 %) as white solid. ^1H NMR (400 MHz, DMSO) δ (ppm): 8.68 (bs, 1H), 8.00 (bs, 1H), 7.95-7.80 (m, 3H), 7.79-7.70 (m, 1H), 7.69-7.62 (m, 1H), 7.59-7.55 (m, 1H), 3.65-3.50 (m, 2H), 2.75-2.65 (m, 1H), 1.80-1.60 (m, 1H), 1.50-1.40 (m, 1H), 1.30-1.15 (m, 3H), 1.29-1.00 (m, 1H); MS (ESI) m/z 410.20 $[\text{C}_{26}\text{H}_{23}\text{N}_3\text{O}_2 + \text{H}]^+$.

Compound 33: 1-(5-(3-methoxyphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



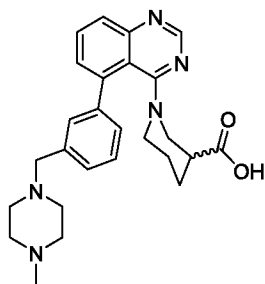
The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (3-methoxyphenyl)boronic acid (68 mg, 0.45 mmol). The residue was purified by preparative HPLC (C18, eluent $\text{CH}_3\text{CN}/\text{H}_2\text{O}/\text{HCOOH}$ 0.01%) to afford 1-(5-(3-methoxyphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid formic salt (9 mg, AUC HPLC 98.53%) as white solid; ^1H NMR (300 MHz, $\text{MeOD}-d_4$) δ (ppm): 8.55 (s, 1H), 8.22 (bs, 1H), 7.90 (t, $J = 7.8$ Hz, 1H), 7.74 (d, $J = 8.0$ Hz, 1H), 7.65 (d, $J = 7.0$ Hz, 1H), 7.40 (t, $J = 7.9$ Hz, 1H), 7.18-6.91 (m, 3H), 4.51-3.50 (m, 5H), 3.28-2.89 (m, 1H), 2.79-2.21 (m, 1H), 2.02-1.54 (m, 2H), 1.53-0.94 (m, 3H); MS (ESI) m/z 364.20 $[\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_3 + \text{H}]^+$.

Compound 34: 1-(5-(3-carboxyphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



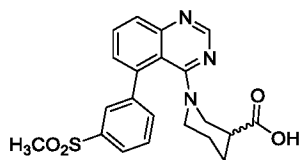
The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (3-(methoxycarbonyl)phenyl)boronic acid (81 mg, 0.45 mmol). The residue was purified by preparative HPLC (C18, eluent CH₃CN/H₂O/HCOOH 0.01%) to afford 1-(5-(3-carboxyphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (10 mg, AUC HPLC 96.08%) as white solid; ¹H NMR (300 MHz, MeOD-*d*₄) δ (ppm): 8.61 (s, 1H), 8.44-8.03 (m, 3H), 7.94 (t, *J* = 7.5 Hz, 1H), 7.86-7.56 (m, 4H), 4.48-3.38 (m, 2H), 3.09-2.53 (m, 1H), 2.50-2.01 (m, 1H), 1.97-1.54 (m, 2H), 1.53-0.80 (m, 3H); MS (ESI) *m/z* 378.50 [C₂₁H₁₉N₃O₄ + H]⁺.

Compound 35: *1-(5-(3-((4-methylpiperazin-1-yl)methyl)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid*



The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (3-((4-methylpiperazin-1-yl)methyl)phenyl)boronic acid (140.46 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford 1-(5-(3-((4-methylpiperazin-1-yl)methyl)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (27.34 mg, 0.061 mmol, 20.5 %, AUC HPLC 96.72 %) as white solid. ¹H NMR (400 MHz, MeOD) δ (ppm): 8.56-8.50 (m, 1H), 8.23 (s, 1H), 7.95-7.85 (m, 1H), 7.80-7.72 (m, 1H), 7.71-7.57 (m, 2H), 7.50-7.33 (m, 2H), 4.10-3.70 (m, 4H), 3.25-3.10 (m, 3H), 3.00-2.70 (m, 9H), 2.60-2.50 (m, 1H), 2.10-1.90 (m, 1H), 1.89-1.80 (m, 1H), 1.70-1.60 (m, 1H), 1.50-1.45 (m, 1H), 1.40-1.25 (m, 1H); MS (ESI) *m/z* 446.20 [C₂₆H₃₁N₅O₂ + H]⁺.

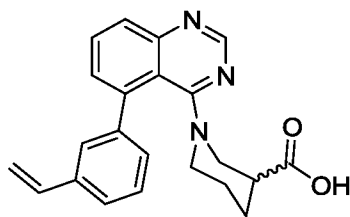
Compound 36: *1-(5-(3-(methylsulfonyl)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid*



The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (3-(methylsulfonyl)phenyl)boronic acid (120.01 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford 1-(5-(3-(methylsulfonyl)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (27.68 mg, 0.067 mmol, 22.4 %, AUC HPLC 99.86 %) as white solid. ¹H NMR (400 MHz, MeOD) δ (ppm): 8.60 (m, 1H), 8.10-8.00 (m, 2H), 7.95-7.70 (m, 4H), 7.65-7.60 (m, 1H), 4.30-3.80

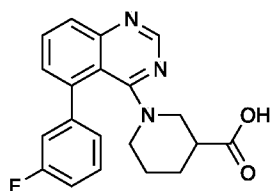
(m, 1H), 3.70-3.50 (m, 1H), 3.57 (s, 3H), 2.90-2.80 (m, 1H), 2.50-2.20 (m, 1H), 2.00-1.70 (m, 1H), 1.60-1.15 (m, 3H), 1.00-0.70 (m, 1H); MS (ESI) m/z 412.10 [$C_{21}H_{21}N_3O_4S + H$] $^+$.

Compound 37: 1-(5-(3-vinylphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid

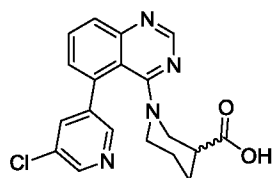


The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (3-vinylphenyl)boronic acid (88.8 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford 1-(5-(3-vinylphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (32.37 mg, 0.090 mmol, 30.0 %, AUC HPLC 99.75 %) as white solid. ^1H NMR (400 MHz, MeOD) δ (ppm): 8.56 (bs, 1H), 8.26 (s, 1H), 7.87 (2d, $J = 8, 7.6$ Hz, 1H), 7.77 (d, $J = 7.2$ Hz, 1H), 7.61 (d, $J = 6.8$ Hz, 1H), 7.52 (d, $J = 7.6$ Hz, 1H), 7.50-7.40 (m, 1H), 7.34 (bs, 1H), 6.81 (2d, $J = 10.8$ Hz, 1H), 5.84 (d, $J = 17.6$ Hz, 1H), 5.30 (d, $J = 10.8$ Hz, 1H), 4.00-3.60 (m, 2H), 3.10-2.70 (m, 1H), 2.50-2.10 (m, 1H), 2.00-1.70 (m, 1H), 1.60-1.50 (m, 1H), 1.49-1.15 (m, 2H), 1.00-0.80 (m, 1H); MS (ESI) m/z 360.10 [$C_{22}H_{21}N_3O_2 + H$] $^+$.

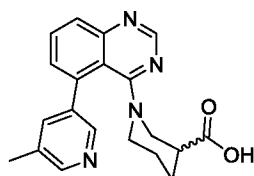
Compound 38: 1-(5-(3-fluorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



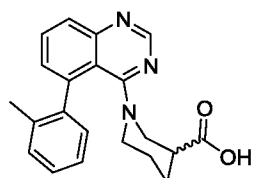
The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (3-fluorophenyl)boronic acid (133.86 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford 1-(5-(3-fluorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (9.26 mg, 0.026 mmol, 8.8 %, AUC HPLC 97.06 %) as white solid. ^1H NMR (400 MHz, MeOD) δ (ppm): 8.70-8.58 (m, 1H), 8.55-8.40 (s, 2H), 7.95-7.75 (m, 3H), 7.63 (bs, 1H), 4.30-4.20 & 3.10-3.00 (2m, 1H), 3.70-3.50 (m, 2H), 2.95-2.60 (m, 1H), 2.50-2.20 (m, 1H), 2.00-1.80 (m, 1H), 1.55-1.20 (m, 3H); MS (ESI) m/z 353.10 [$C_{20}H_{18}FN_3O_2 + H$] $^+$.

Compound 39: 1-(5-(5-chloropyridin-3-yl)quinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (5-chloropyridin-3-yl)boronic acid (143.70 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford 1-(5-(5-chloropyridin-3-yl)quinazolin-4-yl)piperidine-3-carboxylic acid (19.4 mg, 0.053 mmol, 17.5 %, AUC HPLC 95.64 %) as white solid. ¹H NMR (400 MHz, MeOD) δ (ppm): 8.69 (bs, 3H), 8.07 (s, 1H), 7.90 (s, 2H), 7.64 (d, J = 5.6 Hz, 1H), 3.80-3.45 (m, 2H), 3.15-2.75 (m, 1H), 2.70-2.10 (m, 1H), 1.95-1.65 (m, 2H), 1.60-1.10 (m, 2H), 1.00-0.70 (m, 1H); MS (ESI) m/z 369.10 [$C_{19}H_{17}ClN_4O_2 + H$]⁺.

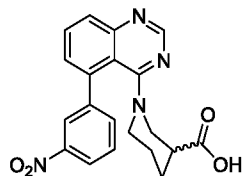
Compound 40: 1-(5-(5-methylpyridin-3-yl)quinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (5-methylpyridin-3-yl)boronic acid (131.46 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford 1-(5-(5-methylpyridin-3-yl)quinazolin-4-yl)piperidine-3-carboxylic acid (5.3 mg, 0.015 mmol, AUC HPLC 99.62 %) as white solid. ¹H NMR (400 MHz, MeOD) δ (ppm): 8.63 & 8.59 (2s, 1H), 8.46 (bs, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.92 (2d, J = 8.0, 7.6 Hz, 1H), 7.90-7.75 (m, 2H), 7.61 (d, J = 7.2 Hz, 1H), 4.35-4.15 & 3.10-2.95 (m, 1H), 3.90-3.61 (m, 1H), 3.60-3.45 (m, 1H), 2.90-2.75 (m, 1H), 2.70-2.45 & 2.35-2.15 (m, 1H), 2.47 (s, 2H), 2.00-1.86 (m, 1H), 1.85-1.60 (m, 1H), 1.50-1.20 (m, 2H), 0.95-0.75 (m, 1H); MS (ESI) m/z 349.10 [$C_{20}H_{20}N_4O_2 + H$]⁺.

Compound 41: Preparation of 1-(5-(*o*-tolyl)quinazolin-4-yl)piperidine-3-carboxylic acid

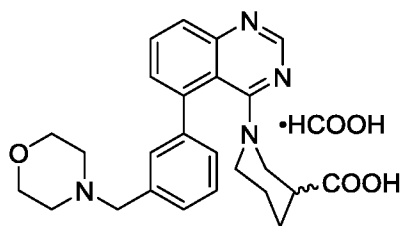
The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and o-tolylboronic acid (81.58 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford 1-(5-(o-tolyl)quinazolin-4-yl)piperidine-3-carboxylic acid (9.52 mg, 0.027 mmol, 9.13 %, AUC HPLC 99.73 %) as white solid. ¹H NMR (400 MHz, MeOD) δ (ppm): 8.57 (s, 1H), 7.90-7.75 (m, 2H), 7.44 (2d, J = 7.6, 7.2 Hz, 2H), 7.38-7.20 (m, 3H), 3.90-3.60 (m, 2H), 2.65 (s, 4H), 2.14 (s, 1H), 2.00-1.86 (bs, 2H), 1.85-1.70 (m, 1H), 1.50-1.20 (m, 2H); MS (ESI) m/z 348.10 [$C_{21}H_{21}N_3O_2 + H$]⁺.

Compound 42: 1-(5-(3-nitrophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid

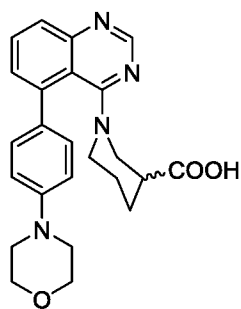


The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (3-nitrophenyl)boronic acid (100.16 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford 1-(5-(3-nitrophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (22.10 mg, 0.058 mmol, 19.5 %, AUC HPLC 99.11 %) as white solid. ¹H NMR (400 MHz, MeOD) δ (ppm): 8.61 (2s, 1H), 8.32 (d, J = 7.2 Hz, 2H), 7.95-7.80 (m, 3H), 7.79-7.69 (m, 1H), 7.64 (d, J = 6.8 Hz, 1H), 4.30-4.15 & 3.55-3.40 (m, 1H), 3.80-3.60 (m, 1H), 3.10-2.95 & 2.85-2.70 (m, 1H), 2.50-2.35 & 2.30-2.15 (m, 1H), 1.79-1.50 (m, 1H), 1.50-1.15 (m, 3H), 1.95-1.80 & 0.90-0.70 (m, 1H); MS (ESI) m/z 379.10 [$C_{20}H_{18}N_4O_4 + H$]⁺.

Compound 43: 1-(5-(3-(morpholinomethyl)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



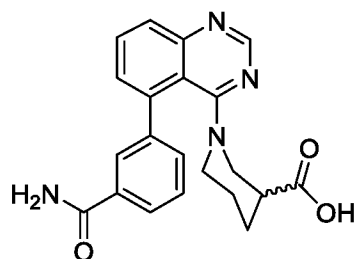
The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (3-(morpholinomethyl)phenyl)boronic acid (99 mg, 0.45 mmol). The residue was purified by preparative HPLC (C18, eluent $CH_3CN/H_2O/HCOOH$ 0.01%) to afford 1-(5-(3-(morpholinomethyl)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (34 mg, 26%, AUC HPLC 99.42%) as white solid; ¹H NMR (300 MHz, MeOD- d_4) δ (ppm): 8.57 (s, 1H), 8.29-8.13 (m, 2H), 7.90 (t, J = 7.8 Hz, 1H), 7.82-7.72 (m, 1H), 7.62 (d, J = 7.2 Hz, 1H), 7.58-7.34 (m, 3H), 4.29-3.47 (m, 8H), 3.26-1.79 (m, 7H), 1.78-1.53 (m, 1H), 1.53-0.82 (m, 3H); MS (ESI) m/z 433.55 [$C_{25}H_{28}N_4O_3 + H$]⁺.

Compound 44: 1-(5-(4-morpholinophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid**Step1: Preparation of methyl 1-(5-(4-morpholinophenyl)quinazolin-4-yl)piperidine-3-carboxylate:**

The title compound was prepared in a similar fashion as described in general procedure E starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate ((250 mg, 0.71 mmol), and 4-chloro-3-methylphenylboronic acid (412 mg, 1.42 mmol). The reaction mixture was filtered through a short pad of celite, and the filtrate was concentrated under reduced pressure to afford methyl 1-(5-(4-morpholinophenyl)quinazolin-4-yl)piperidine-3-carboxylate (130 mg, 42%); (ESI) m/z : 433.54 $[C_{25}H_{28}N_4O_3+1]^+$. The crude product was used without further purification in step 2.

Step 2: Preparation of 1-(5-(4-morpholinophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid:

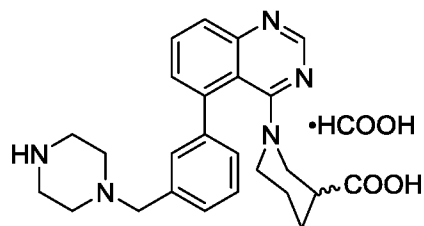
The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 3-(5-(4-morpholinophenyl)quinazolin-4-yl)cyclohexanecarboxylate (130 mg, ~ 0.30 mmol). The crude compound was purified by preparative HPLC to afford 3-(5-(4-morpholinophenyl)quinazolin-4-yl)cyclohexanecarboxylic acid (12 mg, 9.6%, LC-MS 97.90%, AUC-HPLC 98.28 %) as a yellow solid. m.p: 185-195 °C; ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.54–8.47 (m, 1H), 7.76–7.70 (m, 2H), 7.44–7.28 (m, 3H), 7.01 (bs, 2H), 3.76–3.69 (m, 6H), 3.16 (bs, 4H), 2.66–2.50 (m, 1H), 2.14 (bs, 1H), 1.69 (bs, 1H), 1.29–1.17 (m, 3H), 0.61 (bs, 1H); MS (ESI) m/z : 419.31 $[C_{24}H_{26}N_4O_3+1]^+$.

Compound 45: 1-(5-(3-carbamoylphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (3-carbamoylphenyl)boronic acid (98.97 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford 1-(5-(3-carbamoylphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (38.93 mg, 0.10 mmol, 34.47 %, AUC HPLC 99.99 %) as white solid. ^1H NMR (400 MHz, MeOD) δ (ppm): 8.80–8.50 (m, 1H), 8.30–7.90 (m, 4H), 7.89–7.55 (m, 3H), 5.03 (s, 2H), 4.00–3.60 (m, 1H), 3.10–2.80 (m,

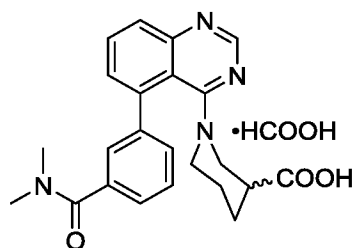
1H), 2.79-2.51 (m, 1H), 2.50-2.10 (m, 1H), 2.09-1.70 (m, 1H), 1.69-1.15 (m, 3H), 1.10-0.70 (m, 1H); MS (ESI) m/z 377.10 [$C_{21}H_{20}N_4O_3 + H$]⁺.

Compound 46: 1-(5-(3-(piperazin-1-ylmethyl)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



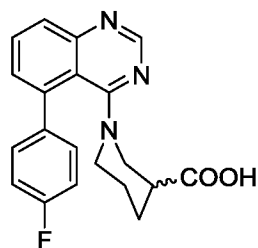
To a solution of 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) in a mixture of dioxane (2.0 mL) and H₂O (0.5 mL) under inert atmosphere was added Cs₂CO₃ (195 mg, 0.60 mmol), 4-((4-(*tert*-butoxycarbonyl)piperazin-1-yl)methyl)phenylboronic acid (144 mg, 0.45 mmol) and tetrakis(triphenylphosphine)palladium (35 mg, 0.03 mmol). The resulting mixture was heated at 120 °C for 2 hours in a microwave apparatus and was concentrated under reduced pressure. The residue was re-dissolved in DCM (2 mL) and treated with trifluoroacetic acid (0.5 mL). The mixture was stirred at room temperature for 18 hours and was concentrated under reduced pressure. The residue was purified by preparative HPLC (C18, eluent CH₃CN/H₂O/HCOOH 0.01%) to afford 1-(5-(4-(piperazin-1-ylmethyl)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (17 mg, 13%, AUC HPLC 99.67%) as white solid; ¹H NMR (300 MHz, MeOD-*d*₄) δ (ppm): 8.58 (s, 1H), 8.19 (s, 2H), 8.01-7.89 (m, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.72-7.62 (m, 1H), 7.61-7.39 (m, 3H), 4.24-3.48 (m, 4H), 3.30-2.94 (m, 5H), 2.84-2.38 (m, 5H), 1.94-1.56 (m, 2H), 1.55-1.41 (m, 1H), 1.40-0.90 (m, 2H); MS (ESI) m/z 432.25 [$C_{25}H_{29}N_5O_2 + H$]⁺.

Compound 47: 1-(5-(3-(dimethylcarbamoyl)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



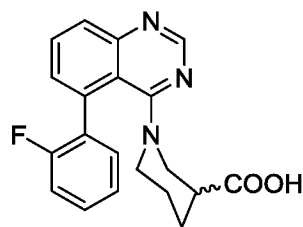
The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and 3-(dimethylcarbamoyl)phenylboronic acid (87 mg, 0.45 mmol). The residue was purified by preparative HPLC (C18, eluent CH₃CN/H₂O/HCOOH 0.01%) to afford 1-(5-(3-(dimethylcarbamoyl)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (5 mg, AUC HPLC 99.38%) as white solid; ¹H NMR (300 MHz, MeOD-*d*₄) δ (ppm): 8.57 (s, 1H), 8.18 (bs, 1H), 7.92 (t, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.73-7.38 (m, 5H), 4.45-3.76 (m, 1H), 3.59-3.38 (m, 1H), 3.25-2.98 (m, 7H), 2.78-2.33 (m, 1H), 2.00-0.91 (m, 5H); MS (ESI) m/z 405.20 [$C_{23}H_{24}N_4O_3 + H$]⁺.

Compound 48: 1-(5-(4-fluorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



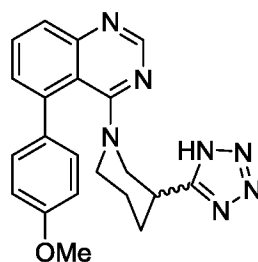
The title compound was prepared in a similar fashion as described in general procedure B starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (122 mg, 0.35 mmol) and (4-fluorophenyl)boronic acid (73 mg, 0.52 mmol). The residue was purified by preparative HPLC (C18, eluent CH₃CN/H₂O/HCOOH 0.01%) to afford 1-(5-(4-fluorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (37 mg, 30%, AUC HPLC 98.79%) as white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 12.27 (s, 1H), 8.76-8.53 (m, 1H), 7.96-7.79 (m, 2H), 7.75-7.60 (m, 1H), 7.58-7.45 (m, 2H), 7.43-7.17 (m, 2H), 4.19-3.62 (m, 1H), 2.93-2.61 (m, 1H), 2.44-1.98 (m, 1H), 1.85-1.57 (m, 2H), 1.52-0.75 (m, 4H); MS (ESI) *m/z* 352.1 [C₂₀H₁₈FN₃O₂ + H]⁺.

Compound 49: 1-(5-(2-fluorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



The title compound was prepared in a similar fashion as described in general procedure B starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (122 mg, 0.35 mmol) and (2-fluorophenyl)boronic acid (73 mg, 0.52 mmol). The residue was purified by preparative HPLC (C18, eluent CH₃CN/H₂O/HCOOH 0.01%) to afford 1-(5-(2-fluorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (17 mg, 14%, AUC HPLC 98.46%) as white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 12.31 (bs, 1H), 8.66-8.52 (m, 1H), 7.89-7.71 (m, 2H), 7.58-7.37 (m, 3H), 7.36-7.21 (m, 2H), 4.08-3.53 (m, 2H), 2.80-2.56 (m, 1H), 2.42-2.11 (m, 1H), 1.78-1.62 (m, 1H), 1.48-1.31 (m, 1H), 1.29-0.44 (m, 3H); MS (ESI) *m/z* 352.1 [C₂₀H₁₈FN₃O₂ + H]⁺.

Compound 50: 4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(4-methoxyphenyl)quinazoline

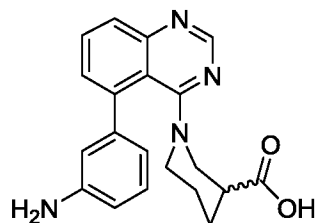


Step 1: Preparation of 1-(5-(4-methoxyphenyl)quinazolin-4-yl)piperidine-3-carbonitrile

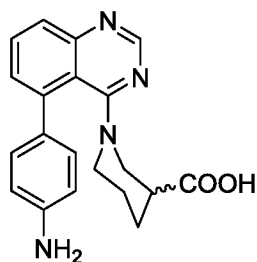
The title compound was prepared in a similar fashion as described in general procedure E starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carbonitrile (180 mg, 0.56 mmol) and 4-methoxyphenylboronic acid (128 mg, 0.85 mmol). The crude product was purified by column chromatography (silica gel, eluent DCM/MeOH 97:3) to afford 1-(5-(4-methoxyphenyl)quinazolin-4-yl)piperidine-3-carbonitrile (240 mg, LC-MS 83%) as a yellow solid. MS (ESI) m/z : 345.49 $[\text{C}_{21}\text{H}_{20}\text{N}_4\text{O}+\text{H}]^+$.

Step 2: Preparation of 4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(4-methoxyphenyl)quinazoline

The title compound was prepared in a similar fashion as described in general procedure F starting from 1-(5-(4-methoxyphenyl)quinazolin-4-yl)piperidine-3-carbonitrile (180 mg, 0.52 mmol). The crude product was purified by column chromatography (silica gel, eluent DCM/MeOH 95:5 to 90:10) to afford 4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(4-methoxyphenyl)quinazoline (40 mg, 20%, AUC-HPLC 96.94%) as an off-white solid. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.58–8.53 (s, 1H), 7.79–7.71 (m, 2H), 7.45–7.30 (m, 3H), 7.0–6.95 (m, 2H), 4.14 (bs, 1H), 3.80 (s, 3H), 3.74–3.70 (m, 1H), 2.86 (bs, 1H), 2.07 (bs, 1H), 1.85 (bs, 1H), 1.52–1.40 (m, 1H), 1.27–1.14 (m, 3H); MS (ESI) m/z : 388.25 $[\text{C}_{21}\text{H}_{21}\text{N}_7\text{O}+\text{H}]^+$.

Compound 51: 1-(5-(3-aminophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (3-aminophenyl)boronic acid (82.16 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford 1-(5-(3-aminophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (8.9 mg, 0.025 mmol, 8.5 %, AUC HPLC 89.77 %) as yellow solid. ^1H NMR (400 MHz, MeOD) δ (ppm): 8.49 (s, 1H), 7.84 (2d, $J = 8.0, 8.0$ Hz, 1H), 7.69 (d, $J = 8.0$ Hz, 1H), 7.59 (d, $J = 7.2$ Hz, 1H), 7.21 (t, $J = 8.0$ Hz, 1H), 6.78 (d, $J = 8.0$ Hz, 3H), 4.00–3.60 (m, 2H), 3.00–2.70 (m, 1H), 2.65 (s, 2H), 2.50–2.20 (m, 1H), 2.00–1.75 (m, 1H), 1.70–1.10 (m, 4H); MS (ESI) m/z 349.10 $[\text{C}_{20}\text{H}_{20}\text{N}_4\text{O}_2+\text{H}]^+$.

Compound 52: 1-(5-(4-aminophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid**Step 1: Preparation of methyl 1-(5-(4-(tert-butoxycarbonylamino)phenyl)quinazolin-4-yl)piperidine-3-carboxylate:**

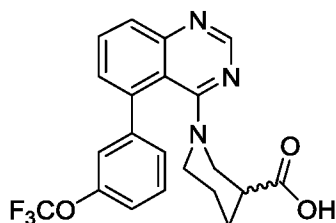
The title compound was prepared in a similar fashion as described in general procedure E starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (600 mg, 1.71 mmol) and 4-(tert-butoxycarbonylamino)phenylboronic acid (800 mg, 3.42 mmol). The crude product was purified by column chromatography (silica gel, pet-ether/EtOAc 75/25) to give methyl 1-(5-(4-(tert-butoxycarbonylamino)phenyl)quinazolin-4-yl)piperidine-3-carboxylate (400 mg, 50%) as a brown solid. MS (ESI) m/z : 463.34 [$C_{26}H_{30}N_4O_4+H$] $^+$.

Step 2: Preparation of methyl 1-(5-(4-aminophenyl)quinazolin-4-yl)piperidine-3-carboxylate:

A solution of methyl 1-(5-(4-(tert-butoxycarbonylamino)phenyl)quinazolin-4-yl)piperidine-3-carboxylate (390 mg, 0.844 mmol) and TFA (3 mL) in DCM (20 mL) was stirred at rt for 3 h. The reaction mixture was neutralized with aq. $NaHCO_3$ solution till pH 6 and extracted with 10% methanol in DCM. The extract was dried over Na_2SO_4 , filtered and concentrated to give methyl-1-(5-(4-aminophenyl)quinazolin-4-yl)piperidine-3-carboxylate (300 mg) as a brown solid. MS (ESI) m/z : 363.34 [$C_{21}H_{22}N_4O_2+H$] $^+$.

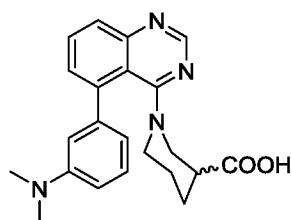
Step 3: Preparation of 1-(5-(4-aminophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid:

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(4-aminophenyl)quinazolin-4-yl)piperidine-3-carboxylate (200 mg, 0.55 mmol). The crude product was purified by prep-HPLC to afford racemic 1-(5-(4-aminophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (70 mg, 36%, AUC-HPLC 95.33%) as a yellow solid. mp: 233-235 °C; ^1H NMR (400 MHz, $DMSO-d_6$) δ (ppm): 8.50–8.42 (m, 1H), 7.73–7.61 (m, 2H), 7.38 (d, $J = 7.2$ Hz, 1H), 7.07 (bs, 2H), 6.61 (d, $J = 8.0$ Hz, 2H), 5.28 (s, 2H), 3.65 (bs, 1H), 3.10–2.78 (m, 1H), 2.07–1.72 (s, 3H), 1.51 (bs, 1H), 1.40–1.23 (m, 3H); MS (ESI) m/z : 349.31 [$C_{20}H_{20}N_4O_2+H$] $^+$.

Compound 53: 1-(5-(3-(trifluoromethoxy)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and 3-(trifluoromethoxy)phenylboronic acid (123.54 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford racemic 1-(5-(3-(trifluoromethoxy)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (35.5 mg, 0.085 mmol, 28.4 %, AUC HPLC 98.92 %) as white solid. ^1H NMR (400 MHz, MeOD) δ (ppm): 8.56 (m, 1H), 7.88 (2d, J = 8.0, 7.2 Hz, 1H), 7.81 (d, J = 7.2 Hz, 1H), 7.56 (d, J = 7.2 Hz, 2H), 7.50-7.40 (m, 1H), 7.36 (d, J = 6.8 Hz, 2H), 4.35-4.20 and 3.95-3.70 (2m, 1H), 3.75-3.55 (m, 1H), 3.10-2.80 (m, 1H), 2.45-2.20 (m, 1H), 2.00-1.70 (m, 1H), 1.65-1.15 (m, 3H), 0.95-0.70 (m, 1H); MS (ESI) m/z 418.10 [$\text{C}_{21}\text{H}_{18}\text{F}_3\text{N}_3\text{O}_3 + \text{H}$] $^+$.

Compound 54: 1-(5-(3-(dimethylamino)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



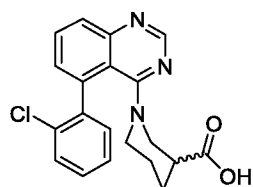
Step 1: Preparation of methyl 1-(5-(3-(dimethylamino)phenyl)quinazolin-4-yl)piperidine-3-carboxylate:

The title compound was prepared in a similar fashion as described in general procedure E starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (250 mg, 0.71 mmol) and 3-(dimethylamino)phenylboronic acid (235 mg, 1.42 mmol). The crude was purified by column chromatography (silica gel, eluent pet-ether/EtOAc 70:30) to afford methyl 1-(5-(3-(dimethylamino)phenyl)quinazolin-4-yl)piperidine-3-carboxylate (250 mg, 89%, LC-MS 88%) as a white solid. MS (ESI) m/z : 391.36 [$\text{C}_{23}\text{H}_{26}\text{N}_4\text{O}_2 + \text{H}$] $^+$.

Step 2: Preparation 1-(5-(3-(dimethylamino)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(3-(dimethylamino)phenyl)quinazolin-4-yl)piperidine-3-carboxylate (250 mg, 0.64 mmol). The residue was purified by Preparative HPLC to afford racemic 1-(5-(3-(dimethylamino)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (40 mg, 16%, AUC-HPLC 98.41%) as a yellow solid. mp: 184-186°C. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 12.10 (bs, 1H), 8.55 (bs, 1H), 7.80-7.53 (m, 2H), 7.64 (d, J = 6.8 Hz, 1H), 7.24 (s, 1H), 6.79 (d, J = 7.2 Hz, 3H), 2.80 (s, 6H), 1.69 (bs, 1H), 1.30-1.20 (m, 5H), 0.85 (t, J = 6.8 Hz, 3H); MS (ESI) m/z : 377.33 [$\text{C}_{22}\text{H}_{24}\text{N}_4\text{O}_2 + \text{H}$] $^+$.

Compound 55: 1-(5-(2-chlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid

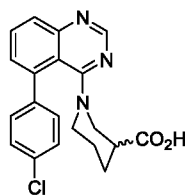


The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (2-chlorophenyl)boronic acid (93.83 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford racemic 1-(5-(2-chlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (3.2 mg, 8.69 μ mol, AUC HPLC 99.03 %) as white solid. ^1H NMR (400 MHz, MeOD) δ (ppm): 8.63 (bs, 1H), 7.98-7.80 (m, 2H), 7.73-7.63 (m, 1H), 7.58 (d, J = 6.4 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.52-7.42 (m, 2H), 4.00-3.50 (m, 1H), 3.20-2.90 (m, 1H), 2.89-2.60 (m, 1H), 2.00-1.60 (m, 2H), 1.50-1.30 (m, 3H), 1.29-1.00 (m, 1H); MS (ESI) m/z 368.10 [$\text{C}_{20}\text{H}_{18}\text{ClN}_3\text{O}_2 + \text{H}$] $^+$.

Compound 56: (racemic)-1-(5-(4-chlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid and

Compound 57: (R)- 1-(5-(4-chlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid

Compound 58: (S)- 1-(5-(4-chlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



Step 1: Preparation of methyl 1-(5-(4-chlorophenyl)quinazolin-4-yl)piperidine-3-carboxylate:

The title compound was prepared in a similar fashion as described in general procedure E starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (600 mg, 1.714 mmol) and 4-chlorophenylboronic acid (470 mg, 3.085 mmol). The crude product was purified by column chromatography (Silica gel, eluent pet-ether/EtOAc 70:30) to afford methyl 1-(5-(4-chlorophenyl)quinazolin-4-yl)piperidine-3-carboxylate (620 mg, 95%, LC-MS 95%) as an off-white solid. MS (ESI) m/z : 382.26 [$\text{C}_{21}\text{H}_{20}\text{ClN}_3\text{O}_2 + \text{H}$] $^+$.

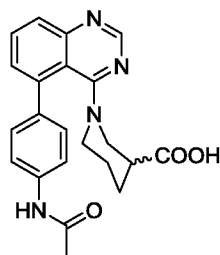
Step 2: Preparation of 1-(5-(4-chlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid:

To a solution of methyl 1-(5-(4-chlorophenyl)quinazolin-4-yl)piperidine-3-carboxylate (620 mg, 1.627 mmol) in a mixture of THF (10 mL) and H_2O (10 mL) was added LiOH (139 mg, 3.254 mmol). The reaction mixture was stirred at rt for 4 hours and was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95:5 to 90:10) to afford 1-(5-(4-chlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (400 mg, 67%, AUC-HPLC 97%) as an off-white solid which was resolved by chiral HPLC to give (R)- 1-(5-(4-chlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (80 mg, AUC-HPLC 98.06%) and peak-2 (85 mg, AUC-HPLC 99.21%).

(R)- 1-(5-(4-chlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (Peak-1): white solid, mp:153-158 $^{\circ}\text{C}$; ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 12.23 (bs, 1H), 8.61-8.56 (m, 1H), 7.83-7.81 (m, 2H), 7.50 (bs, 5H), 3.67-3.52 (m, 2H), 2.71-2.60 (m, 2H), 2.38-2.20 (m, 1H), 1.70 (bs, 1H), 1.47-1.08 (m, 3H); MS (ESI) m/z : 368.16 [$\text{C}_{20}\text{H}_{18}\text{ClN}_3\text{O}_2 + \text{H}$] $^+$.

(S)- 1-(5-(4-chlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (Peak-2): white solid, mp:154-159 °C; ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 12.23 (bs, 1H), 8.61–8.56 (m, 1H), 7.83–7.81 (m, 2H), 7.50 (bs, 5H), 3.67–3.51 (m, 2H), 2.71–2.60 (m, 2H), 2.38–2.20 (m, 1H), 1.71 (bs, 1H), 1.48–1.08 (m, 3H); MS (ESI) m/z : 368.16 [$\text{C}_{20}\text{H}_{18}\text{ClN}_3\text{O}_2+\text{H}$] $^+$.

Compound 59: 1-(5-(4-acetamidophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



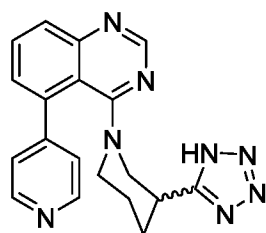
Step 1: Preparation of methyl 1-(5-(4-acetamidophenyl)quinazolin-4-yl)piperidine-3-carboxylate

The title compound was prepared in a similar fashion as described in general procedure E starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (250 mg, 0.714 mmol) and 4-acetamidophenylboronic acid (255 mg, 1.428 mmol). The crude product was purified by column chromatography (silica gel, eluent, DCM/MeOH 96/4) to afford 1-(5-(4-acetamidophenyl)quinazolin-4-yl)piperidine-3-carboxylate (170 mg, 60%, LC-MS 52%) as a brown solid. MS (ESI) m/z : 405.95 [$\text{C}_{23}\text{H}_{24}\text{N}_4\text{O}_3+\text{H}$] $^+$.

Step 2: Preparation of 1-(5-(4-acetamidophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid:

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(4-acetamidophenyl)quinazolin-4-yl)piperidine-3-carboxylate (170 mg, 0.420 mmol). The crude product was purified by preparative HPLC to afford 1-(5-(4-acetamidophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (30 mg, 18%, AUC-HPLC 93.09%) as a pale yellow solid. mp: 236-243 °C; ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.06 (s, 1H), 8.58–8.52 (m, 1H), 7.80–7.65 (m, 4H), 7.47 (d, $J = 6.8$ Hz, 1H), 7.36–7.31 (m, 2H), 3.69–3.61 (m, 2H), 2.70–2.60 (m, 2H), 2.42–2.38 (m, 1H), 2.07 (s, 3H), 1.80–1.65 (m, 1H), 1.49–1.23 (m, 3H); MS (ESI) m/z : 391.29 [$\text{C}_{22}\text{H}_{22}\text{N}_4\text{O}_3+\text{H}$] $^+$.

Compound 60: 4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(pyridin-4-yl)quinazoline

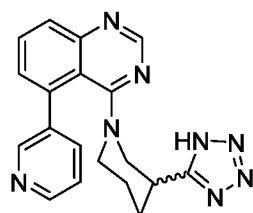


Step 1: Preparation of 1-(5-(pyridin-4-yl)quinazolin-4-yl)piperidine-3-carbonitrile:

The title compound was prepared in a similar fashion as described in general procedure E starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carbonitrile (300 mg, 0.949 mmol) and 4-pyridineboronic acid (230 mg, 1.89 mmol). The crude product was purified by column chromatography (silica gel, eluent DCM/MeOH 97:3) to afford 1-(5-(pyridin-4-yl)quinazolin-4-yl)piperidine-3-carbonitrile (190 mg, 65%) as a brown solid. MS (ESI) m/z : 316.45 [$C_{19}H_{17}N_5 + H$] $^+$.

Step 2: Preparation of 4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(pyridin-4-yl)quinazoline:

The title compound was prepared in a similar fashion as described in general procedure F starting from 1-(5-(pyridin-4-yl)quinazolin-4-yl)piperidine-3-carbonitrile (80 mg, 0.253 mmol). The crude product was purified by preparative HPLC to afford 4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(pyridin-4-yl)quinazoline (10 mg, 11%, AUC-HPLC 95.41%) as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 16.18 (bs, 1H), 8.70–8.53 (s, 3H), 7.91–7.88 (m, 2H), 7.60–7.39 (m, 3H), 4.25–4.02 (m, 1H), 3.61–3.50 (m, 1H), 2.96–2.82 (m, 1H), 2.29–2.13 (m, 1H), 1.90–1.85 (m, 1H), 1.65–1.07 (m, 3H), 0.43–0.40 (m, 1H); MS (ESI) m/z : 359.24 [$C_{19}H_{18}N_8 + H$] $^+$.

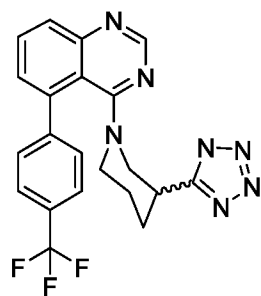
Compound 61: 4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(pyridin-3-yl)quinazoline**Step 1: Preparation of 1-(5-(pyridin-3-yl)quinazolin-4-yl)piperidine-3-carbonitrile:**

The title compound was prepared in a similar fashion as described in general procedure E starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carbonitrile (250 mg, 0.788 mmol) and 3-pyridineboronic acid (145 mg, 1.182 mmol). The crude product was purified by column chromatography (silica gel, eluent DCM/MeOH 97:3) to afford 1-(5-(pyridin-3-yl)quinazolin-4-yl)piperidine-3-carbonitrile (200 mg, 83%, LC-MS 93%) as a viscous liquid. MS (ESI) m/z : 316.26 [$C_{19}H_{17}N_5 + H$] $^+$.

Step 2: Preparation of 4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(pyridin-3-yl)quinazoline:

The title compound was prepared in a similar fashion as described in general procedure F starting from 1-(5-(pyridin-3-yl)quinazolin-4-yl)piperidine-3-carbonitrile (220 mg, 0.698 mmol). The crude product was purified by preparative TLC to afford 4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(pyridin-3-yl)quinazoline (10 mg, AUC-HPLC 95.20%) as an off-white solid. ^1H NMR (400 MHz, $DMSO-d_6$) δ (ppm): 16.18 (bs, 1H), 8.71–8.58 (m, 3H), 7.93–7.86 (m, 3H), 7.61–7.35 (m, 2H), 4.0 (d, $J = 11.2$ Hz, 1H), 3.56 (d, $J = 11.2$ Hz, 1H), 3.17 (bs, 1H), 2.86–2.81 (m, 1H), 2.10 (bs, 1H), 1.88–1.85 (m, 1H), 1.48–1.44 (m, 1H), 1.23 (bs, 1H), 0.43–0.31 (m, 1H); MS (ESI) m/z : 359.28 [$C_{19}H_{18}N_8 + H$] $^+$.

Compound 62: 4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(4-(trifluoromethyl)phenyl)quinazoline



Step 1: Preparation of 1-(5-bromoquinazolin-4-yl)piperidine-3-carbonitrile

The title compound was prepared in a similar fashion as described in general procedure G starting from 5-bromo-4-chloroquinazoline (3 g, 12.39 mmol) and piperidine-3-carbonitrile (1.77 g, 16.11 mmol). The residue was filtered through a silica gel column (100-200 mesh) eluting with 30% ethyl acetate in pet-ether to afford 1-(5-bromoquinazolin-4-yl)piperidine-3-carbonitrile (3 g, 76%, LC-MS 88%) as a yellow solid. MS (ESI) m/z : 319.14 [$C_{14}H_{13}BrN_4+3$] $^+$.

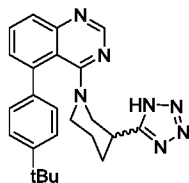
Step 2: Preparation of 1-(5-(4-(trifluoromethyl)phenyl)quinazolin-4-yl)piperidine-3-carbonitrile

The title compound was prepared in a similar fashion as described in general procedure E starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carbonitrile (250 mg, 0.788 mmol) and 4-(trifluoromethyl)phenylboronic acid (298 mg, 1.577 mmol). The crude product was purified by column chromatography (Silica gel, eluent DCM/MeOH 96:4) to afford 1-(5-(4-(trifluoromethyl)phenyl)quinazolin-4-yl)piperidine-3-carbonitrile (300 mg, 99%, LC-MS 74%) as a colourless semi-solid. MS (ESI) m/z : 383.28 [$C_{21}H_{17}F_3N_4+H$] $^+$.

Step 3: Preparation of 4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(4-(trifluoromethyl)phenyl)quinazoline

The title compound was prepared in a similar fashion as described in general procedure F starting from 1-(5-(4-(trifluoromethyl)phenyl)quinazolin-4-yl)piperidine-3-carbonitrile (300 mg, 0.785 mmol). The crude product was purified by prep-HPLC to afford 4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(4-(trifluoromethyl)phenyl)quinazoline (20 mg, 6%, AUC-HPLC 92.28%) as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.65–8.58 (m, 1H), 8.21 (s, 1H), 7.85–7.55 (m, 6H), 4.20–4.04 (m, 1H), 3.77–3.63 (m, 1H), 2.77 (bs, 1H), 2.07 (bs, 1H), 1.90–1.72 (m, 2H), 1.46–1.23 (m, 3H); MS (ESI) m/z : 424.31 [$C_{21}H_{18}F_3N_7+H$] $^+$.

Compound 63: 4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(4-tert-butylphenyl)quinazoline



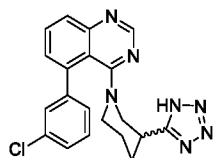
Step 1: Preparation of 1-(5-(4-*tert*-butylphenyl)quinazolin-4-yl)piperidine-3-carbonitrile:

The title compound was prepared in a similar fashion as described in general procedure E starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carbonitrile (250 mg, 0.788 mmol) and 4-*tert*-butylphenylboronic acid (281 mg, 1.577 mmol). The crude product was purified by column chromatography (silica gel, DCM/MeOH 96:4) to afford 1-(5-(4-*tert*-butylphenyl)quinazolin-4-yl)piperidine-3-carbonitrile (250 mg, 86%) as an off-white solid. MS (ESI) m/z : 371.93 $[\text{C}_{24}\text{H}_{26}\text{N}_4+\text{H}]^+$.

Step 2: Preparation of 4-(3-(1*H*-tetrazol-5-yl)piperidin-1-yl)-5-(4-*tert*-butylphenyl)quinazoline

The title compound was prepared in a similar fashion as described in general procedure F starting from 1-(5-(4-*tert*-butylphenyl)quinazolin-4-yl)piperidine-3-carbonitrile (310 mg, 0.83 mmol). The residue was purified by preparative HPLC to afford 4-(3-(1*H*-tetrazol-5-yl)piperidin-1-yl)-5-(4-*tert*-butylphenyl)quinazoline (20 mg, AUC-HPLC 95.41%) as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.63 (bs, 1H), 7.86–7.81 (m, 2H), 7.54–7.26 (m, 5H), 4.05 (d, J = 11.6 Hz, 1H), 3.79 (d, J = 10.4 Hz, 1H), 3.08 (bs, 2H), 2.57 (br, 1H), 1.84–1.75 (m, 2H), 1.47–1.44 (m, 1H), 1.31 (s, 9H), 0.59–0.57 (m, 1H); MS (ESI) m/z : 414.38 $[\text{C}_{24}\text{H}_{27}\text{N}_7+\text{H}]^+$.

Compound 64: 4-(3-(1*H*-tetrazol-5-yl)piperidin-1-yl)-5-(3-chlorophenyl)quinazoline



Step 1: Preparation of 1-(5-bromoquinazolin-4-yl)piperidine-3-carbonitrile

To a solution of 5-bromo-4-chloroquinazoline (3 g, 12.39 mmol) in THF (60 mL) was added piperidine-3-carbonitrile (1.77 g, 16.11 mmol) and TEA (5.2 mL, 37.19 mmol) and the reaction mixture was stirred at 85 °C for 16 h. After completion, reaction mixture was concentrated and purified by column chromatography (Silica gel, eluent Pet ether/EtOAc 70:30) to afford 1-(5-bromoquinazolin-4-yl)piperidine-3-carbonitrile (3 g, 76%, LC-MS 88%) as a yellow solid.

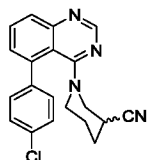
Step 2: Preparation of 1-(5-(3-chlorophenyl)quinazolin-4-yl)piperidine-3-carbonitrile

The title compound was prepared in a similar fashion as described in general procedure E starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carbonitrile (250 mg, 0.788 mmol) and 3-chlorophenylboronic acid (184 mg, 1.182 mmol). The crude product was purified by column chromatography (silica gel, eluent DCM/MeOH 97:3) to afford 1-(5-(3-chlorophenyl)quinazolin-4-yl)piperidine-3-carbonitrile (230 mg, 85%, LC-MS 70%) as a viscous liquid. MS (ESI) m/z : 349.24 $[\text{C}_{20}\text{H}_{17}\text{ClN}_4+\text{H}]^+$.

Step 3: Preparation of 4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(3-chlorophenyl)quinazoline:

The title compound was prepared in a similar fashion as described in general procedure F starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carbonitrile (150 mg, ~0.301 mmol). The crude product was purified by preparative HPLC to afford 4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(3-chlorophenyl)quinazoline (30 mg, 25%, AUC-HPLC 97.36%) as an off-white solid. mp: 230-240 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.68–8.62 (s, 1H), 7.87 (bs, 2H), 7.56–7.48 (m, 5H), 4.02 (bs, 1H), 3.74 (bs, 1H), 3.12 (bs, 1H), 2.78–2.65 (m, 2H), 1.91 (bs, 2H), 1.56 (bs, 1H), 1.35–1.24 (m, 1H); MS (ESI) *m/z*: 392.15 [C₂₀H₁₈ClN₇+H]⁺.

Compound 65: 1-(5-(4-chlorophenyl)quinazolin-4-yl)piperidine-3-carbonitrile

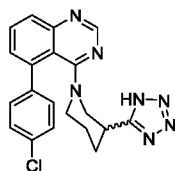


The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(4-chlorophenyl) quinazoline (1.6 g, 5.81 mmol) and piperidine-3-carbonitrile (1.27 g, 11.63 mmol). The crude compound was purified by column chromatography (silica gel, petroleum/ethyl acetate 50:50) to afford 1-(5-(4-chlorophenyl)quinazolin-4-yl)piperidine-3-carbonitrile (800 mg, LC-MS 76%) as a yellow solid MS. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.64 (s, 1H), 7.86–7.82 (m, 2H), 7.52 (bs, 5H), 3.80–3.60 (m, 1H), 3.20–2.90 (m, 3H), 2.18 (bs, 1H), 1.73–1.53 (m, 3H), 1.10–0.78 (m, 1H); MS (ESI) *m/z*: 392.25 [C₂₀H₁₈ClN₇+H]⁺

Compound 66: Racemic 4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(4-chlorophenyl)quinazoline

Compound 67: (R)-4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(4-chlorophenyl)quinazoline

Compound 68: (S)-4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(4-chlorophenyl)quinazoline



Step 2: Preparation of (R)-4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(4-chlorophenyl)quinazoline (peak-1 and peak-2):

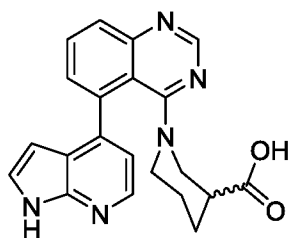
The title compound was prepared in a similar fashion as described in general procedure F starting from 1-(5-(4-chlorophenyl)quinazolin-4-yl)piperidine-3-carbonitrile (800 mg, 2.29 mmol). The reaction crude product was purified by preparative HPLC afforded racemic 4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(4-chlorophenyl)quinazoline (190 mg, 22%, LC-MS 98%), HPLC 97%) which was resolved by chiral SFC preparative purification to give (R)-4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(4-chlorophenyl)quinazoline (**peak-1**) (24 mg, LC-MS 99%, HPLC-99%) and (S)-4-(3-(1H-

tetrazol-5-yl)piperidin-1-yl)-5-(4-chlorophenyl)quinazoline (**peak-2**) (16 mg, LC-MS 98%, HPLC 98%)

Peak 1: White fluffy solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ (ppm): 16.0 (s, 1H) 8.65 (s, 1H), 7.84 (s, 2H), 7.70-7.10 (m, 5H), 4.02 (s, 1H), 3.56 (s, 1H), 2.84 (s, 1H), 2.20 (s, 1H), 1.92 (d, $J = 10.0$ Hz, 1H), 1.15-1.79 (m, 4H); MS (ESI) m/z : 392.25 [$\text{C}_{20}\text{H}_{18}\text{ClN}_7 + \text{H}$] $^+$

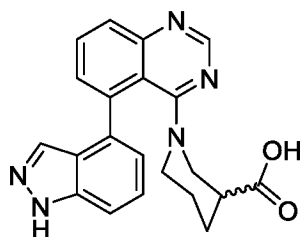
Peak 2: Off-white fluffy solid. (^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ (ppm): 16.0 (s, 1H), 8.76 (d, $J = 20.0$ Hz, 1H), 7.98 (s, 1H), 7.82 (d, $J = 7.2$ Hz, 1H), 7.79-7.29 (m, 5H), 3.51 (s, 2H), 3.29-2.98 (m, 2H), 2.53 (s, 1H), 1.95 (s, 1H), 1.80-1.32 (m, 3H); MS (ESI) m/z : 392.25 [$\text{C}_{20}\text{H}_{18}\text{ClN}_7 + \text{H}$] $^+$.

Compound 69: 1-(5-(1H-pyrrolo[2,3-b]pyridin-4-yl)quinazolin-4-yl)piperidine-3-carboxylic acid



The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine (146.46 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford 1-(5-(1H-pyrrolo[2,3-b]pyridin-4-yl)quinazolin-4-yl)piperidine-3-carboxylic acid (10.57 mg, 0.028 mmol, 9.4 %, AUC HPLC 99.46 %) as yellow solid. ^1H NMR (400 MHz, MeOD) δ (ppm): 8.61 (s, 1H), 8.32 (s, 1H), 8.00-7.90 (m, 1H), 7.88 (d, $J = 8.4$ Hz, 1H), 7.78 (bs, 1H), 7.44 (bs, 1H), 7.31 & 7.18 (2bs, 1H), 6.25 & 6.04 (2bs, 1H), 3.70-3.50 (m, 1H), 2.90-2.65 (m, 1H), 2.40-2.25 & 0.40-0.20 (m, 1H), 2.10-1.71 (m, 1H), 1.70-1.51 (m, 1H), 1.50-1.20 (m, 3H), 1.19-0.70 (m, 1H); MS (ESI) m/z 374.10 [$\text{C}_{21}\text{H}_{19}\text{N}_5\text{O}_2 + \text{H}$] $^+$.

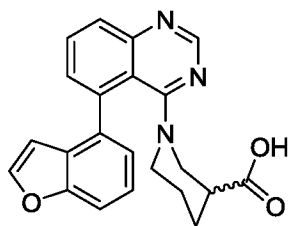
Compound 70: 1-(5-(1H-indazol-4-yl)quinazolin-4-yl)piperidine-3-carboxylic acid



The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (146.46 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford 1-(5-(1H-indazol-4-yl)quinazolin-4-yl)piperidine-3-carboxylic acid (3.71 mg, 9.94 μmol , AUC HPLC 95.33 %) as white solid. ^1H NMR (400 MHz, MeOD) δ (ppm): 8.60 (bs, 1H), 7.92 (2d, $J = 8.4, 7.6$ Hz, 1H), 7.90-7.70 (m, 3H), 7.64 (d, $J = 8.4$ Hz, 1H), 7.60-7.45

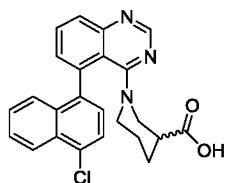
(m, 2H), 3.70-3.50 (m, 1H), 2.90-2.60 (m, 1H), 2.00-1.50 (m, 2H), 1.49-1.10 (m, 4H), 1.00-0.80 (m, 1H); MS (ESI) m/z 374.10 [$C_{21}H_{19}N_5O_2 + H$] $^+$.

Compound 71: 1-(5-(benzofuran-4-yl)quinazolin-4-yl)piperidine-3-carboxylic acid

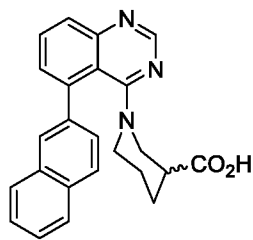


The title compound was prepared in a similar fashion as described in general procedure B starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (100 mg, 0.29 mmol) and 2-(benzofuran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (93.96 mg, 0.58 mmol). The residue was purified by preparative HPLC to afford 1-(5-(benzofuran-4-yl)quinazolin-4-yl)piperidine-3-carboxylic acid (4.97 mg, 0.013 mmol, AUC HPLC 96.32 %) as white solid. ^1H NMR (400 MHz, MeOD) δ (ppm): 8.54 (bs, 1H), 7.90-7.81 (m, 2H), 7.74 (bs, 2H), 7.62 (2d, $J = 8.4, 6.4$ Hz, 2H), 7.37 (bs, 1H), 6.93 (s, 1H), 4.40-4.20 & 4.00-3.80 (2m, 1H), 3.79-3.60 (m, 1H), 3.10-2.80 (m, 1H), 2.40-2.10 (m, 1H), 1.90-1.80 & 0.80-0.60 (2m, 1H), 1.70-1.40 (m, 1H), 1.39-1.10 (m, 3H); MS (ESI) m/z 374.10 [$C_{22}H_{19}N_3O_3 + H$] $^+$.

Compound 72: 1-(5-(4-chloronaphthalen-1-yl)quinazolin-4-yl)piperidine-3-carboxylic acid



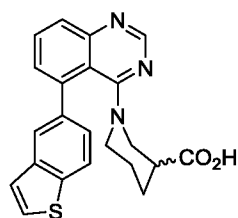
The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (4-chloronaphthalen-1-yl)boronic acid (123.86 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford 1-(5-(4-chloronaphthalen-1-yl)quinazolin-4-yl)piperidine-3-carboxylic acid (4.33 mg, 0.010 mmol, AUC HPLC 99.13%) as white solid. ^1H NMR (400 MHz, MeOD) δ (ppm): 8.62 (bs, 1H), 8.39 (2d, $J = 6.0, 6.0$ Hz, 1H), 8.00-7.90 (m, 2H), 7.74 (t, $J = 8.2$ Hz, 1H), 7.70-7.58 (m, 3H), 7.53-7.48 (m, 1H), 7.43 (d, $J = 4.0$ Hz, 1H), 4.15-4.10 (m, 1H), 3.05-2.95 (m, 1H), 2.90-2.80 (m, 1H), 2.75-2.55 (m, 1H), 1.70-1.50 (m, 2H), 1.20-1.10 (m, 2H), 0.95-0.80 (m, 1H); MS (ESI) m/z 418.10 [$C_{24}H_{20}ClN_3O_2 + H$] $^+$.

Compound 73: 1-(5-(naphthalen-2-yl)quinazolin-4-yl)piperidine-3-carboxylic acid**Step 1: Preparation of methyl 1-(5-(naphthalen-2-yl)quinazolin-4-yl)piperidine-3-carboxylate**

The title compound was prepared in a similar fashion as described in general procedure E starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (250 mg, 0.714 mmol) and naphthalen-2-ylboronic acid (245 mg, 1.42 mmol). The crude product was purified by column chromatography (silica gel, eluent pet-ether/EtOAc 70:30) to afford methyl 1-(5-(naphthalen-2-yl)quinazolin-4-yl)piperidine-3-carboxylate (220 mg, 77%, LC-MS 88%) as an off-white solid. MS (ESI) m/z : 398.34 [$C_{25}H_{23}N_3O_2 + H$] $^+$.

Step 2: Preparation of 1-(5-(naphthalen-2-yl)quinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(naphthalen-2-yl)quinazolin-4-yl)piperidine-3-carboxylate (220 mg, 0.554 mmol). The crude product was purified by preparative HPLC to afford 1-(5-(naphthalen-2-yl)quinazolin-4-yl)piperidine-3-carboxylic acid (40 mg, 18%, AUC-HPLC 98.50%) as an off-white solid. mp: 199–203 °C; ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.61–8.54 (m, 1H), 7.98–7.93 (m, 4H), 7.84–7.80 (m, 2H), 7.62–7.52 (m, 4H), 3.69–3.49 (m, 2H), 3.03 (bs, 2H), 2.15 (bs, 1H), 1.84 (bs, 1H), 1.30–1.02 (m, 3H); MS (ESI) m/z : 384.47 [$C_{24}H_{21}N_3O_2 + H$] $^+$.

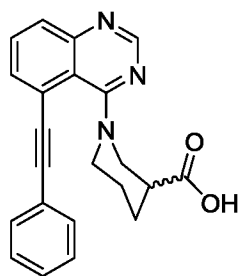
Compound 74: 3-(5-(benzo[b]thiophen-5-yl)quinazolin-4-yl)cyclohexanecarboxylic acid**Step 1: Preparation of methyl 3-(5-(benzo[b]thiophen-5-yl)quinazolin-4-yl)cyclohexanecarboxylate**

The title compound was prepared in a similar fashion as described in general procedure E starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (300 mg, 0.85 mmol) and 2-(benzo[b]thiophen-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (445 mg, 1.71 mmol). The residue was purified by column chromatography (silica gel column, eluent pet-ether/EtOAc 60:40 to afford methyl 3-(5-(benzo[b]thiophen-5-yl)quinazolin-4-yl)cyclohexanecarboxylate (200 mg, 34%, LC-MS 89%); (ESI) m/z : 404.30 [$C_{24}H_{22}N_2O_2S + 1$] $^+$.

Step 2: Preparation of 3-(5-(benzo[b]thiophen-5-yl)quinazolin-4-yl)cyclohexanecarboxylic acid:

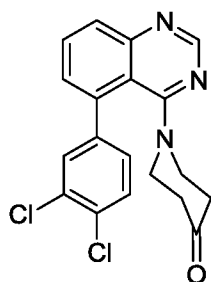
The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 3-(5-(benzo[b]thiophen-5-yl)quinazolin-4-yl)cyclohexanecarboxylate (200 mg, 0.49 mmol) and LiOH.H₂O in a mixture of THF (8 mL) and H₂O (8 mL) was stirred for 2 h. The reaction mixture was concentrated to half the volume and acidified with aq.KHSO₄ solution till pH 5. The precipitate was isolated by filtration and dried to afford 3-(5-(benzo[b]thiophen-5-yl)quinazolin-4-yl)cyclohexanecarboxylic acid (98 mg, 40%, LC-MS 98.85, AUC-HPLC 97.88 %) as an off-white solid. m.p: 185–191 °C, ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.68–8.52 (m, 1H), 8.05 (bs, 1H), 7.94 (s, 1H), 7.84–7.79 (m, 2H), 7.58–7.52 (m, 2H), 7.45–7.36 (m, 2H), 3.76–3.57 (m, 2H), 2.67–2.60 (m, 1H), 2.32–2.05 (m, 1H), 1.88 (s, 1H), 1.39 (bs, 1H), 1.20–1.03 (m, 3H); MS (ESI) *m/z*: 390.27 [C₂₂H₁₉N₃O₂S+1]⁺.

Compound 75: 1-(5-(phenylethynyl)quinazolin-4-yl)piperidine-3-carboxylic acid



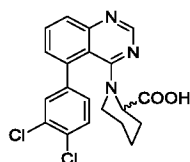
To a solution of 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) in acetonitrile (2 mL) was added phenylacetylene (0.05 mL, 0.60 mmol), Pd(PPh₃)₄ (45.07 mg, 0.039 mmol), triphenylphosphine (27.54 mg, 0.11 mmol), copper iodide (5.71 mg, 0.03 mmol), and DIPEA (1 mL, 6.60 mmol). The reaction mixture was microwaved at 120 °C for 2.0 hours under nitrogen, was then quenched with 2 eq. of 1N HCl and extracted with dichloromethane (3 x 25 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to afford 1-(5-(phenylethynyl)quinazolin-4-yl)piperidine-3-carboxylic acid (48.94 mg, 0.137 mmol, 45.6 %, AUC HPLC 99.57 %) as white solid. ¹H NMR (400 MHz, MeOD) δ (ppm): 8.53 (bs, 1H), 7.94 (t, *J* = 7.2 Hz, 1H), 7.82–7.75 (m, 4H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.62–7.55 (m, 1H), 7.44 (d, *J* = 5.2 Hz, 2H), 4.60–4.00 (m, 1H), 3.85–3.40 (m, 2H), 2.80–2.60 (bs, 1H), 2.15–2.00 (bs, 1H), 1.99–1.55 (m, 2H), 1.54–1.20 (m, 1H); MS (ESI) *m/z* 358.10 [C₂₂H₁₉N₃O₂+ H]⁺.

Compound 76: 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-4-one



The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)quinazoline (1.5 g, 4.88 mmol) and piperidin-4-one (966 mg, 9.76 mmol). The crude compound was purified by column chromatography (silica gel, eluent petroleum ether/ethyl acetate 6:4) to afford 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-4-one (1.7 g, 94%, LC-MS 94%, AUC-HPLC 93%) as a brown gummy solid. m.p: 124–132 °C. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.77 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.81 (t, *J* = 8 Hz, 1H), 7.57–7.47 (m, 3H), 7.35 (d, *J* = 8 Hz, 1H), 3.67–3.26 (m, 4H), 2.31–1.99 (m, 4H); MS (ESI) *m/z*: 372.22 [C₁₉H₁₅Cl₂N₃O+H]⁺.

Compound 77: 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-2-carboxylic acid



Step 1: Preparation of methyl 1-(5-bromoquinazolin-4-yl)piperidine-2-carboxylate

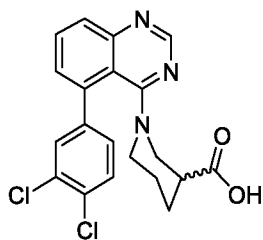
The title compound was prepared in a similar fashion as described in general procedure G starting from 5-bromo-4-chloroquinazoline (100 mg, 0.41 mmol) and methyl piperidine-2-carboxylate (118 mg, 0.82 mmol). The residue was purified by column chromatography (silica gel, eluent CH₂Cl₂/MeOH 100:0 to 90:10) to afford methyl 1-(5-bromoquinazolin-4-yl)piperidine-2-carboxylate (143 mg, 99.9%) as a yellow sticky oil.

Step 2: Preparation of methyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-2-carboxylate

The title compound was prepared in a similar fashion as described in general procedure B starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-2-carboxylate (143 mg, 0.41 mmol) and (3,4-dichlorophenyl)boronic acid (120 mg, 0.62 mmol). The residue was purified by column chromatography (silica gel, eluent CH₂Cl₂/MeOH 100:0 to 90:10) to afford methyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-2-carboxylate (58 mg, 34%) as yellow solid.

Step 3: Preparation of 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-2-carboxylic acid

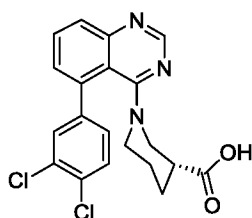
The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-2-carboxylate (58 mg, 0.14 mmol). The residue was purified by preparative HPLC (C18, eluents ACN/H₂O/HCOOH 0.01%) to afford 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-2-carboxylic acid (15 mg, 27%, AUC HPLC 98.02%) as white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 12.60 (s, 1H), 8.80–8.53 (m, 1H), 8.19–7.41 (m, 6H), 4.67–3.44 (m, 2H), 3.14–2.96 (m, 1H), 2.47–0.68 (m, 6H); MS (ESI) *m/z* 402.1 [C₂₀H₁₇Cl₂N₃O₂+H]⁺.

Compound 78: 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid**Step 1: Preparation of methyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxylate:**

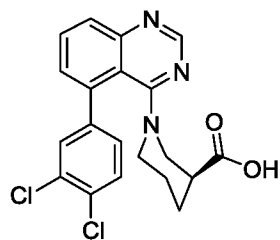
The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)quinazoline (400 mg, 1.30 mmol) and methyl piperidine-3-carboxylate (370 mg, 2.60 mmol). The crude compound was purified by column chromatography (silica gel, pet-ether/EtOAc 80:20) to afford methyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxylate (500 mg, 92%, LC-MS 85%) as an off-white solid. MS (ESI) m/z : 416.18 $[C_{21}H_{19}Cl_2N_3O_2+H]^+$.

Step 2: Preparation of 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid:

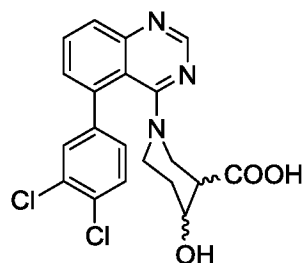
The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxylate (400 mg, 0.963 mmol). The crude compound was purified by column chromatography (silica gel, eluent DCM/MeOH 95:5 to 90:10) to afford 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (280 mg, 73%, AUC-HPLC 99.21%) a white solid. mp: 179-183 °C; ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 12.38 (bs, 1H), 8.65–8.58 (m, 1H), 7.84–7.72 (m, 4H), 7.56–7.34 (m, 2H), 3.62–3.53 (m, 2H), 2.73–2.61 (m, 2H), 1.74 (bs, 1H), 1.48–1.10 (m, 4H); MS (ESI) m/z : 402.15 $[C_{20}H_{17}Cl_2N_3O_2+H]^+$.

Compound 79: (R)-1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)quinazoline (100 mg, 0.325 mmol) and (R)-piperidine-3-carboxylic acid (63 mg, 0.488 mmol). The crude compound was purified by prep-HPLC to afford (R)-1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (80 mg, 61%, AUC-HPLC 98.53%) as a white solid. mp: 183-192 °C; ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 12.38 (bs, 1H), 8.65–8.58 (m, 1H), 7.84–7.71 (m, 4H), 7.56–7.48 (m, 2H), 3.63–3.54 (m, 2H), 2.71–2.59 (m, 2H), 2.38–2.21 (m, 1H), 1.74 (bs, 1H), 1.47–1.10 (m, 3H); MS (ESI) m/z : 402.25 $[C_{20}H_{17}Cl_2N_3O_2+H]^+$.

Compound 80: (S)-1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid**Step 1: (S)-1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid**

The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)quinazoline (100 mg, 0.32 mmol) and (S)-piperidine-3-carboxylic acid (63 mg, 0.48 mmol). The crude product was purified by preparative HPLC to afford (S)-1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (40 mg, 30%, AUC-HPLC 97.38%) as an off-white solid. mp: 175–181 °C; ¹H NMR (400 MHz, DMSO-*d*₆): 12.37 (bs, 1H), 8.71 (bs, 1H), 7.94–7.62 (m, 5H), 7.50–7.20 (m, 1H), 3.61–3.54 (m, 2H), 3.20–2.61 (m, 2H), 2.59 (bs, 1H), 1.75 (bs, 1H), 1.58–1.10 (m, 3H); MS (ESI) *m/z*: 402.21 [C₂₀H₁₇Cl₂N₃O₂+H]⁺.

Compound 81: 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-4-hydroxypiperidine-3-carboxylic acid**Step 1: Preparation of ethyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-4-hydroxypiperidine-3-carboxylate**

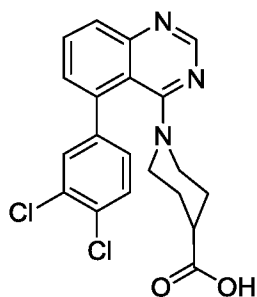
The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)quinazoline (200 mg, 0.65 mmol) and ethyl 4-hydroxypiperidine-3-carboxylate (200 mg, 1.30 mmol). The residue was purified by column chromatography, (silica gel, eluent pet ether/ethyl acetate 6:4) to afford ethyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-4-hydroxypiperidine-3-carboxylate (250 mg, 89%, LC-MS 63%) as a colourless liquid. MS (ESI) *m/z*: 446.2 [C₂₂H₂₁Cl₂N₃O₃+H]⁺.

Step 2: Preparation of 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-4-hydroxypiperidine-3-carboxylic acid

To a solution of ethyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-4-hydroxypiperidine-3-carboxylate (220 mg) in a mixture of THF, H₂O and MeOH (9 mL) was added 2M aqueous solution of NaOH (1.1 mL). The reaction mixture was stirred at rt for 6 hours and was concentrated under reduced pressure. The residue was purified by prep-HPLC to afford 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-4-

hydroxypiperidine-3-carboxylic acid (50 mg, 27%, AUC-HPLC 95%) as an off-white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 8.65–8.53 (m, 1H), 7.86–7.77 (m, 2H), 7.70 (bs, 2H), 7.57–7.55 (m, 1H), 7.47 (bs, 1H), 4.06–3.95 (m, 1H), 3.80–2.70 (m, 2H), 2.93–2.69 (m, 1H), 2.51–2.34 (m, 1H), 1.50–1.20 (m, 2H), 0.71 (bs, 1H); MS (ESI) m/z : 418.22 $[\text{C}_{20}\text{H}_{17}\text{Cl}_2\text{N}_3\text{O}_3+\text{H}]^+$.

Compound 82: 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-4-carboxylic acid



Step 1: ethyl 1-(5-bromoquinazolin-4-yl)piperidine-4-carboxylate

The title compound was prepared in a similar fashion as described in General procedure A starting from 5-bromo-4-chloroquinazoline (250 mg, 1.03 mmol) and ethyl isonipecotate (0.16 mL, 1.03 mmol) to afford ethyl 1-(5-bromoquinazolin-4-yl)piperidine-4-carboxylate (187.5 mg, 0.51 mmol, 50 %, AUC HPLC 89.6 %) as a yellow thick oil. ^1H NMR (400 MHz, $\text{MeOD}-d_4$) δ (ppm): 8.50 (d, J = 24.8 Hz, 1H), 7.80 (d, J = 7.5 Hz, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.61 (q, J = 8.5 Hz, 1H), 4.30-4.15 (m, 2H), 4.09 (d, J = 7.11 Hz, 1H), 4.05-3.95 (m, 1H), 3.52 (t, J = 11.8 Hz, 1H), 3.12 (t, J = 10.5 Hz, 1H), 2.80-2.65 & 2.64-2.50 (m, 1H), 2.20-2.05 (m, 1H), 2.04-1.95 (m, 1H), 1.90 (d, J = 11.6 Hz, 1H), 1.65-1.50 (m, 1H), 1.29 (d, J = 7.1 Hz, 1H), 1.21 (d, J = 7.1 Hz, 2H); MS (ESI) m/z 364.10 $[\text{C}_{16}\text{H}_{18}\text{BrN}_3\text{O}+\text{H}]^+$.

Step 2: ethyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-4-carboxylate

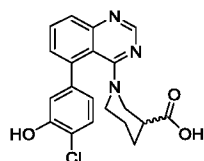
The title compound was prepared in a similar fashion as described in general procedure B starting from ethyl 1-(5-bromoquinazolin-4-yl)piperidine-4-carboxylate (175 mg, 0.48 mmol) and (3,4-dichlorophenyl)boronic acid (183.19 mg, 0.96 mmol). The crude product was purified by flash column chromatography (silica gel, 100% DCM to DCM/Methanol 96:4) to afford ethyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-4-carboxylate (162.3 mg, 0.37 mmol, 78.6 %) as a yellow thick oil; MS (ESI) m/z 403.45 $[\text{C}_{20}\text{H}_{17}\text{Cl}_2\text{N}_3\text{O}_2+\text{H}]^+$.

Step 3 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-4-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-4-carboxylate to afford 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-4-carboxylic acid (78.14 mg, 0.19 mmol, 52.5 %, AUC HPLC 96.45 %) as yellow solid. ^1H NMR (400 MHz, $\text{MeOD}-d_4$) δ (ppm): 8.58 (2s, 1H), 7.86 (2d, J = 8.0, 7.2 Hz, 1H), 7.83-7.77 (m, 1H), 7.70-7.60 (m, 2H), 7.57 (d, J = 6.8 Hz, 1H), 7.52-7.37 (m, 1H), 4.05-3.90 (m, 1H), 3.70-3.85 (m, 1H), 2.90-2.75 (m, 1H), 2.70-2.60 (m, 1H), 2.50-2.40 & 2.30-2.20

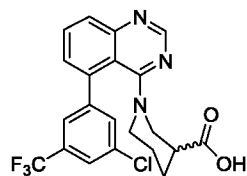
(2m, 1H), 1.80-1.60 (m, 2H), 1.55-1.40 (m, 1H), 1.00-0.70 (m, 1H); MS (ESI) m/z 402.00 [$C_{20}H_{17}Cl_2N_3O_2 + H$]⁺.

Compound 83: 1-(5-(4-chloro-3-hydroxyphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



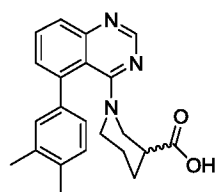
The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (4-chloro-3-hydroxyphenyl)boronic acid (103.42 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford 1-(5-(4-chloro-3-hydroxyphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (6.09 mg, 0.016 mmol, AUC HPLC 99.33%) as a white solid. ¹H NMR (400 MHz, MeOD) δ (ppm): 8.53 (bs, 1H), 7.89-7.80 (m, 1H), 7.74 (d, J = 7.2 Hz, 1H), 7.56 (dd, J = 7.2, 0.8 Hz, 1H), 7.41 (d, J = 6.4 Hz, 1H), 7.01 (bs, 2H), 4.00-3.55 (m, 2H), 3.00-2.60 (m, 1H), 2.45-2.25 (m, 1H), 2.00-1.75 (m, 1H), 1.65-1.45 (m, 2H), 1.40-1.20 (m, 1H), 1.00-0.83 (m, 1H); MS (ESI) m/z 384.10 [$C_{20}H_{18}ClN_3O_3 + H$]⁺.

Compound 84: 1-(5-(3-chloro-5-(trifluoromethyl)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (3-chloro-5-(trifluoromethyl)phenyl)boronic acid (134.62 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford 1-(5-(3-chloro-5-(trifluoromethyl)phenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (33.76 mg, 0.077 mmol, 25.8 %, AUC HPLC 98.47 %) as white solid. ¹H NMR (400 MHz, MeOD) δ (ppm): 8.64 (m, 1H), 8.24 (s, 1H), 7.95-7.70 (m, 4H), 7.62 (dd, J = 6.4, 1.6 Hz, 1H), 3.95-3.65 (m, 1H), 3.64-3.50 (m, 1H), 3.00-2.70 (m, 1H), 2.50-2.35 (m, 1H), 2.25-1.90 (m, 1H), 1.89-1.60 (m, 1H), 1.50-1.20 (m, 2H), 1.00-0.80 (m, 1H); MS (ESI) m/z 436.10 [$C_{21}H_{17}ClF_3N_3O_2 + H$]⁺.

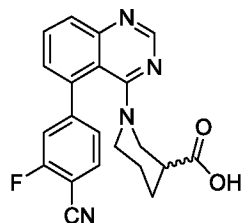
Compound 85: 1-(5-(3,4-dimethylphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and ((3,4-

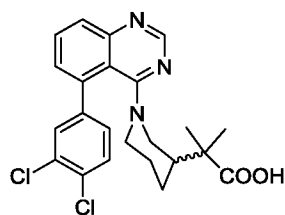
dimethylphenyl)boronic acid (139.28 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford 1-(5-(3,4-dimethylphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (21.84 mg, 0.060 mmol, 20.1 %, AUC HPLC 99.36 %) as white solid. ^1H NMR (400 MHz, MeOD) δ (ppm): 8.53 (s, 1H), 7.88 (d, $J = 8.0, 7.2$ Hz, 1H), 7.70 (d, $J = 8.4$ Hz, 1H), 7.61 (d, $J = 6.4$ Hz, 1H), 7.26 (d, $J = 6.4$ Hz, 2H), 7.15 (bs, 1H), 4.60-4.30 (m, 1H), 4.10-3.80 (m, 1H), 3.65-3.50 (m, 1H), 3.10-2.60 (m, 1H), 2.56 (s, 6H), 2.00-1.70 (m, 1H), 1.69-1.40 (m, 2H), 1.39-0.95 (m, 2H); MS (ESI) m/z 362.10 [$\text{C}_{22}\text{H}_{23}\text{N}_3\text{O}_2 + \text{H}$] $^+$.

Compound 86: 1-(5-(4-cyano-3-fluorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (4-cyano-3-fluorophenyl)boronic acid (98.94 mg, 0.60 mmol). The residue was purified by preparative HPLC to afford 1-(5-(4-cyano-3-fluorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (10.2 mg, 0.027 mmol, 9.0 %, AUC HPLC 97.25 %) as white solid. ^1H NMR (400 MHz, MeOD) δ (ppm): 8.60 (d, $J = 9.2$ Hz, 1H), 7.88 (m, 3H), 7.65-7.55 (m, 1H), 7.54-7.35 (m, 2H), 4.20-4.10 and 3.25-3.10 (2m, 1H), 3.70-3.40 (m, 2H), 3.05-2.85 (m, 1H), 2.60-2.40 (m, 1H), 1.95-1.80 (m, 1H), 1.70-1.45 (m, 2H), 1.40-0.80 (m, 1H); MS (ESI) m/z 377.10 [$\text{C}_{21}\text{H}_{17}\text{FN}_4\text{O}_2 + \text{H}$] $^+$.

Compound 87: 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)-2-methylpropanoic acid



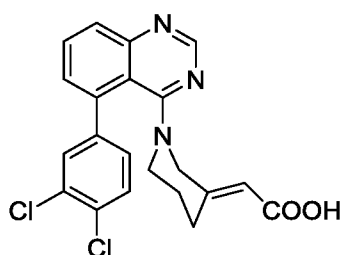
Step 1: methyl 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)-2-methylpropanoate

The title compound was prepared in a similar fashion as described in general procedure D starting from 5-(3,4-dichlorophenyl)quinazolin-4(3H)-one (250 mg, 0.86 mmol) and methyl 2-methyl-2-(piperidin-3-yl)propanoate (318.65 mg, 1.72 mmol). The residue was purified by flash column chromatography (silica gel, 100% Hex to Hex:EA 60:40) to afford methyl 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)-2-methylpropanoate (11 mg, 0.024 mmol, 2.8 %) as yellow thick oil; MS (ESI) m/z 458.10 [$\text{C}_{24}\text{H}_{25}\text{Cl}_2\text{N}_3\text{O}_2 + \text{H}$] $^+$.

Step 2: 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)-2-methylpropanoic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)-2-methylpropanoate (11 mg, 0.024 mmol). The residue was purified by preparative HPLC to afford 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)-2-methylpropanoic acid (0.52 mg, 1.17 μ mol, AUC HPLC 95.91 %) as white solid; ^1H NMR (400 MHz, $\text{MeOD-}d_4$) δ (ppm): 8.59 & 8.49 (2s, 1H), 7.90-7.75 (m, 2H), 7.65-7.50 (m, 4H), 7.50-7.35 (m, 1H), 4.20-3.90 (m, 1H), 3.80-3.50 (m, 2H), 3.30-3.05 (m, 1H), 2.80-2.50 (m, 1H), 2.20-1.90 (m, 2H), 1.80-1.45 (m, 3H), 1.20-1.00 (m, 4H), 0.99-0.80 (m, 1H); MS (ESI) m/z 444.10 [$\text{C}_{23}\text{H}_{23}\text{Cl}_2\text{N}_3\text{O}_2 + \text{H}$] $^+$.

Compound 88: (E)-2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-ylidene)acetic acid

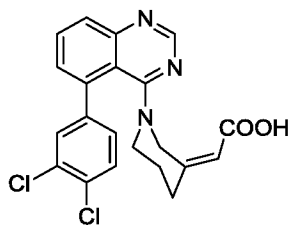


Step 1: ethyl (E)-2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-ylidene)acetate

The title compound was prepared in a similar fashion as described in general procedure D starting from 5-(3,4-dichlorophenyl)quinazolin-4(3H)-one (200 mg, 0.69 mmol) and ethyl (E)-2-(piperidin-3-ylidene)acetate hydrochloride (281.78 mg, 1.37 mmol). The residue was purified using combiflash (100% DCM to DCM:MeOH 90:10 to afford ethyl (E)-2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-ylidene)acetate (63.5 mg, 0.144 mmol, 21.0 %) as yellow-gel form; MS (ESI) m/z 442.10 [$\text{C}_{23}\text{H}_{21}\text{Cl}_2\text{N}_3\text{O}_2 + \text{H}$] $^+$.

Step 2: (E)-2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-ylidene)acetic acid

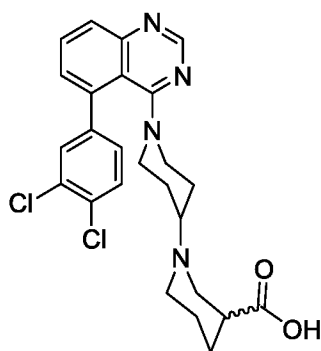
The title compound was prepared in a similar fashion as described in general procedure C starting from ethyl (E)-2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-ylidene)acetate (63.5 mg, 0.14 mmol). The residue was purified by preparative HPLC to afford (E)-2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-ylidene)acetic acid (44.04 mg, 0.11 mmol, 73.8 %, AUC HPLC 99.10 %) as yellow solid; ^1H NMR (400 MHz, DMSO) δ (ppm): 8.69 (s, 1H), 7.92 (2d, $J = 8.0$, 7.6 Hz, 2H), 7.82 (d, $J = 7.60$ Hz, 1H), 7.64 (d, $J = 7.60$ Hz, 1H), 7.60 (d, $J = 7.2$ Hz, 2H), 5.89 (s, 1H), 4.32 (d, $J = 13.2$ Hz, 1H), 3.15-3.05 (m, 2H), 2.85-2.70 (m, 1H), 2.10-1.90 (m, 1H), 1.89-1.80 (m, 1H), 1.65-1.50 (m, 2H); MS (ESI) m/z 414.00 [$\text{C}_{21}\text{H}_{17}\text{Cl}_2\text{N}_3\text{O}_2 + \text{H}$] $^+$.

Compound 89: (Z)-2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-ylidene)acetic acid**Step 1: ethyl (Z)-2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-ylidene)acetate**

The title compound was prepared in a similar fashion as described in general procedure D starting from 5-(3,4-dichlorophenyl)quinazolin-4(3H)-one (200 mg, 0.69 mmol) and ethyl (Z)-2-(piperidin-3-ylidene)acetate hydrochloride (283.84 mg, 1.37 mmol). The residue was purified using combiflash (100% DCM to DCM:MeOH 90:10 to afford ethyl (Z)-2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-ylidene)acetate (85.8 mg, 0.19 mmol, 28.1 %) as yellow gel; MS (ESI) m/z 442.10 [$C_{23}H_{21}Cl_2N_3O_2 + H$]⁺.

Step 2: (Z)-2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-ylidene)acetic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from ethyl (Z)-2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-ylidene)acetate (85 mg, 0.19 mmol). The residue was purified by preparative HPLC to afford (Z)-2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-ylidene)acetic acid (62.66 mg, 0.15 mmol, 79.6 %, AUC HPLC 97.27 %) as yellow solid; ¹H NMR (400 MHz, DMSO) δ (ppm): 12.07 (bs, 1H), 8.70 (s, 1H), 7.93 (2d, $J = 7.60, 7.60$ Hz, 2H), 7.83 (d, $J = 8.40$ Hz, 1H), 7.65 (d, $J = 7.60$ Hz, 2H), 7.61 (d, $J = 6.80$ Hz, 1H), 5.90 (s, 1H), 4.40-4.25 (m, 1H), 3.09 (t, $J = 11.8$ Hz, 1H), 2.85-2.70 (m, 1H), 2.44 (s, 1H), 2.10-1.80 (m, 2H), 1.65-1.50 (m, 2H); MS (ESI) m/z 415.45 [$C_{21}H_{17}Cl_2N_3O_2 + H$]⁺.

Compound 90: 1'-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-[1,4'-bipiperidine]-3-carboxylic acid**Step 1: methyl 1'-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-[1,4'-bipiperidine]-3-carboxylate**

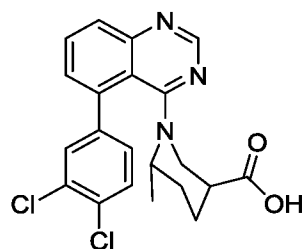
The title compound was prepared in a similar fashion as described in general procedure C starting from 5-(3,4-dichlorophenyl)quinazolin-4(3H)-one (200 mg, 0.69 mmol) and methyl [1,4'-bipiperidine]-3-carboxylate (312.32 mg, 1.38 mmol). The residue was purified using combiflash (100% DCM to DCM: MeOH 90:10 to afford methyl 1'-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-[1,4'-

bipiperidine]-3-carboxylate (10.32 mg, 0.021 mmol) as yellow gel; MS (ESI) m/z 499.10 [$C_{26}H_{28}Cl_2N_4O_2 + H$]⁺.

Step 2: 1'-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-[1,4'-bipiperidine]-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1'-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-[1,4'-bipiperidine]-3-carboxylate (10 mg, 0.02 mmol). The residue was purified by preparative HPLC to afford 1'-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-[1,4'-bipiperidine]-3-carboxylic acid (2.10 mg, 4.20 μ mol, 21.6 %, AUC HPLC 86.60 %) as white solid; ¹H NMR (400 MHz, DMSO) δ (ppm): 8.65 (s, 1H), 7.90-7.82 (m, 2H), 7.78 (d, J = 8.4 Hz, 1H), 7.68 (s, 1H), 7.57 (d, J = 6.8 Hz, 2H), 4.00-3.90 (m, 1H), 3.60 (s, 1H), 2.70-2.55 (m, 1H), 2.45-2.35 (m, 2H), 2.34-2.20 (m, 4H), 2.15-2.00 (m, 1H), 1.80-1.55 (m, 2H), 1.50-1.25 (m, 5H), 1.24-1.10 (m, 1H); MS (ESI) m/z 486.10 [$C_{25}H_{26}Cl_2N_4O_2 + H$]⁺.

Compound 91: Trans-1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-6-methylpiperidine-3-carboxylic acid

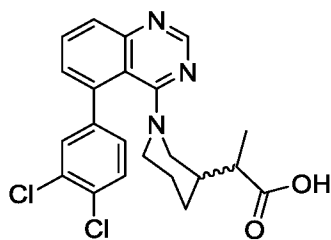


Step 1: methyl trans-1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-6-methylpiperidine-3-carboxylate

The title compound was prepared in a similar fashion as described in general procedure D starting from 5-(3,4-dichlorophenyl)quinazolin-4(3H)-one (250 mg, 0.86 mmol) and methyl trans-6-methylpiperidine-3-carboxylate (269.99 mg, 1.72 mmol). The residue was purified using combiflash (silica gel, 100% DCM to DCM: MeOH 95:5) to afford methyl trans-1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-6-methylpiperidine-3-carboxylate (34 mg, 0.079 mmol, 9.2 %) as yellow sticky gel; MS (ESI) m/z 431.10 [$C_{22}H_{21}Cl_2N_3O_2 + H$]⁺.

Step 2: Trans-1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-6-methylpiperidine-3-carboxylic acid

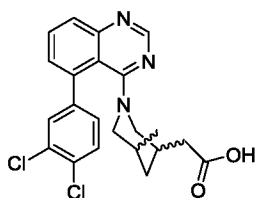
The title compound was prepared in a similar fashion as described in general procedure C starting from methyl trans-1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-6-methylpiperidine-3-carboxylate (34 mg, 0.079 mmol). The residue was purified by preparative HPLC to afford trans-1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-6-methylpiperidine-3-carboxylic acid (9.70 mg, 0.023 mmol, 29.5 %, AUC HPLC 97.24 %) as white solid; ¹H NMR (400 MHz, MeOD- d_4) δ (ppm): 8.51 (s, 1H), 7.83 (2d, J = 8.0, 7.6 Hz, 2H), 7.75 (d, J = 8.4 Hz, 1H), 7.68-7.62 (m, 1H), 7.51 (d, J = 7.2 Hz, 2H), 5.15-5.00 (m, 1H), 3.50-3.45 (m, 1H), 2.70-2.50 (m, 1H), 2.05-1.95 (m, 1H), 1.94-1.70 (m, 3H), 1.40-1.25 (m, 1H), 1.19 (d, J = 7.2 Hz, 2H), 0.90-0.85 & 0.80-0.70 (2m, 1H); MS (ESI) m/z 416.10 [$C_{21}H_{19}Cl_2N_3O_2 + H$]⁺.

Compound 92: 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)propanoic acid**Step 1: methyl 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)propanoate**

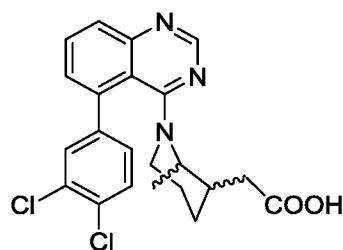
The title compound was prepared in a similar fashion as described in general procedure D starting from 5-(3,4-dichlorophenyl)quinazolin-4(3H)-one (250 mg, 0.86 mmol) and methyl 2-(piperidin-3-yl)propanoate (294.53 mg, 1.72 mmol). The residue was purified by column chromatography (silica gel, 100% DCM to DCM: MeOH 90:10) to afford methyl 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)propanoate (10 mg, 0.023 mmol) as off-white sticky liquid; MS (ESI) m/z 444.10 $[\text{C}_{23}\text{H}_{23}\text{Cl}_2\text{N}_3\text{O}_2 + \text{H}]^+$.

Step 2: 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)propanoic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)propanoate (10 mg, 0.0225 mmol). The residue was purified by preparative HPLC to afford 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)propanoic acid (4.96 mg, 0.012 mmol, AUC HPLC 96.13 %) as white solid; ^1H NMR (400 MHz, $\text{MeOD}-d_4$) δ (ppm): 8.54 (2s, 1H), 7.86-7.70 (m, 2H), 7.66-7.60 (m, 2H), 7.59-7.52 (m, 1H), 7.40 (2d, $J = 7.8$ Hz, 1H), 4.30-4.00 (2m, 1H), 3.80-3.60 & 3.59-3.50 (2m, 2H), 2.90-2.50 (m, 1H), 2.45-2.30 (m, 1H), 2.20-2.10 & 2.00-1.85 (2m, 2H), 1.70-1.66 (m, 1H), 1.65-1.40 (m, 2H), 1.20-1.10 & 0.95-0.85 (m, 1H), 1.01 (d, $J = 6.8$ Hz, 2H); MS (ESI) m/z 430.10 $[\text{C}_{22}\text{H}_{21}\text{Cl}_2\text{N}_3\text{O}_2 + \text{H}]^+$.

Compound 93: 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-5-methylpiperidin-3-yl)acetic acid

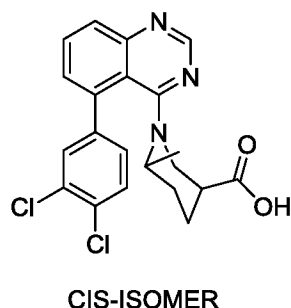
The title compound was prepared in a similar fashion as described in general procedure E using (3,4-dichlorophenyl)boronic acid (469.42 mg, 2.46 mmol). The residue was purified by preparative HPLC to afford 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-5-methylpiperidin-3-yl)acetic acid (4.96 mg, 2.50 μmol , AUC HPLC 96.13 %) as white solid; ^1H NMR (400 MHz, $\text{MeOD}-d_4$) δ (ppm): 8.59 & 8.50 (2s, 1H), 7.90-7.73 (m, 2H), 7.70-7.60 (m, 2H), 7.55 (d, $J = 6.6$ Hz, 1H), 7.50-7.35 (m, 1H), 4.20-4.00 (m, 1H), 3.80-3.60 (m, 1H), 2.30-2.20 (m, 1H), 2.15-2.00 (m, 2H), 1.95-1.85 (m, 1H), 1.80-1.60 (m, 1H), 1.55-1.45 (m, 1H), 1.40-1.10 (m, 1H), 0.76 (d, $J = 5.6$ Hz, 3H), 0.65-0.50 (m, 1H); MS (ESI) m/z 430.00 $[\text{C}_{22}\text{H}_{21}\text{Cl}_2\text{N}_3\text{O}_2 + \text{H}]^+$.

Compound 94: 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-2-methylpiperidin-3-yl)acetic acid**Step 1: 2-(1-(5-bromoquinazolin-4-yl)-2-methylpiperidin-3-yl)acetic acid**

The title compound was prepared in a similar fashion as described in general procedure A starting from 5-bromo-4-chloroquinazoline (400 mg, 1.64 mmol) and 2-(2-methylpiperidin-3-yl)acetic acid (635 mg, 3.28 mmol) to afford 2-(1-(5-bromoquinazolin-4-yl)-2-methylpiperidin-3-yl)acetic acid as off-white solid; MS (ESI) m/z 364.00 [$C_{16}H_{18}BrN_3O_2 + H$] $^+$.

Step 2: 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-2-methylpiperidin-3-yl)acetic acid

The title compound was prepared in a similar fashion as described in general procedure E starting from 2-(1-(5-bromoquinazolin-4-yl)-2-methylpiperidin-3-yl)acetic acid (~ 1.64 mmol) and (3,4-dichlorophenyl)boronic acid (625.89 mg, 3.28 mmol). The residue was purified by preparative HPLC to afford 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-2-methylpiperidin-3-yl)acetic acid (1.74 mg, 4.04 μ mol, AUC HPLC 99.38 %) as white solid; ^1H NMR (400 MHz, MeOD- d_4) δ (ppm): 8.56 & 8.49 (2s, 1H), 7.88-7.70 (m, 3H), 7.63 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 6.6 Hz, 1H), 7.48 (d, J = 6.6 Hz, 1H), 3.85-3.75 & 3.60-3.55 (2m, 1H), 3.05-2.90 & 2.85-2.75 (2m, 1H), 2.50-2.40 & 2.20-2.10 (2m, 1H), 2.10-1.80 (m, 3H), 1.60-1.10 (m, 5H), 0.85 (d, J = 6.4 Hz, 1H), 0.69 (d, J = 6.4 Hz, 1H); MS (ESI) m/z 430.00 [$C_{22}H_{21}Cl_2N_3O_2 + H$] $^+$.

Compound 95: Cis-1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-6-methylpiperidine-3-carboxylic acid**Step 1: methyl cis-1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-6-methylpiperidine-3-carboxylate**

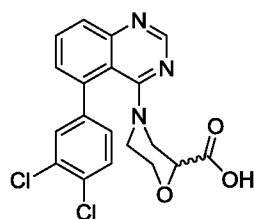
The title compound was prepared in a similar fashion as described in general procedure D starting from 5-(3,4-dichlorophenyl)quinazolin-4(3H)-one (200 mg, 0.69 mmol) and methyl (cis)-6-methylpiperidine-3-carboxylate (433.90 mg, 2.76 mmol). The residue was purified using combiflash (silica gel, 100% DCM to DCM: MeOH 85:15) to afford methyl cis-1-(5-(3,4-

dichlorophenyl)quinazolin-4-yl)-6-methylpiperidine-3-carboxylate (32.8 mg, 0.076 mmol, 11.1 %) as yellow solid; MS (ESI) m/z 429.10 [$C_{23}H_{22}Cl_2N_2O_2 + H$] $^+$.

Step 2: *Cis-1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-6-methylpiperidine-3-carboxylic acid*

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl *cis-1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-6-methylpiperidine-3-carboxylate* (32 mg, 0.075 mmol). The residue was purified by preparative HPLC to afford *cis-1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-6-methylpiperidine-3-carboxylic acid* (13.03 mg, 0.031 mmol, 41.7 %, AUC HPLC 99.82 %) as white solid; ^1H NMR (400 MHz, DMSO) δ (ppm): 8.67 (s, 1H), 7.90-7.78 (m, 2H), 7.74 (d, J = 8.0 Hz, 2H), 7.60-7.40 (m, 2H), 4.10-3.90 & 3.70-3.50 (2m, 1H), 3.79 (d, J = 12.0 Hz, 1H), 2.91 (t, J = 12.0 Hz, 1H), 2.08 & 0.48 (2bs, 1H), 1.70-1.30 (m, 3H), 1.29-1.20 (m, 1H), 0.84 (bs, 1H), 0.73 (s, 2H); MS (ESI) m/z 416.10 [$C_{21}H_{19}Cl_2N_3O_2 + H$] $^+$.

Compound 96: *4-(5-(3,4-dichlorophenyl)quinazolin-4-yl)morpholine-2-carboxylic acid*

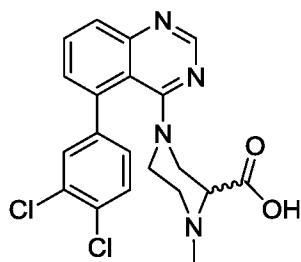


Step 1: synthesis of *4-(5-bromoquinazolin-4-yl)morpholine-2-carboxylic acid*

The title compound was prepared in a similar fashion as described in general procedure A starting from *5-bromo-4-chloroquinazoline* (300 mg, 1.23 mmol) and *morpholine-2-carboxylic acid* (322.51 mg, 2.46 mmol). The residue was then purified using combiflash (silica gel, DCM/MeOH 95:5) to afford *4-(5-bromoquinazolin-4-yl)morpholine-2-carboxylic acid* (20.46 mg) as yellow gel-formed; MS (ESI) m/z 338.00 [$C_{13}H_{12}BrN_3O_3 + H$] $^+$.

Step 2 synthesis of *4-(5-(3,4-dichlorophenyl)quinazolin-4-yl)morpholine-2-carboxylic acid*

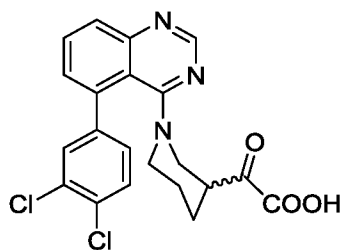
The title compound was prepared in a similar fashion as described in general procedure B starting from *(S)-4-(5-bromoquinazolin-4-yl)morpholine-2-carboxylic acid* (20 mg, 0.059 mmol) and *(3,4-dichlorophenyl)boronic acid* (22.57 mg, 0.12 mmol). The residue was by preparative HPLC to afford *4-(5-(3,4-dichlorophenyl)quinazolin-4-yl)morpholine-2-carboxylic acid* (3.90 mg, 9.65 μ mol, 16.3 %, AUC HPLC 97.44 %) as white solid; ^1H NMR (400 MHz, DMSO) δ (ppm): 8.72 (s, 1H), 7.89 (s, 2H), 7.80-7.70 (m, 2H), 7.65-7.55 (m, 1H), 7.53-7.45 (m, 1H), 3.75-3.55 (m, 2H), 3.45-3.35 (m, 2H), 3.00-2.70 (m, 3H); MS (ESI) m/z 405.00 [$C_{19}H_{15}Cl_2N_3O_3 + H$] $^+$.

Compound 97: 4-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-1-methylpiperazine-2-carboxylic acid**Step 1: 4-(5-bromoquinazolin-4-yl)-1-methylpiperazine-2-carboxylic acid**

The title compound was prepared in a similar fashion as described in general procedure A starting from 5-bromo-4-chloroquinazoline (320 mg, 1.31 mmol) and 1-methylpiperazine-2-carboxylic acid dihydrochloride (307 mg, 1.41 mmol) to afford 4-(5-bromoquinazolin-4-yl)-1-methylpiperazine-2-carboxylic acid as off-white solid; MS (ESI) m/z 351.00 [$C_{14}H_{15}BrN_4O_2 + H$] $^+$. The reaction crude product was used without further purification in the next step.

Step 2: 4-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-1-methylpiperazine-2-carboxylic acid

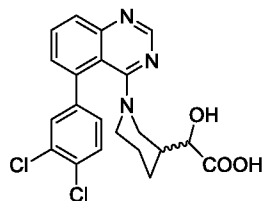
The title compound was prepared in a similar fashion as described in general procedure E starting from 4-(5-bromoquinazolin-4-yl)-1-methylpiperazine-2-carboxylic acid (~ 1.31 mmol) and (3,4-dichlorophenyl)boronic acid (499 mg, 2.62 mmol). The residue was purified by preparative HPLC to afford 4-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-1-methylpiperazine-2-carboxylic acid (14.12 mg, 0.0338 mmol, AUC HPLC 98.94 %) as off-white solid; ^1H NMR (400 MHz, DMSO) δ (ppm): 8.68 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.88 (s, 1H), 7.78-7.68 (m, 2H), 7.61 (dd, J = 6.6, 1.8 Hz, 1H), 7.55-7.48 (m, 1H), 3.65-3.55 (m, 1H), 3.00-2.80 (m, 2H), 2.70-2.60 (m, 2H), 2.35-2.25 (m, 2H), 2.08 (s, 2H), 1.24 (s, 1H); MS (ESI) m/z 417.00 [$C_{20}H_{18}Cl_2N_4O_2 + H$] $^+$.

Compound 98: 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)-2-oxoacetic acid

The title compound was prepared in a similar fashion as described in general procedure D starting from 5-(3,4-dichlorophenyl)quinazolin-4(3H)-one (250 mg, 0.86 mmol) and methyl 2-hydroxy-2-(piperidin-3-yl)acetate hydrobromide (437 mg, 1.72 mmol). The residue was purified by preparative HPLC to afford 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)-2-oxoacetic acid (17.74 mg, 0.041 mmol, AUC HPLC 99.56%) as white solid; ^1H NMR (400 MHz, MeOD- d_4) δ (ppm): 8.60 & 8.53 (2s, 1H), 7.90-7.75 (m, 2H), 7.70-7.55 (m, 3H), 7.55-7.35 (m, 1H), 4.15-4.05 & 4.00-3.90 (m, 1H), 3.80-3.70 & 3.65-3.55 (m, 1H), 2.90-2.80 & 2.60-2.45 (m, 1H), 2.40-2.15 (m, 1H), 2.14-1.95 (m,

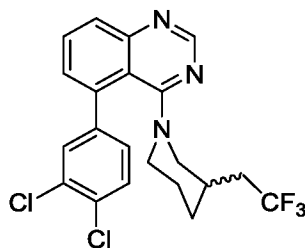
1H), 1.90-1.55 (m, 2H), 1.45-1.25 (m, 1H), 1.20-0.80 (m, 2H); MS (ESI) m/z 430.00 [$C_{21}H_{17}Cl_2N_3O_3 + H$]⁺.

Compound 99: 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)-2-hydroxyacetic acid



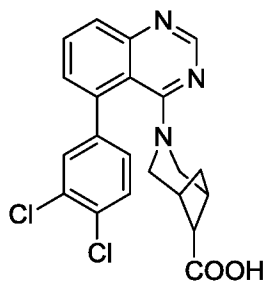
To a solution of 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)-2-oxoacetic acid (20 mg, 0.046 mmol) in a mixture of methanol (3.0 mL) was added sodium borohydride (3.52 mg, 0.093 mmol). The reaction mixture was stirred at room temperature overnight, was then diluted with water (5 mL) and extracted with ethyl acetate (3 x 25 mL). The aqueous layer was acidified to pH 2-3 and extracted with EA (3 x 25 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to afford 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)-2-hydroxyacetic acid (4.89 mg, 0.011 mmol, 24.6 %, AUC HPLC 99.72 %) as yellow solid; ¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.71 & 8.42 (2s, 1H), 7.90-7.70 (m, 1H), 7.60-7.45 (m, 2H), 7.44-7.35 (m, 1H), 7.10-6.90 (m, 1H), 6.89-6.80 (m, 1H), 4.85-4.40 (m, 1H), 3.45-3.25 (m, 1H), 2.80-2.20 (m, 1H), 2.20-2.00 (m, 2H), 1.40-1.20 (m, 2H), 1.19-0.55 (m, 4H); MS (ESI) m/z 432.10 [$C_{21}H_{19}Cl_2N_3O_3 + H$]⁺.

Compound 100: 5-(3,4-dichlorophenyl)-4-(3-(2,2,2-trifluoroethyl)piperidin-1-yl)quinazoline



The title compound was prepared in a similar fashion as described in general procedure D starting from 5-(3,4-dichlorophenyl)quinazolin-4(3H)-one (250 mg, 0.86 mmol) and 3-(2,2,2-trifluoroethyl)piperidine (350.24 mg, 1.72 mmol). The residue was purified using combiflash (silica gel, 100% DCM to DCM: MeOH 90:10) to afford 5-(3,4-dichlorophenyl)-4-(3-(2,2,2-trifluoroethyl)piperidin-1-yl)quinazoline (107.91 mg, 0.245 mmol, 28.5 %, AUC HPLC 97.38%) as yellow solid; ¹H NMR (400 MHz, DMSO) δ (ppm): 8.86 (d, J = 7.2 Hz, 1H), 8.06 (q, J = 7.7 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.92-7.75 (m, 3H), 7.60-7.40 (m, 1H), 3.57 (d, J = 11.2 Hz, 1H), 3.17 (s, 1H), 3.00-2.90 (m, 1H), 2.35-2.05 (m, 3H), 1.90-1.70 (m, 1H), 1.69-1.60 (m, 1H), 1.59-1.40 (m, 1H), 1.39-1.10 (m, 2H); MS (ESI) m/z 440.10 [$C_{21}H_{18}Cl_2F_3N_3 + H$]⁺.

Compound 101: 3-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-3-azabicyclo[3.1.1]heptane-6-carboxylic acid



Step 1: Preparation of methyl 3-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-3-azabicyclo[3.1.1]heptane-6-carboxylate

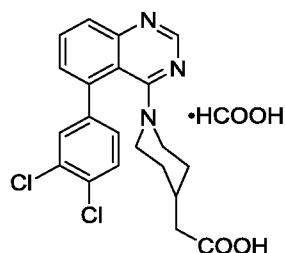
The title compound was prepared in a similar fashion as described in general procedure G starting from 5-bromo-4-chloroquinazoline (100 mg, 0.41 mmol) and methyl 3-azabicyclo[3.1.1]heptane-6-carboxylate (127 mg, 0.82 mmol). The residue was purified by column chromatography (silica gel, eluent $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 100:0 to 90:10) to afford 3-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-3-azabicyclo[3.1.1]heptane-6-carboxylate (75 mg, 51%) as a yellow sticky oil.

Step 2: Preparation of methyl 3-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-3-azabicyclo[3.1.1]heptane-6-carboxylate

The title compound was prepared in a similar fashion as described in general procedure B starting from 3-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-3-azabicyclo[3.1.1]heptane-6-carboxylate (75 mg, 0.21 mmol) and (3,4-dichlorophenyl)boronic acid (61 mg, 0.32 mmol). The residue was purified by column chromatography (silica gel, eluent $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 100:0 to 90:10) to afford methyl 3-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-3-azabicyclo[3.1.1]heptane-6-carboxylate (44 mg, 49%) as yellow solid.

Step 3: Preparation of 3-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-3-azabicyclo[3.1.1]heptane-6-carboxylic acid

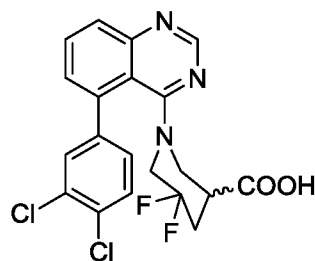
The title compound was prepared in a similar fashion as described in general procedure C starting from methyl methyl 3-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-3-azabicyclo[3.1.1]heptane-6-carboxylate (44 mg, 0.10 mmol). The residue was purified by preparative HPLC (C18, eluents $\text{ACN}/\text{H}_2\text{O}/\text{HCOOH}$ 0.01%) to afford 3-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-3-azabicyclo[3.1.1]heptane-6-carboxylic acid (5 mg, 12 %, AUC HPLC 97.45%) as white solid; ^1H NMR (400 MHz, DMSO) δ (ppm): 8.47 (s, 1H), 7.86-7.43 (m, 6H), 4.10-3.93 (m, 2H), 3.12-3.05 (m, 1H), 2.73-2.64 (m, 1H), 2.37-2.27 (m, 2H), 1.95-1.54 (m, 1H), 1.31-1.21 (m, 1H), 0.89-0.35 (m, 1H); MS (ESI) m/z 414.0 $[\text{C}_{21}\text{H}_{17}\text{Cl}_2\text{N}_3\text{O}_2 + \text{H}]^+$.

Compound 102: 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-4-yl)acetic acid**Step 1: Preparation of methyl 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-4-yl)acetate**

The title compound was prepared in a similar fashion as described in general procedure D starting from 5-(3,4-dichlorophenyl)quinazolin-4(3H)-one (200 mg, 0.69 mmol) and methyl 2-(piperidin-4-yl)acetate (325 mg, 2.07 mmol). The residue was purified by column chromatography (silica gel, eluent $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 100:0 to 90:10) to afford methyl 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-4-yl)acetate (60 mg, 20%) as yellow solid.

Step 2: Preparation of 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-4-yl)acetic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-4-yl)acetate (60 mg, 0.14 mmol). The residue was purified by preparative HPLC (C18, eluents $\text{ACN}/\text{H}_2\text{O}/\text{HCOOH}$ 0.01%) to afford 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-4-yl)acetic acid (5 mg, 8 %, AUC HPLC 95.38%) as white solid; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 12.07 (bs, 1H), 8.69-8.49 (m, 1H), 7.92-7.65 (m, 5H), 7.62-7.33 (m, 2H), 4.18-3.55 (m, 4H), 2.64-2.55 (m, 1H), 2.38-1.96 (m, 1H), 1.90-1.84 (m, 1H), 1.78-1.54 (m, 1H), 1.52-0.81 (m, 3H); MS (ESI) m/z 416.00 [$\text{C}_{21}\text{H}_{19}\text{Cl}_2\text{N}_3\text{O}_2 + \text{H}$] $^+$.

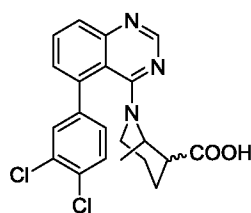
Compound 103: 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-5,5-difluoropiperidine-3-carboxylic acid**Step 1: Preparation of methyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-5,5-difluoropiperidine-3-carboxylate**

The title compound was prepared in a similar fashion as described in general procedure D starting from 5-(3,4-dichlorophenyl)quinazolin-4(3H)-one (225 mg, 0.77 mmol) and methyl 5,5-difluoropiperidine-3-carboxylate hydrochloride (332 mg, 1.54 mmol). The residue was purified by column chromatography (silica gel, eluent $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 100:0 to 90:10) to afford methyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-5,5-difluoropiperidine-3-carboxylate (348 mg, 99.9%) as yellow solid.

Step 2: Preparation of 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-5,5-difluoropiperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-5,5-difluoropiperidine-3-carboxylate (348 mg, 0.77 mmol). The residue was purified by preparative HPLC (C18, eluents ACN/H₂O/HCOOH 0.01%) to afford 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-5,5-difluoropiperidine-3-carboxylic acid (159 mg, 47 %, AUC HPLC 99.07%) as white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 12.77 (s, 1H), 8.83-8.63 (m, 1H), 8.32-6.85 (m, 6H), 4.61-4.07 (m, 1H), 3.25-2.55 (m, 3H), 2.40-0.80 (m, 3H); MS (ESI) *m/z* 437.95 [C₂₀H₁₅Cl₂F₂N₃O₂+ H]⁺.

Compound 104: 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-2-methylpiperidine-3-carboxylic acid



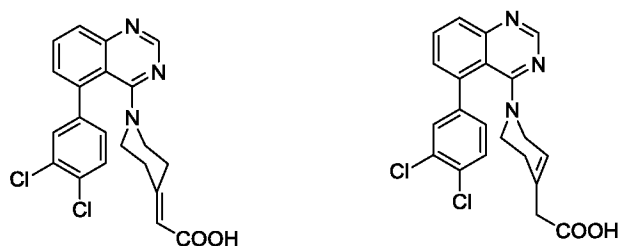
Step 1: Preparation of methyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-2-methylpiperidine-3-carboxylate

The title compound was prepared in a similar fashion as described in general procedure D starting from 5-(3,4-dichlorophenyl)quinazolin-4(3H)-one (205 mg, 0.70 mmol) and methyl 2-methylpiperidine-3-carboxylate (330 mg, 2.10 mmol). The residue was purified by column chromatography (silica gel, eluent CH₂Cl₂/MeOH 100:0 to 90:10) to afford methyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-2-methylpiperidine-3-carboxylate (160 mg, 53%) as yellow solid.

Step 2: Preparation of 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-2-methylpiperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-2-methylpiperidine-3-carboxylate (160 mg, 0.37 mmol). The residue was purified by preparative HPLC (C18, eluents ACN/H₂O/HCOOH 0.01%) to afford 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-2-methylpiperidine-3-carboxylic acid (57 mg, 37 %, AUC HPLC 99.61%) as white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 12.39 (bs, 1H), 8.74-8.54 (m, 1H), 8.02-7.18 (m, 6H), 5.41-4.13 (m, 1H), 3.68-3.10 (m, 1H), 2.99-2.57 (m, 1H), 2.31-1.34 (m, 3H), 1.32-1.12 (m, 1H), 0.98-0.46 (m, 4H); MS (ESI) *m/z* 416.00 [C₂₁H₁₉Cl₂N₃O₂+ H]⁺.

Compound 105: 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-4-ylidene)acetic acid and
Compound 106: 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-1,2,3,6-tetrahydropyridin-4-yl)acetic acid



Step 1: Preparation of ethyl 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-4-ylidene)acetate

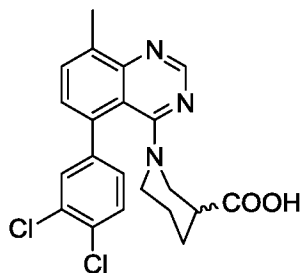
The title compound was prepared in a similar fashion as described in general procedure D starting from 5-(3,4-dichlorophenyl)quinazolin-4(3H)-one (152 mg, 0.52 mmol) and ethyl 2-(piperidin-4-ylidene)acetate (177 mg, 1.04 mmol). The residue was purified by column chromatography (silica gel, eluent $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 100:0 to 90:10) to afford ethyl 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-4-ylidene)acetate (22 mg, 9%) as yellow solid.

Step 2: Preparation of 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-4-ylidene)acetic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from ethyl 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-4-ylidene)acetate (22 mg, 0.09 mmol). The residue was purified by preparative HPLC (C18, eluents $\text{ACN}/\text{H}_2\text{O}/\text{HCOOH}$ 0.01%) to afford 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-4-ylidene)acetic acid (3.3 mg, AUC HPLC 95.38%) as yellow solid; ^1H NMR (400 MHz, $\text{MeOD}-d_4$) δ (ppm): 8.84-8.45 (m, 1H), 7.98-7.76 (m, 2H), 7.75-7.56 (m, 3H), 7.54-7.44 (m, 1H), 5.64 (s, 1H), 3.63-3.38 (m, 2H), 3.26-3.02 (m, 2H), 2.77-2.39 (m, 1H), 2.23-1.77 (m, 1H), 1.37-1.24 (m, 2H); MS (ESI) m/z 414.15 $[\text{C}_{21}\text{H}_{17}\text{Cl}_2\text{N}_3\text{O}_2 + \text{H}]^+$.

Compound 106 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-1,2,3,6-tetrahydropyridin-4-yl)acetic acid (2.5 mg, AUC HPLC 96.86%): ^1H NMR (400 MHz, $\text{MeOD}-d_4$) δ (ppm): 8.81-8.41 (m, 1H), 7.96-7.74 (m, 2H), 7.73-7.56 (m, 3H), 7.49-7.34 (m, 1H), 5.24 (s, 1H), 4.00-3.80 (m, 1H), 3.78-3.61 (m, 1H), 3.51-3.35 (m, 1H), 2.92-2.75 (m, 2H), 2.47-2.12 (m, 1H), 1.87-1.56 (m, 1H), 1.38-1.25 (m, 1H); MS (ESI) m/z 414.05 $[\text{C}_{21}\text{H}_{17}\text{Cl}_2\text{N}_3\text{O}_2 + \text{H}]^+$.

Compound 107: 1-(5-(3,4-dichlorophenyl)-8-methylquinazolin-4-yl)piperidine-3-carboxylic acid



Step 1: Preparation of 5-(3,4-dichlorophenyl)-8-methylquinazolin-4(3H)-one:

The title compound was prepared in a similar fashion as described in general procedure B starting from 5-bromo-8-methylquinazolin-4(3H)-one (800 mg, 3.34 mmol) and 3,4-dichlorophenylboronic acid (767 mg, 4.01 mmol). The residue was purified by column chromatography (silica gel, dichloromethane/methanol 98:2) to afford 5-(3,4-dichlorophenyl)-8-methylquinazolin-4(3H)-one (800 mg, LC-MS 60%) as a colorless oil. MS (ESI) m/z : 305.17 [$C_{15}H_{10}Cl_2N_2O+H$] $^+$.

Step 2: Preparation of 4-chloro-5-(3,4-dichlorophenyl)-8-methylquinazoline :

A solution of 5-(3,4-dichlorophenyl)-8-methylquinazolin-4(3H)-one (800 mg, 2.63 mmol) and DMF (0.1 mL) in thionyl chloride (8 mL) was heated at 80 °C for 5 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (neutral alumina, eluent pet ether/EtOAc 8:2) to afford 4-chloro-5-(3,4-dichlorophenyl)-8-methylquinazoline (320 mg, LC-MS 59%) as an off-white solid. MS (ESI) m/z : 323.12 [$C_{15}H_9Cl_3N_2+H$] $^+$.

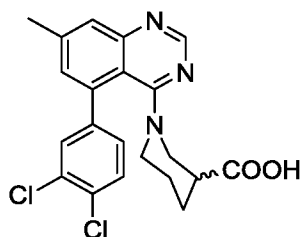
Step 3: Preparation of methyl 1-(5-(3,4-dichlorophenyl)-8-methylquinolin-4-yl)piperidine-3-carboxylate

The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)-8-methylquinazoline (300 mg, 0.928 mmol) and methyl piperidine-3-carboxylate (200 mg, 1.39 mmol). The residue was purified by column chromatography (silica gel, eluent, hexane/ethyl acetate 8/2) to afford methyl 1-(5-(3,4-dichlorophenyl)-8-methylquinolin-4-yl)piperidine-3-carboxylate (300 mg, LC-MS 70%) as a colorless oil. MS (ESI) m/z : 430.44 [$C_{23}H_{22}Cl_2N_2O_2+H$] $^+$.

Step 4: Preparation of 1-(5-(3,4-dichlorophenyl)-8-methylquinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(3,4-dichlorophenyl)-8-methylquinolin-4-yl)piperidine-3-carboxylate (300 mg, 0.699 mmol). The residue was purified by preparative HPLC to afford 1-(5-(3,4-dichlorophenyl)-8-methylquinazolin-4-yl)piperidine-3-carboxylic acid (35 mg, 12%, AUC-HPLC 95%) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 12.10–12.0 (bs, 1H), 8.70 (s, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.77–7.72 (m, 2H), 7.46–7.40 (m, 2H), 4.26 (d, J = 11.6 Hz, 1H), 4.02 (d, J = 13.2 Hz, 1H), 3.46–3.35 (m, 2H), 2.72–2.69 (m, 1H), 2.53 (s, 3H), 2.10–2.00 (m, 1H), 1.82–1.66 (m, 3H); MS (ESI) m/z : 416.17 [$C_{21}H_{19}Cl_2N_3O_2+H$] $^+$.

Compound 108: 1-(5-(3,4-dichlorophenyl)-7-methylquinazolin-4-yl)piperidine-3-carboxylic acid



Step 1: Preparation of 5-(3,4-dichlorophenyl)-7-methylquinazolin-4(3H)-one

The title compound was prepared in a similar fashion as described in general procedure E starting from 5-bromo-7-methylquinazolin-4(3H)-one (400 mg, 1.68 mmol) and 3,4-dichlorophenylboronic acid (630 mg, 3.36 mmol). The crude product was purified by chromatography (silica gel, DCM/MeOH 96/4) 100-200 mesh) to afford 5-(3,4-dichlorophenyl)-7-methylquinazolin-4(3H)-one (400 mg, 78%, LC-MS 51%) as an off-white solid. MS (ESI) m/z : 305.17 [$C_{15}H_{10}Cl_2N_2O+H$]⁺.

Step 2: Preparation of 4-chloro-5-(3,4-dichlorophenyl)-7-methylquinazoline

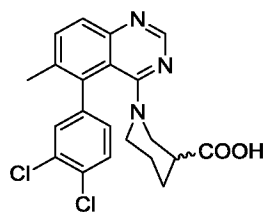
A mixture of 5-(3,4-dichlorophenyl)-7-methylquinazolin-4(3H)-one (400 mg, 1.315 mmol), $SOCl_2$ (5 mL) and catalytic amount of DMF (0.03 mL) was heated at 80 °C for 10 h. The reaction mixture was concentrated and diluted in dichloromethane, washed with aq. $NaHCO_3$ solution, dried with Na_2SO_4 , filtered and concentrated. The crude compound was purified by column chromatography (silica gel, eluent pet ether/EtOAc 8:2) to afford 4-chloro-5-(3,4-dichlorophenyl)-7-methylquinazoline (300 mg, 71%, LC-MS 96%) as a colour less liquid. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.99 (s, 1H), 7.91 (s, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.38 (d, J = 1.6 Hz, 1H), 7.17 (dd, J = 4.0 Hz, J = 8.0 Hz, 1H), 2.61 (s, 3H); MS (ESI) m/z : 323.22 [$C_{15}H_9Cl_3N_2+H$]⁺.

Step 3: Preparation of methyl 1-(5-(3,4-dichlorophenyl)-7-methylquinazolin-4-yl)piperidine-3-carboxylate

The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)-7-methylquinazoline (300 mg, 0.93 mmol) and methyl piperidine-3-carboxylate (199 mg, 1.39 mmol). The crude compound was purified by column chromatography (silica gel, eluent pet ether/EtOAc 8/2) to afford methyl 1-(5-(3,4-dichlorophenyl)-7-methylquinazolin-4-yl)piperidine-3-carboxylate (220 mg, 56%, LC-MS 93%) as an off-white solid. MS (ESI) m/z : 430.28 [$C_{22}H_{21}Cl_2N_3O_2+H$]⁺.

Step 4: Preparation of (1-(5-(3,4-dichlorophenyl)-7-methylquinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(3,4-dichlorophenyl)-7-methylquinazolin-4-yl)piperidine-3-carboxylate (200 mg, 0.466 mmol). The crude compound was triturated with diethyl ether and n-pentane, filtered and dried to afford (1-(5-(3,4-dichlorophenyl)-7-methylquinazolin-4-yl)piperidine-3-carboxylic acid (150 mg, 80%, AUC-HPLC 95%) as an off-white solid, mp: 181-195 °C; ^1H NMR (400 MHz, $DMSO-d_6$) δ (ppm): 12.21 (bs, 1H), 8.62–8.56 (m, 1H), 7.72–7.60 (m, 3H), 7.43 (bs, 2H), 4.20–3.54 (m, 2H), 2.71–2.62 (m, 1H), 2.38–2.22 (m, 1H), 2.51 (s, 3H), 1.74 (bs, 1H), 1.50–1.34 (m, 2H), 1.23–1.09 (m, 1H), 0.58 (bs, 1H); MS (ESI) m/z : 416.21 [$C_{21}H_{19}Cl_2N_3O_2+H$]⁺.

Compound 109: 1-(5-(3,4-dichlorophenyl)-6-methylquinazolin-4-yl)piperidine-3-carboxylic acid**Step 1: Preparation of 5-(3,4-dichlorophenyl)-6-methylquinazolin-4(3H)-one**

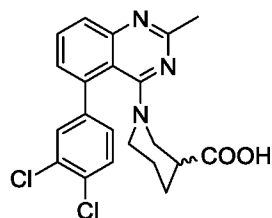
The title compound was prepared in a similar fashion as described in general procedure E starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (815 mg, 3.4 mmol) and (3-fluorophenyl)boronic acid (976 mg, 5.1 mmol). The reaction mixture was heated at 120 °C for 2 hours in a microwave apparatus. The cooled reaction media was poured into 250 mL of water to give a precipitate, which was isolated by filtration, washed with water and dried in vacuum oven at 50°C overnight to afford 5-(3,4-dichlorophenyl)-6-methylquinazolin-4(3H)-one (909 mg, 88%) as brown solid.

Step 2: Preparation of methyl 1-(5-(3,4-dichlorophenyl)-6-methylquinazolin-4-yl)piperidine-3-carboxylate

The title compound was prepared in a similar fashion as described in general procedure D starting from 5-(3,4-dichlorophenyl)-6-methylquinazolin-4(3H)-one (244 mg, 0.80 mmol) and methyl piperidine-3-carboxylate (343 mg, 2.40 mmol). The residue was purified by column chromatography (silica gel, eluent CH₂Cl₂/MeOH 100:0 to 90:10) to afford methyl 1-(5-(3,4-dichlorophenyl)-6-methylquinazolin-4-yl)piperidine-3-carboxylate (98 mg, 29%) as yellow solid.

Step 3: Preparation of 1-(5-(3,4-dichlorophenyl)-6-methylquinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(3,4-dichlorophenyl)-6-methylquinazolin-4-yl)piperidine-3-carboxylate (98 mg, 0.23 mmol). The residue was purified by preparative HPLC (C18, eluents ACN/H₂O/HCOOH 0.01%) to afford 1-(5-(3,4-dichlorophenyl)-6-methylquinazolin-4-yl)piperidine-3-carboxylic acid (28 mg, 29 %, AUC HPLC 98.73%) as yellow solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 12.32 (bs, 1H), 8.70-8.44 (m, 1H), 7.92-6.97 (m, 5H), 4.21-3.46 (m, 2H), 2.73-2.54 (m, 1H), 2.46-2.17 (m, 4H), 2.14-0.39 (m, 5H); MS (ESI) *m/z* 416.1 [C₂₁H₁₉Cl₂N₃O₂+ H]⁺.

Compound 110: 1-(5-(3,4-dichlorophenyl)-2-methylquinazolin-4-yl)piperidine-3-carboxylic acid

Step 1: 5-(3,4-dichlorophenyl)-2-methylquinazolin-4(3H)-one:

The title compound was prepared in a similar fashion as described in general procedure E starting from 5-bromo-2-methylquinazolin-4(3H)-one (450 mg, 1.88 mmol) and 3,4-dichlorophenylboronic acid (431 mg, 2.25 mmol). An aqueous work-up gave the crude 5-(3,4-dichlorophenyl)-2-methylquinazolin-4(3H)-one (380 mg, LC-MS 66%) as a pale brown solid. MS (ESI) m/z : 305.20 $[\text{C}_{15}\text{H}_{10}\text{Cl}_2\text{N}_2\text{O}+\text{H}]^+$.

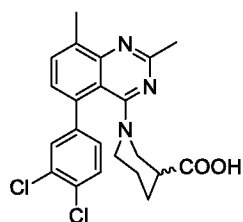
Step 2: methyl 1-(5-(3,4-dichlorophenyl)-2-methylquinazolin-4-yl)piperidine-3-carboxylate:

A solution of 5-(3,4-dichlorophenyl)-2-methylquinazolin-4(3H)-one (300 mg, 0.983 mmol), PyBop (767 mg, 1.47 mmol) and DBU (300 mg, 1.96 mmol) in acetonitrile was stirred at room temperature for 1 h, prior to the addition of methyl piperidine-3-carboxylate (210 mg, 1.47 mmol). The reaction mixture was stirred at room temperature for 15 h. The reaction mixture was diluted with water and extracted into EtOAc. The organic layer was washed with water, brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate 8:2) to afford methyl 1-(5-(3,4-dichlorophenyl)-2-methylquinazolin-4-yl)piperidine-3-carboxylate (250 mg, 59%, LC-MS 85%) as a colour less sticky mass. MS (ESI) m/z : 430.41 $[\text{C}_{22}\text{H}_{21}\text{Cl}_2\text{N}_3\text{O}_2+\text{H}]^+$.

Step 3: Preparation of 1-(5-(3,4-dichlorophenyl)-2-methylquinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(3,4-dichlorophenyl)-2-methylquinazolin-4-yl)piperidine-3-carboxylate (250 mg, 0.582 mmol). The residue was acidified with 50% KHSO_4 solution, and the precipitate was isolated by filtration and dried to afford 1-(5-(3,4-dichlorophenyl)-2-methylquinazolin-4-yl)piperidine-3-carboxylic acid (210 mg, 86%, AUC-HPLC 97%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 7.83–7.66 (m, 4H), 7.50–7.47 (m, 2H), 3.85–3.90 (m, 1H), 3.58–3.56 (m, 2H), 2.57–2.70 (4H), 1.50–1.46 (m, 1H), 1.47–1.11 (4H), 0.50–0.47 (m, 1H); MS (ESI) m/z : 416.17 $[\text{C}_{21}\text{H}_{19}\text{Cl}_2\text{N}_3\text{O}_2+\text{H}]^+$.

Compound 111: 1-(5-(3,4-dichlorophenyl)-2,8-dimethylquinazolin-4-yl)piperidine-3-carboxylic acid



Step 1: 5-(3,4-dichlorophenyl)-2,8-dimethylquinazolin-4(3H)-one

The title compound was prepared in a similar fashion as described in general procedure E starting from 5-bromo-2,8-dimethylquinazolin-4(3H)-one (550 mg, 2.16 mmol) and 3,4-dichlorophenylboronic acid (620 mg, 3.24 mmol). The reaction mixture was concentrated under reduced pressure, residue was diluted with water. The precipitate was isolated by filtration and dried to afford 5-(3,4-dichlorophenyl)-2,8-dimethylquinazolin-4(3H)-one (320 mg, LC-MS 80%) as an off-

white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 12.2 (bs, 1H), 7.97 (d, $J = 8.4$ Hz, 1H), 7.75 (d, $J = 8.4$ Hz, 1H), 7.67 (s, 1H), 7.40 (d, $J = 7.6$ Hz, 1H), 7.29 (d, $J = 8.0$ Hz, 1H), 2.41 (s, 3H), 2.38 (s, 3H); MS (ESI) m/z : 319.16 [$\text{C}_{16}\text{H}_{12}\text{Cl}_2\text{N}_2\text{O} + \text{H}$] $^+$.

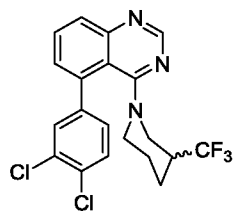
Step 2: methyl 1-(5-(3,4-dichlorophenyl)-2,8-dimethylquinazolin-4-yl)piperidine-3-carboxylate

The title compound was prepared in a similar fashion as described in general procedure D starting from 5-(3,4-dichlorophenyl)-2,8-dimethylquinazolin-4(3H)-one (400 mg, 1.25 mmol) and methyl piperidine-3-carboxylate (268 mg, 1.88 mmol). The residue was purified by column chromatography (silica gel, hexane/ethyl acetate 8:2) to afford methyl 1-(5-(3,4-dichlorophenyl)-2,8-dimethylquinazolin-4-yl)piperidine-3-carboxylate (400 mg, 72%, LC-MS 96%) as a colour less solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 7.74 (d, $J = 8.8$ Hz, 1H), 7.54 (d, $J = 4.4$ Hz, 1H), 7.47 (d, $J = 2.0$ Hz, 1H), 7.22–7.19 (m, 2H), 4.35 (d, $J = 11.6$ Hz, 1H), 4.11 (d, $J = 13.2$ Hz, 1H), 3.71 (s, 3H), 3.38–3.32 (m, 1H), 3.24–3.18 (m, 1H), 2.87–2.82 (m, 1H), 2.70 (s, 3H), 2.60 (s, 3H), 2.19–2.16 (m, 1H), 1.92–1.76 (m, 3H); MS (ESI) m/z : 444.47 [$\text{C}_{23}\text{H}_{23}\text{Cl}_2\text{N}_3\text{O}_2 + \text{H}$] $^+$.

Step 3: Preparation of 1-(5-(3,4-dichlorophenyl)-2,8-dimethylquinazolin-4-yl)piperidine-3-carboxylic acid

A mixture of methyl 1-(5-(3,4-dichlorophenyl)-2,8-dimethylquinazolin-4-yl)piperidine-3-carboxylate (400 mg, 0.902 mmol) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (76 mg, 1.80 mmol) in a mixture of THF (5 mL) and H_2O (5 mL) was stirred at rt for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was acidified with 50% KHSO_4 solution, and extracted with diethyl ether. The organic layer was dried over Na_2SO_4 , filtered and concentrated to afford 1-(5-(3,4-dichlorophenyl)-2,8-dimethylquinazolin-4-yl)piperidine-3-carboxylic acid (330 mg, 85%, AUC-HPLC 97%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 12.20 (bs, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 7.74 (d, $J = 7.6$ Hz, 1H), 7.69 (d, $J = 2.0$ Hz, 1H), 7.41 (dd, $J = 8.4$ Hz, 2.0 Hz, 1H), 7.31 (d, $J = 8.4$ Hz, 1H), 4.21 (d, $J = 10.4$ Hz, 1H), 3.99 (d, $J = 11.2$ Hz, 1H), 3.29–3.19 (m, 2H), 2.67–2.64 (m, 1H), 2.2.55 (s, 3H), 2.39 (s, 3H), 2.02–2.00 (m, 1H), 1.80–1.66 (m, 3H); MS (ESI) m/z : 430.20 [$\text{C}_{22}\text{H}_{21}\text{Cl}_2\text{N}_3\text{O}_2 + \text{H}$] $^+$.

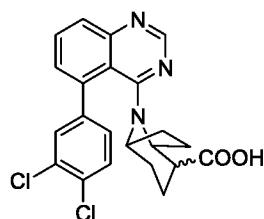
Compound 112: 5-(3,4-dichlorophenyl)-4-(3-(trifluoromethyl)piperidin-1-yl)quinazoline



The title compound was prepared in a similar fashion as described in general procedure D starting from 5-(3,4-dichlorophenyl)quinazolin-4(3H)-one (221 mg, 0.76 mmol) and 3-(trifluoromethyl)piperidine hydrochloride (288 mg, 1.52 mmol). The residue was purified by column chromatography (silica gel, eluent $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 100:0 to 90:10) and preparative HPLC (C18, eluent $\text{CH}_3\text{CN}/\text{H}_2\text{O}/\text{HCOOH}$ 0.01%) to afford 5-(3,4-dichlorophenyl)-4-(3-(trifluoromethyl)piperidin-1-yl)quinazoline (78 mg, 24 %, AUC HPLC 99.07%) as white solid; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ

(ppm): 8.79-8.58 (m, 1H), 7.96-7.46 (m, 6H), 4.49-3.73 (m, 1H), 3.70-3.45 (m, 1H), 2.70-2.01 (m, 2H), 1.83-1.64 (m, 1H), 1.62-0.32 (m, 4H); MS (ESI) m/z 426.0 $[\text{C}_{20}\text{H}_{16}\text{Cl}_2\text{F}_3\text{N}_3 + \text{H}]^+$.

Compound 113: 8-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-8-azabicyclo[3.2.1]octane-2-carboxylic acid



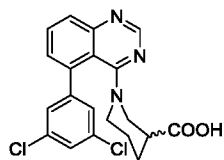
Step 1: Preparation of 8-(5-bromoquinazolin-4-yl)-8-azabicyclo[3.2.1]octane-2-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure A starting from 5-bromo-4-chloroquinazoline (243 mg, 1 mmol) and 8-azabicyclo[3.2.1]octane-2-carboxylic acid (310 mg, 2 mmol). After an aqueous work-up, the combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 8-(5-bromoquinazolin-4-yl)-8-azabicyclo[3.2.1]octane-2-carboxylic acid (120 mg, 33 %) as a brown solid. The crude product was used without further purification in the next step.

Step 2: Preparation of 8-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-8-azabicyclo[3.2.1]octane-2-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure B starting from 8-(5-bromoquinazolin-4-yl)-8-azabicyclo[3.2.1]octane-2-carboxylic acid (120 mg, 0.33 mmol) and (3,4-dichlorophenyl)boronic acid (93 mg, 0.49 mmol). The residue was purified by preparative HPLC (C18, eluent $\text{CH}_3\text{CN}/\text{H}_2\text{O}/\text{HCOOH}$ 0.01%) to afford 8-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-8-azabicyclo[3.2.1]octane-2-carboxylic acid (5 mg, 4%, AUC HPLC 97.87%) as white solid; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 8.69-8.36 (m, 1H), 8.23-7.41 (m, 6H), 5.74-3.47 (m, 2H), 2.37-2.07 (m, 1H), 1.81-0.17 (m, 8H); MS (ESI) m/z 428.1 $[\text{C}_{22}\text{H}_{19}\text{Cl}_2\text{N}_3\text{O}_2 + \text{H}]^+$.

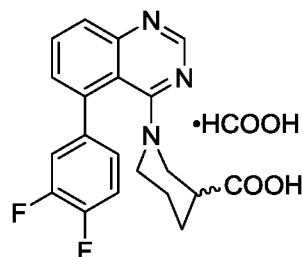
Compound 114: 1-(5-(3,5-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (3,5-dichlorophenyl)boronic acid (85 mg, 0.45 mmol). The residue was purified by preparative HPLC (C18, eluent $\text{CH}_3\text{CN}/\text{H}_2\text{O}/\text{HCOOH}$ 0.01%) to afford 1-(5-(3,5-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (22 mg, 18%, AUC HPLC 99.00%) as white solid; ^1H NMR (300 MHz, $\text{MeOD}-d_4$) δ (ppm): 8.66-8.52 (m, 1H), 7.93-7.77 (m, 2H), 7.60 (d, $J = 6.8$ Hz, 1H), 7.55 (s,

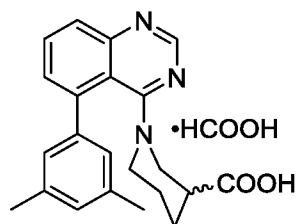
1H), 7.52-7.34 (m, 2H), 4.47-3.83 (m, 1H), 3.82-3.59 (m, 1H), 3.10-2.76 (m, 1H), 2.66-2.18 (m, 1H), 2.03-1.58 (m, 2H), 1.55-0.91 (m, 3H); MS (ESI) m/z 403.45 [$C_{20}H_{17}Cl_2N_3O_2 + H$] $^+$.

Compound 115: 1-(5-(3,4-difluorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid

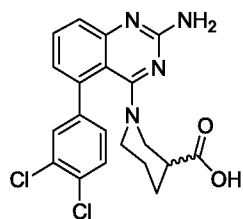


The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (3,4-difluorophenyl)boronic acid (71 mg, 0.45 mmol). The residue was purified by preparative HPLC (C18, eluent $CH_3CN/H_2O/HCOOH$ 0.01%) to afford 1-(5-(3,4-difluorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (12 mg, 11%, AUC HPLC 98.61%) as white solid; ^1H NMR (300 MHz, $MeOD-d_4$) δ (ppm): 8.58 (s, 1H), 8.17 (bs, 1H), 7.91 (t, $J = 7.8$ Hz, 1H), 7.78 (d, $J = 8.0$ Hz, 1H), 7.62 (d, $J = 7.2$ Hz, 1H), 7.58-7.15 (m, 3H), 4.40-3.76 (m, 1H), 3.64-3.36 (m, 1H), 3.22-2.79 (m, 1H), 2.55-2.35 (m, 1H), 1.99-1.46 (m, 3H), 1.44-0.98 (m, 2H); MS (ESI) m/z 370.45 [$C_{20}H_{17}F_2N_3O_2 + H$] $^+$.

Compound 116: 1-(5-(3,5-dimethylphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



The title compound was prepared in a similar fashion as described in general procedure B starting from 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.30 mmol) and (3,5-dimethylphenyl)boronic acid (67 mg, 0.45 mmol). The residue was purified by preparative HPLC (C18, eluent $CH_3CN/H_2O/HCOOH$ 0.01%) to afford 1-(5-(3,5-dimethylphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (33 mg, 30%, AUC HPLC 97.72%) as white solid; ^1H NMR (300 MHz, $MeOD-d_4$) δ (ppm): 8.54 (s, 1H), 8.23 (bs, 1H), 7.88 (t, $J = 7.7$ Hz, 1H), 7.72 (d, $J = 8.2$ Hz, 1H), 7.60 (d, $J = 6.5$ Hz, 1H), 7.44-6.72 (m, 3H), 4.54-3.53 (m, 2H), 3.18-2.80 (m, 1H), 2.64-2.15 (m, 7H), 2.01-1.57 (m, 2H), 1.53-0.97 (m, 3H); MS (ESI) m/z 362.55 [$C_{22}H_{23}N_3O_2 + H$] $^+$.

Compound 117: 1-(2-amino-5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid**Step 1: *N*-(5-bromo-4-oxo-3,4-dihydroquinazolin-2-yl)acetamide:**

A solution of 2-amino-5-bromoquinazolin-4(3*H*)-one (1.0 g, 4.184 mmol) in acetic anhydride (10 mL) was heated at 120 °C for 16 hours. The reaction mixture was filtered and the cake was dried to afford *N*-(5-bromo-4-oxo-3,4-dihydroquinazolin-2-yl)acetamide (0.910 g, 77%, LC-MS 94%) as a yellow solid. MS (ESI) *m/z*: 282.09 [$C_{10}H_8BrN_3O + H$]⁺.

Step 2: *N*-(5-(3,4-dichlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)acetamide:

The title compound was prepared in a similar fashion as described in general procedure E starting from *N*-(5-bromo-4-oxo-3,4-dihydroquinazolin-2-yl)acetamide (0.9 g, 3.209 mmol) and 3,4-dichlorophenylboronic acid (1.1 g, 5.77 mmol). The crude compound was purified by column chromatography (silica gel, eluent pet-ether/EtOAc 60:40) to afford *N*-(5-(3,4-dichlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)acetamide (700 mg, LC-MS 81%) as a solid. MS (ESI) *m/z*: 248.18 [$C_{16}H_{11}Cl_2N_3O_2 + H$]⁺.

Step 3: 2-amino-5-(3,4-dichlorophenyl)quinazolin-4(3*H*)-one:

A solution of *N*-(5-(3,4-dichlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)acetamide (600 mg, 1.729 mmol), aqueous. 4*N* NaOH (3 mL) in 1,4-dioxane (6 mL) was stirred at 100 °C for 16 hours. The reaction mixture was diluted with water and extracted into ethyl acetate (2 x 20 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated to afford 2-amino-5-(3,4-dichlorophenyl)quinazolin-4(3*H*)-one (510 mg, LC-MS 70%) as a liquid. MS (ESI) *m/z*: 306.15 [$C_{14}H_9Cl_2N_3O + H$]⁺.

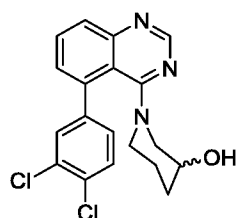
Step 4: methyl 1-(2-amino-5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxylate:

To a solution of 2-amino-5-(3,4-dichlorophenyl)quinazolin-4(3*H*)-one (500 mg, 1.639 mmol) in ACN (8 mL) were added PyBOP (1.278 g, 2.459 mmol), DBU (498 mg, 3.278 mmol) and the resulting mixture was stirred at rt for 30 minutes, prior to the addition of methyl piperidine-3-carboxylate (468 mg, 3.278 mmol). The reaction mixture was stirred at rt for 16 h, was diluted with water and was extracted with ethyl acetate (2 x 50 mL). The extracts were dried over Na₂SO₄, filtered and concentrated to afford methyl 1-(2-amino-5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxylate (600 mg, LC-MS 63%) as a brown liquid. MS (ESI) *m/z*: 431.32 [$C_{21}H_{20}Cl_2N_4O_2 + H$]⁺.

Step 5: 1-(2-amino-5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid:

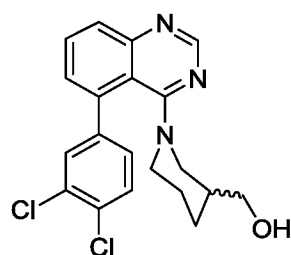
A solution of methyl 1-(2-amino-5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxylate (300 mg, 0.697 mmol), LiOH.H₂O (73 mg, 1.744 mmol) in a mixture of THF (3 mL) and H₂O (3 mL) was stirred at rt for 4 hours. The reaction mixture was concentrated to half the volume and acidified with aq. KHSO₄. The precipitate was isolated by filtration dried to afford 1-(2-amino-5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (50 mg, 17%, AUC-HPLC 95.53%) as a white solid. mp: 304-308 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 7.76-7.5 (m, 3H), 7.5-7.25 (m, 2H), 7.16-6.95 (m, 1H), 6.64-6.12 (m, 2H), 3.60-3.41 (m, 2H), 2.48-2.34 (m, 2H), 1.73 (bs, 1H), 1.41-1.14 (m, 4H); MS (ESI) *m/z*: 417.29 [C₂₀H₁₈Cl₂N₄O₂+H]⁺.

Compound 118: 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-ol



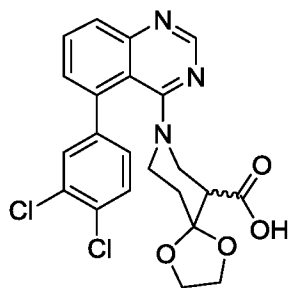
A solution of 4-chloro-5-(3,4-dichlorophenyl)quinazoline (150 mg, 0.488 mmol), piperidin-3-ol (74 mg, 0.732 mmol) and TEA (0.2 mL, 1.46 mmol) in IPA (10 mL) was heated to 80 °C for 10 hours. The reaction mixture was concentrated and was purified by preparative HPLC to afford 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-ol (15 mg, AUC-HPLC 97.55%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.62-8.53 (m, 1H), 7.82 (bs, 2H), 7.72-7.68 (m, 2H), 7.56-7.41 (m, 2H), 4.78-4.58 (m, 1H), 3.91-3.74 (m, 1H), 3.25 (bs, 1H), 2.96-2.77 (m, 1H), 2.18-2.01 (m, 1H), 1.72-1.49 (m, 2H), 1.11 (bs, 2H); MS (ESI) *m/z*: 374.15 [C₁₉H₁₇Cl₂N₃O+H]⁺.

Compound 119: (1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)methanol



To a solution of 4-chloro-5-(3,4-dichlorophenyl)quinazoline (200 mg, 0.651 mmol), piperidin-3-ylmethanol (119 mg, 1.042 mmol) and TEA (0.281 mL, 1.95 mmol) in propane-2-ol (3 mL) was stirred at 80 °C for 10 hours. The reaction mixture was concentrated and diluted with water, acidified with an aqueous solution of KHSO₄, extracted with a mixture of dichloromethane and methanol (90:10) (2 x 20 mL). The combined organic phase was dried over Na₂SO₄, and concentrated. The crude compound was purified by preparative HPLC to afford (1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)methanol (30 mg, 12%, HPLC 95.01%) as an off-white solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.70-8.50 (m, 1H), 7.95-7.60 (m, 4H), 7.60-7.30 (m, 2H), 4.55-4.40 (m, 1H), 4.15-4.0 (m, 1H), 3.90-3.70 (m, 1H), 3.7-3.50 (m, 1H), 3.20-3.00 (m, 2H), 2.40-2.00 (m, 2H), 1.65-1.30 (m, 2H), 1.10-0.65 (m, 2H); MS (ESI) *m/z*: 388.29 [C₂₀H₁₉Cl₂N₃O₂+H]⁺.

Compound 120: 8-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-1,4-dioxo-8-azaspiro[4.5]decane-6-carboxylic acid



Step 1: *ethyl 8-benzyl-1,4-dioxo-8-azaspiro[4.5]decane-6-carboxylate*

A mixture of ethyl 1-benzyl-4-oxopiperidine-3-carboxylate (5 g, 19.15 mmol), ethane-1,2-diol (12 mL) and PTSA (167 mg, 0.99 mmol) in toluene (80 mL) was heated at 110 °C for 16 hours. The reaction mixture was diluted with water and basified with an aqueous solution of NaHCO₃, then extracted with ethyl acetate. The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford ethyl 8-benzyl-1,4-dioxo-8-azaspiro[4.5]decane-6-carboxylate (3 g, 51.72%, LC-MS 21%) as a gummy solid. MS (ESI) *m/z*: 306.42 [C₁₇H₂₃NO₄+H]⁺.

Step 2: *ethyl 1,4-dioxo-8-azaspiro[4.5]decane-6-carboxylate*

To a solution of ethyl 8-benzyl-1,4-dioxo-8-azaspiro[4.5]decane-6-carboxylate (3 g, 9.83 mmol) in methanol (60 mL) was added Pd/C (600 mg) and stirred at rt under hydrogen atmosphere at a pressure of 60 Psi for 16 hours. The reaction mixture was filtered through a short pad of celite which was subsequently washed with methanol. The filtrate was concentrated to afford ethyl 1,4-dioxo-8-azaspiro[4.5]decane-6-carboxylate (2.0 g, 95.23%) as a yellow liquid. MS (ESI) *m/z*: 216.24 [C₁₀H₁₇NO₄+H]⁺

Step 3: *ethyl 8-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-1,4-dioxo-8-azaspiro[4.5]decane-6-carboxylate:*

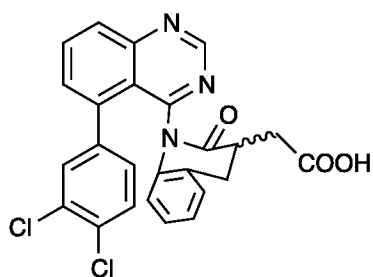
To a solution of 4-chloro-5-(3,4-dichlorophenyl)quinazoline (350 mg, 1.14 mmol) in IPA (30 mL) were added ethyl 1,4-dioxo-8-azaspiro[4.5]decane-6-carboxylate (392 mg, 1.82 mmol) and TEA (0.5 mL, 3.42 mmol) at rt. The reaction mixture was heated at 85 °C for 16 hours and was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent Pet-ether/EtOAc 60/40) to afford ethyl 8-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-1,4-dioxo-8-azaspiro[4.5]decane-6-carboxylate (320 mg, 39.7%, LC-MS 69%) as a yellow liquid. MS (ESI) *m/z*: 488.43 [C₂₄H₂₃Cl₂N₃O₄+H]⁺.

Step 4: *8-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-1,4-dioxo-8-azaspiro[4.5]decane-6-carboxylic acid*

To a solution of ethyl 8-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-1,4-dioxo-8-azaspiro[4.5]decane-6-carboxylate (320 mg, ~ 0.45 mmol) in a mixture of THF and H₂O (20 mL) was added LiOH·H₂O (54 mg, 1.31 mmol) and the mixture was stirred at rt for 16 hours then was concentrated to a smaller volume under reduced pressure. The residue was acidified with an aqueous solution of KHSO₄

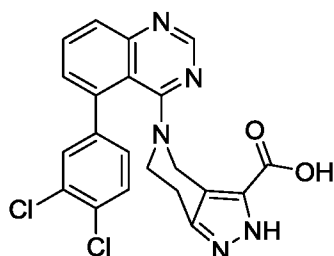
solution till pH 5. The resulting solution was extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 , filtered and concentrated. The crude compound was purified by preparative HPLC to afford ethyl 8-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-1,4-dioxo-8-azaspiro[4.5]decane-6-carboxylic acid (62 mg, 20%, AUC-HPLC 96.42 %) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 8.63 (s, 1H), 7.84 (q, $J = 8.4$ Hz, 2H), 7.71 (d, $J = 8.4$ Hz, 2H), 7.45 (bs, 2H), 3.79 (s, 4H), 3.56 (d, $J = 9.2$ Hz, 1H), 2.76–2.67 (m, 1H), 2.32–2.23 (m, 1H), 1.85 (bs, 1H), 1.73 (bs, 1H), 1.36 (d, $J = 11.6$ Hz, 1H), 1.30–1.15 (m, 1H); MS (ESI) m/z : 460.20 [$\text{C}_{22}\text{H}_{19}\text{Cl}_2\text{N}_3\text{O}_4 + \text{H}$] $^+$.

Compound 121: 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)acetic acid



The title compound was prepared in a similar fashion as described in general procedure D starting from 5-(3,4-dichlorophenyl)quinazolin-4(3H)-one (200 mg, 0.69 mmol) and methyl 2-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)acetate (302.55 mg, 1.38 mmol). The residue was purified by preparative HPLC to afford 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)acetic acid (1.19 mg, 2.43 μmol , AUC HPLC 97.55 %) as yellow solid; ^1H NMR (400 MHz, $\text{MeOD}-d_4$) δ (ppm): 8.80 (s, 1H), 7.95–7.92 (m, 1H), 7.87 (2d, $J = 8.0, 7.6$ Hz, 1H), 7.30 (d, $J = 7.2$ Hz, 1H), 6.90 & 6.85 (2d, $J = 7.2$ Hz, 3H), 6.80–6.75 (m, 1H), 6.14 & 6.10 (2d, $J = 8.4, 7.6$ Hz, 1H), 3.18–3.08 (m, 1H), 2.65–2.55 (m, 1H), 2.44–2.38 (m, 2H), 2.37–2.25 (m, 2H); MS (ESI) m/z 478.10 [$\text{C}_{25}\text{H}_{17}\text{Cl}_2\text{N}_3\text{O}_3 + \text{H}$] $^+$.

Compound 122: 5-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-3-carboxylic acid



Step 1: methyl 5-(5-(3,4-dichlorophenyl)-3,4-dihydroquinazolin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-3-carboxylate

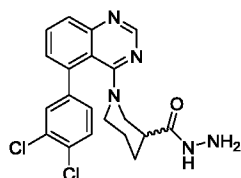
The title compound was prepared in a similar fashion as described in general procedure D starting from 5-(3,4-dichlorophenyl)quinazolin-4(3H)-one (250 mg, 0.86 mmol) and methyl 4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-3-carboxylate dihydrochloride (434.05 mg, 1.72 mmol). The

residue was purified using combiflash (silica gel, 100% DCM to DCM/MeOH 80:20) to afford methyl 5-(5-(3,4-dichlorophenyl)-3,4-dihydroquinazolin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-3-carboxylate (94 mg, 0.207 mmol) as yellow solid; MS (ESI) m/z 454.10 $[C_{22}H_{17}Cl_2N_5O_2 + H]^+$.

Step 2: 5-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-3-carboxylic acid

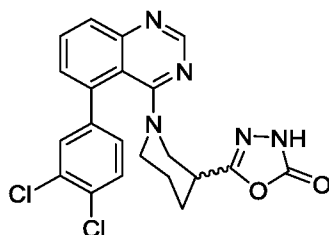
The title compound was prepared in a similar fashion as described in general procedure C starting from 5-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-3-carboxylic acid (94 mg, 0.21 mmol). The residue was purified by preparative HPLC to afford 5-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-3-carboxylic acid (3.0 mg, 6.81 μ mol, AUC HPLC 98.57 %) as white solid; ^1H NMR (400 MHz, MeOD- d_4) δ (ppm): 8.61 (s, 1H), 7.88 (2d, $J = 8.0$, 7.2 Hz, 1H), 7.82 (t, $J = 6.8$ Hz, 1H), 7.58 (d, $J = 6.8$ Hz, 2H), 7.42 (bs, 2H), 4.70-4.50 (m, 5H), 4.49-4.30 (m, 1H), 4.29-4.15 (m, 1H), 4.14-4.00 (m, 1H), 3.70-3.50 (m, 1H), 2.90-2.80 (m, 1H), 2.75-2.55 (m, 1H), 1.00-0.85 (m, 1H); MS (ESI) m/z 440.10 $[C_{21}H_{15}Cl_2FN_5O_2 + H]^+$.

Compound 123: 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carbohydrazide



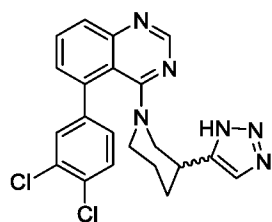
A solution of methyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxylate (200 mg, 0.481 mmol) and NH_2NH_2 (3 mL) in EtOH (20 mL) was heated at 85 $^{\circ}C$ for 16 hours and the reaction mixture was concentrated under reduced pressure. The residue was diluted with water, extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 , filtered and concentrated. The crude compound was purified by preparative HPLC to afford 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carbohydrazide (40 mg, 20%, AUC-HPLC 95.32%) as an off-white solid. mp: 154-161 $^{\circ}C$; ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 9.0-8.93 (m, 1H), 8.65-8.57 (m, 1H), 7.84-7.86 (m, 2H), 7.70 (d, $J = 8.4$ Hz, 2H), 7.55 (d, $J = 6.8$ Hz, 1H), 7.40 (bs, 1H), 4.39 (bs, 2H), 3.99-3.86 (m, 1H), 3.41 (d, $J = 7.6$ Hz, 1H), 2.59 (bs, 1H), 2.50-2.41 (m, 1H), 2.10 (bs, 1H), 1.62 (d, $J = 10.8$ Hz, 1H), 1.44-1.36 (m, 2H), 1.23-1.15 (m, 1H); MS (ESI) m/z : 416.21 $[C_{20}H_{19}Cl_2N_5O + H]^+$.

Compound 124: Preparation of 5-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)-1,3,4-oxadiazol-2(3H)-one



To a solution of 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carbohydrazide (200 mg, 0.481 mmol) in dichloromethane (10 mL) were added CDI (230 mg, 1.445 mmol) and DIPEA (0.25 mL, 1.445 mmol) and the mixture was stirred at for 16 hours. The reaction mixture was diluted with water and extracted with dichloromethane. The extract was dried over Na₂SO₄, filtered and concentrated. The crude compound was purified by preparative HPLC to afford 5-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)-1,3,4-oxadiazol-2(3H)-one (80 mg, 38%, AUC-HPLC 96.50%) as an off-white solid, mp: 146-154 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.65–8.63 (m, 1H), 7.86 (bs, 2H), 7.77–7.72 (m, 2H), 7.63–7.58 (m, 1H), 7.48 (d, *J* = 7.2 Hz, 1H), 3.68 (d, *J* = 12.0 Hz, 1H), 3.48 (bs, 1H), 2.90–2.75 (m, 2H), 1.78 (bs, 2H), 1.55 (bs, 1H), 1.39–1.36 (m, 1H), 1.25–1.10 (m, 1H); MS (ESI) *m/z*: 442.18 [C₂₁H₁₇Cl₂N₅O₂+H]⁺.

Compound 125: 4-(3-(1H-1,2,3-triazol-5-yl)piperidin-1-yl)-5-(3,4-dichlorophenyl)quinazoline

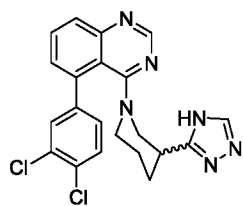


Step 1: 5-(3,4-dichlorophenyl)-4-(3-ethynylpiperidin-1-yl)quinazoline

The title compound was prepared in a similar fashion as described in general procedure G starting from methyl 3-ethynylpiperidine TFA salt (100 mg, 0.454 mmol), 4-chloro-5-(3,4-dichlorophenyl)quinazoline (125 mg, 0.409 mmol). The residue was purified by silica gel column chromatography (eluent hexane/EtOAc 8:2) to afford 5-(3,4-dichlorophenyl)-4-(3-ethynylpiperidin-1-yl)quinazoline (120 mg, 77%, LC-MS 92%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.65–8.60 (m, 1H), 7.86–7.73 (m, 4H), 7.57–7.46 (m, 2H), 3.61–3.53 (m, 1H), 3.32–2.99 (s, 3H), 2.81–2.67 (m, 2H), 1.77–1.56 (m, 3H), 1.23–1.13 (m, 1H); MS (ESI) *m/z*: 382.30 [C₂₁H₁₇Cl₂N₃+H]⁺.

Step 2: 4-(3-(1H-1,2,3-triazol-5-yl)piperidin-1-yl)-5-(3,4-dichlorophenyl)quinazoline:

A solution of 5-(3,4-dichlorophenyl)-4-(3-ethynylpiperidin-1-yl)quinazoline (120 mg, 0.306 mmol), sodium azide (60 mg, 0.918 mmol), sodium ascorbate (48 mg, 0.244 mmol) and CuSO₄·5H₂O (cat) in dioxane (5 mL) was heated at 80 °C for 6 hours. Reaction mixture was concentrated under reduced pressure and the residue was diluted with water. The solid was isolated by filtration and purified by preparative HPLC to afford 4-(3-(1H-1,2,3-triazol-5-yl)piperidin-1-yl)-5-(3,4-dichlorophenyl)quinazoline (32 mg, 25%, AUC-HPLC 99%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.83–8.76 (m, 1H), 8.10–8.04 (m, 1H), 7.83–7.54 (m, 6H), 3.35–3.32 (m, 2H), 3.08–2.92 (m, 1H), 2.35–2.09 (m, 2H), 1.93–1.89 (m, 1H), 1.57–1.42 (m, 3H), 1.05–0.98 (m, 1H); MS (ESI) *m/z*: 425.39 [C₂₁H₁₈Cl₂N₆+H]⁺.

Compound 126: 4-(3-(4H-1,2,4-triazol-3-yl)piperidin-1-yl)-5-(3,4-dichlorophenyl)quinazoline**Step 1: 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxamide:**

The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)quinazoline (500 mg, 1.62 mmol) and piperidine-3-carboxamide (417 mg, 3.25 mmol). The residue was purified by column chromatography to afford 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxamide (300 mg, LC-MS 85%) as an off-white solid. MS (ESI) m/z : 402.32 [$C_{20}H_{18}Cl_2N_4O+H$] $^{+}$.

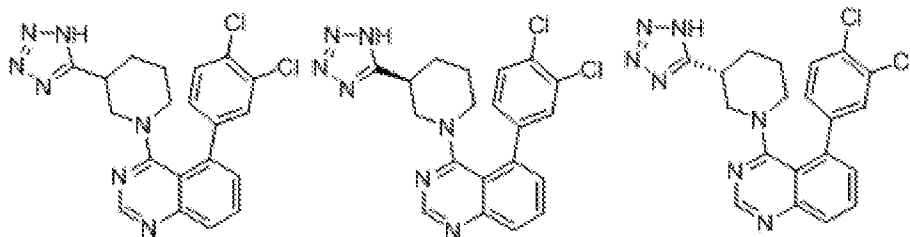
Step 2: (Z)-1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-N-((dimethylamino)methylene)piperidine-3-carboxamide

A solution of 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxamide (300 mg, 0.75 mmol) in DMF-DMA (10 mL) was heated at 100 °C for 4 h. The reaction mixture was concentrated under reduced pressure to afford (Z)-1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-N-((dimethylamino)methylene)piperidine-3-carboxamide (250 mg) as a pale yellow oil. Crude product was used in the next step without further purification.

Step 3: 4-(3-(4H-1,2,4-triazol-3-yl)piperidin-1-yl)-5-(3,4-dichlorophenyl)quinazoline :

A solution of (Z)-1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-N-((dimethylamino)methylene)piperidine-3-carboxamide (250 mg, 0.54 mmol) and hydrazine hydrate (0.2 mL) in acetic acid (5 mL) was heated at 80 °C for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was treated with 1M aqueous sodium hydroxide solution then was extracted with ethyl acetate. The extract was washed with brine and dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude was purified by Preparative HPLC to afford 4-(3-(4H-1,2,4-triazol-3-yl)piperidin-1-yl)-5-(3,4-dichlorophenyl)quinazoline (20 mg, 21%, AUC-HPLC 99%) as a white solid, mp: 174–184 °C. ^1H NMR (400 MHz, $DMSO-d_6$) δ (ppm): 13.70 (s, 1H), 8.79–8.55 (m, 1H), 8.55–8.25 (m, 1H), 8.05–7.29 (m, 7H), 3.67 (bs, 1H), 2.67 (s, 1H), 2.18 (bs, 1H), 1.88 (bs, 2H), 1.64–1.25 (m, 3H). MS (ESI) m/z : 425.25 [$C_{21}H_{18}Cl_2N_6+H$] $^{+}$.

Compound 127, 128 and 129: (Racemic)-4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(3,4-dichlorophenyl)quinazoline;
 (S)-4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(3,4-dichlorophenyl)quinazoline and (R)-4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(3,4-dichlorophenyl)quinazoline



Step 1: 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carbonitrile:

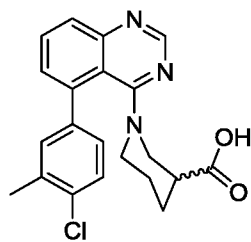
A mixture of 4-chloro-5-(3,4-dichlorophenyl)quinazoline (800 mg, 2.60 mmol), piperidine-3-carbonitrile (560 mg, 5.21 mmol) and TEA (1 mL, 7.81 mmol) in THF (80 mL) was heated to reflux for 16 hours and the reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was dried over Na₂SO₄, filtered and concentrated. The crude compound was purified by column chromatography (silica gel, eluent pet-ether/EtOAc 70:30 30%) to afford 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carbonitrile (412 mg, 82%, LC-MS 98%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.78–8.72 (m, 1H), 7.93 (s, 1H), 7.79 (t, *J* = 8.0 Hz, 1H), 7.52–7.43 (bs, 3H), 7.37–7.29 (m, 1H), 3.37 (bs, 2H), 2.98–2.86 (m, 2H), 2.36–2.18 (m, 1H), 2.03–1.95 (m, 1H), 1.59 (s, 1H), 1.41 (bs, 1H), 1.32–1.23 (m, 1H); MS (ESI) *m/z*: 383.23 [C₂₀H₁₆Cl₂N₄+H]⁺.

Step 2: 4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(3,4-dichlorophenyl)quinazoline

The title compound was prepared in a similar fashion as described in general procedure F starting from 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carbonitrile (400 mg, 1.04 mmol). The crude compound was purified by preparative HPLC to afford racemic 4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(3,4-dichlorophenyl)quinazoline (200 mg, 45%, HPLC-97%) as an off-white solid. Further purification by chiral prep-HPLC gave peak-1 (40 mg, AUC-HPLC 98%), and peak-2 (10 mg, AUC-HPLC 98.83%).

Peak-1: (S)-4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(3,4-dichlorophenyl)quinazoline, m.p.: 192–245 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.70 (bs, 1H), 7.90–7.49 (m, 6H), 3.99 (d, *J* = 5.2 Hz, 1H), 3.63 (d, *J* = 11.6 Hz, 1H), 2.92 (bs, 2H), 2.18 (bs, 1H), 1.96 (d, *J* = 10.4 Hz, 1H), 1.57–1.55 (m, 1H), 1.41–1.27 (m, 1H), 1.17–1.07 (m, 1H); MS (ESI) *m/z*: 426.24 [C₂₀H₁₇Cl₂N₇+H]⁺

Peak-2: (R)-4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(3,4-dichlorophenyl)quinazoline, ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 16.10 (bs, 1H), 8.61 (d, *J* = 17.2 Hz, 1H), 7.88–7.72 (m, 4H), 7.51–7.35 (m, 2H), 4.08–4.01 (m, 1H), 3.64 (d, *J* = 13.2 Hz, 1H), 3.17 (t, *J* = 10.8 Hz, 1H), 2.85 (t, *J* = 12 Hz, 1H), 2.50 (s, 1H), 2.12 (bs, 1H), 1.95 (d, *J* = 11.6 Hz, 1H), 1.75–1.55 (m, 1H), 1.41–1.38 (m, 1H); MS (ESI) *m/z*: 426.21 [C₂₀H₁₇Cl₂N₇+H]⁺.

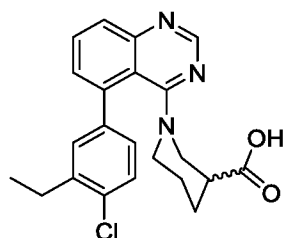
Compound 130: 1-(5-(4-chloro-3-methylphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid

Step-1: Preparation of methyl 1-(5-(4-chloro-3-methylphenyl)quinazolin-4-yl)piperidine-3-carboxylate:

The title compound was prepared in a similar fashion as described in general procedure E starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (250 mg, 0.71 mmol) and 4-chloro-3-methylphenylboronic acid (242 mg, 1.42 mmol). The crude compound was purified by column chromatography (silica gel, eluent pet-ether/EtOAc 80:20) to afford methyl 1-(5-(4-chloro-3-methylphenyl)quinazolin-4-yl)piperidine-3-carboxylate (290 mg, 98%, LC-MS 84%) as a solid. MS (ESI) m/z : 396.31 [$C_{22}H_{22}ClN_3O_2+1$] $^+$.

Step-2: Preparation of 1-(5-(4-chloro-3-methylphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid:

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 3-(5-(4-chloro-3-methylphenyl)quinazolin-4-yl)cyclohexanecarboxylate (330 mg, 0.83 mmol). The reaction mixture was concentrated to half the volume and acidified with aq. $KHSO_4$ till pH 5. The precipitate was isolated by filtration and dried to afford methyl 1-(5-(4-chloro-3-methylphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (102 mg, 32%, AUC-HPLC 97.88%) as a white solid. m.p: 185-195 °C. ^1H NMR (400 MHz, $DMSO-d_6$) δ (ppm): 8.60–8.52 (m, 1H), 7.82–7.66 (m, 2H), 7.55–7.46 (m, 3H), 7.33–7.25 (m, 1H), 3.67 (bs, 2H), 2.67–2.62 (m, 1H), 2.38 (s, 3H), 2.11 (bs, 1H), 1.69 (bs, 1H), 1.44 (d, J = 12 Hz, 1H), 1.35–1.29 (m, 1H), 1.14 (bs, 2H); MS (ESI) m/z : 382.12 [$C_{21}H_{20}ClN_3O_2+H$] $^+$.

Compound 131: 3-(5-(4-chloro-3-ethylphenyl)quinazolin-4-yl)cyclohexanecarboxylic acid

Step 1: Preparation of methyl 3-(5-(4-chloro-3-ethylphenyl)quinazolin-4-yl)cyclohexanecarboxylate

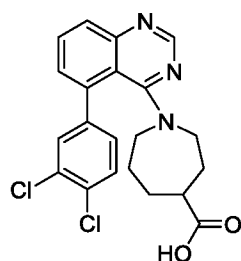
The title compound was prepared in a similar fashion as described in general procedure E starting from methyl 1-(5-bromoquinazolin-4-yl)piperidine-3-carboxylate (250 mg, 0.71 mmol) and 4-chloro-3-ethylphenylboronic acid (262 mg, 1.42 mmol). The crude product was purified by column chromatography (silica gel, eluent pet-ether/EtOAc 70:30) to afford 3-(5-(4-chloro-3-

ethylphenyl)quinazolin-4-yl)cyclohexanecarboxylate (330 mg, LC-MS 95%) as white solid. MS (ESI) m/z : 410.84 [$C_{24}H_{25}ClN_2O_2+1$]⁺.

Step 2: Preparation of 3-(5-(4-chloro-3-ethylphenyl)quinazolin-4-yl)cyclohexanecarboxylic acid:

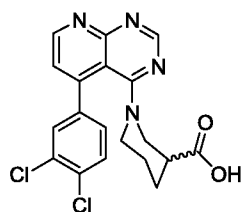
The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 3-(5-(4-chloro-3-ethylphenyl)quinazolin-4-yl)cyclohexanecarboxylate. The reaction mixture was concentrated to half the volume and acidified with aq.KHSO₄ solution till pH 5, the precipitate was isolated by filtration and dried to afford 3-(5-(4-chloro-3-ethylphenyl)quinazolin-4-yl)cyclohexanecarboxylic acid (169 mg, 49%, AUC-HPLC 99.06%) as a white solid. m.p: 177-181 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.60–8.51 (m, 1H), 7.79–7.74 (m, 2H), 7.48–7.28 (m, 4H), 3.73–3.61 (m, 4H), 2.74 (d, *J* = 6.8 Hz, 2H), 2.10 (bs, 1H), 1.75 (bs, 1H), 1.22–1.11 (m, 6H); MS (ESI) m/z : 396.31 [$C_{22}H_{22}ClN_3O_2+1$]⁺.

Compound 132: 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)azepane-4-carboxylic acid



The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)quinazoline (150 mg, 0.48 mmol) and azepane-4-carboxylic acid (139 mg, 0.97 mmol). The crude compound was purified by preparative HPLC to afford 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)azepane-4-carboxylic acid (90 mg, 44%, AUC-HPLC 91%) as an off-white solid. mp: 165-175 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 12.2 (s, 1H), 8.48 (s, 1H), 7.82-7.67 (m, 4H), 7.56 (d, *J* = 6.8 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 3.55 (bs, 1H), 3.48 (bs, 1H), 3.03 (bs, 1H), 2.65–2.59 (m, 1H), 2.22-2.07 (m, 1H), 1.93 (bs, 1H), 1.78–1.40 (m, 2H), 1.58–1.30 (m, 3H); MS (ESI) m/z : 416.11 [$C_{21}H_{19}Cl_2N_3O_2+H$]⁺.

Compound 133: 1-(5-(3,4-dichlorophenyl)pyrido[2,3-*d*]pyrimidin-4-yl)piperidine-3-carboxylic acid



Step 1: Preparation of 5-chloropyrido[2,3-*d*]pyrimidin-4(3*H*)-one:

A solution of 2-amino-4-chloronicotinic acid (1.0 g, 5.84 mmol), a catalytic amount of DMF and SOCl₂ (2.13 mL, 29.2 mmol) in 1,2-dichloroethane (12 mL) was heated at 80 °C for 4 hours. The reaction mixture was concentrated under vacuum. A solution of the crude compound in diethyl ether

and ammonia was stirred at room temperature for 15 h. The reaction mixture was concentrated under vacuum. The residue was dissolved in triethyl orthoformate and the resulting mixture was heated at 80 °C for 16 h. The reaction mixture was again concentrated under vacuum and the crude was purified by column chromatography (silica gel, eluent dichloromethane/methanol 98:2) to afford 5-chloropyrido[2,3-d]pyrimidin-4(3H)-one (100 mg) as a yellow solid. MS (ESI) m/z : 182.31 $[\text{C}_7\text{H}_4\text{ClN}_3\text{O}+\text{H}]^+$.

Step 2: Preparation of 5-(3,4-dichlorophenyl)pyrido[2,3-d]pyrimidin-4(3H)-one:

The title compound was prepared in a similar fashion as described in general procedure E starting from 5-chloropyrido[2,3-d]pyrimidin-4(3H)-one (200 mg, 1.104 mmol) and 3,4-dichlorophenylboronic acid (419 mg, 2.20 mmol). The crude product was purified by column chromatography (silica gel, eluent dichloromethane/methanol 95:5) to afford 5-(3,4-dichlorophenyl)pyrido[2,3-d]pyrimidin-4(3H)-one (80 mg, 25%) as an off-white solid; MS (ESI) m/z : 291.11 $[\text{C}_{13}\text{H}_7\text{Cl}_2\text{N}_3\text{O}+\text{H}]^+$.

Step 3: Preparation of 4-chloro-5-(3,4-dichlorophenyl)pyrido[2,3-d]pyrimidine:

A solution of 5-(3,4-dichlorophenyl)pyrido[2,3-d]pyrimidin-4(3H)-one (130 mg, 0.44 mmol) in SOCl_2 (10 mL) was heated at 80 °C for 2 h. The reaction mixture was concentrated under vacuum to afford 4-chloro-5-(3,4-dichlorophenyl)pyrido[2,3-d]pyrimidine (50 mg (crude), LC-MS 40%) as a yellow solid. MS (ESI) m/z : 308.96 $[\text{C}_{13}\text{H}_6\text{Cl}_3\text{N}_3+\text{H}]^+$.

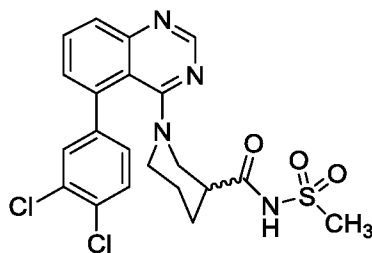
Step 4: Preparation of methyl 1-(5-(3,4-dichlorophenyl)pyrido[2,3-d]pyrimidin-4-yl)piperidine-3-carboxylate:

The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)pyrido[2,3-d]pyrimidine (130 mg, 0.422 mmol) and methyl piperidine-3-carboxylate (120 mg, 0.844 mmol). The residue was purified by column chromatography ((silica gel, eluent dichloromethane/methanol 98:2) to afford methyl 1-(5-(3,4-dichlorophenyl)pyrido[2,3-d]pyrimidin-4-yl)piperidine-3-carboxylate (80 mg, 45%, LC-MS 80%) as a pale brown solid. MS (ESI) m/z : 417.47 $[\text{C}_{22}\text{H}_{21}\text{Cl}_2\text{N}_3\text{O}_2+\text{H}]^+$.

Step 5: Preparation of 1-(5-(3,4-dichlorophenyl)pyrido[2,3-d]pyrimidin-4-yl)piperidine-3-carboxylic acid:

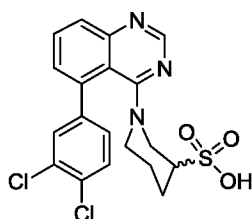
The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-4-methylpiperidine-3-carboxylate (80 mg, 0.19 mmol). The crude compound was purified by preparative HPLC to afford 1-(5-(3,4-dichlorophenyl)pyrido[2,3-d]pyrimidin-4-yl)piperidine-3-carboxylic acid (10 mg, 13%, AUC-HPLC 92%) as an off-white solid; ^1H NMR (400 MHz, CDCl_3) δ (ppm): 9.10–8.89 (m, 1H), 8.65 (d, J = 26 Hz, 1H), 7.89–7.65 (m, 2H), 7.65–7.35 (m, 2H), 3.75–3.61 (m, 1H), 3.55–3.47 (m, 1H), 2.95–2.75 (m, 1H), 2.45–2.35 (m, 1H), 2.20–1.99 (m, 1H), 1.80–1.65 (m, 1H), 1.35–1.09 (m, 3H); MS (ESI) m/z : 403.15 $[\text{C}_{19}\text{H}_{16}\text{Cl}_2\text{N}_4\text{O}_2+\text{H}]^+$.

Compound 134: *1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-N-(methylsulfonyl)piperidine-3-carboxamide:*

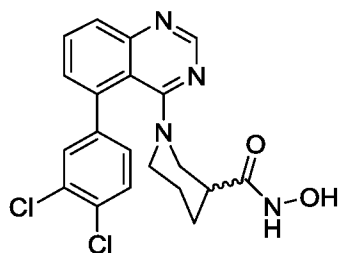


A mixture of 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (200 mg, 0.49 mmol), methanesulfonamide (230 mg, 2.49 mmol), HATU (280 mg, 0.74 mmol), and DIPEA (0.44 mL, 2.49 mmol) in 10 mL of DMF was stirred at rt for 16 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was dried over Na₂SO₄, filtered and concentrated. The crude compound was purified by preparative HPLC to afford 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-N-(methylsulfonyl)piperidine-3-carboxamide (15 mg, AUC HPLC 97.45%) as an off-white solid. mp: 186-212 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 12.79 (bs, 1H), 8.64–8.57 (m, 1H), 7.83–7.69 (m, 4H), 7.54 (d, *J* = 6.0 Hz, 1H), 7.56–7.34 (m, 1H), 4.11 (d, *J* = 11.6 Hz, 1H), 3.95–3.72 (m, 1H), 2.97 (s, 3H), 2.67 (bs, 1H), 2.18–2.07 (m, 1H), 1.75–1.62 (m, 2H), 1.37–1.27 (m, 2H), 1.16–1.10 (m, 1H), 1.25–1.10 (m, 1H); MS (ESI) *m/z*: 479.16 [C₂₁H₂₀Cl₂N₄O₃S+H]⁺.

Compound 135: *1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-sulfonic acid*



The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)quinazoline (200 mg, 0.65 mmol) and piperidine-3-sulfonic acid (128 mg, 0.78 mmol). The residue was purified by preparative HPLC to afford 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-sulfonic acid (10 mg, AUC-HPLC 98.80%) as a pale yellow solid, mp: 253-244 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 14.10 (bs, 1H), 8.79 (d, *J* = 15.6 Hz, 1H), 8.03–7.94 (m, 1H), 7.80–7.68 (m, 4H), 7.48 (bs, 1H), 4.30–3.82 (m, 1H), 3.48 (s, 1H), 2.95 (bs, 1H), 2.40 (bs, 1H), 1.87–1.71 (m, 2H), 1.50–1.40 (m, 2H), 1.23 (bs, 1H); MS (ESI) *m/z*: 438.11 [C₁₉H₁₇Cl₂N₃O₃S+H]⁺.

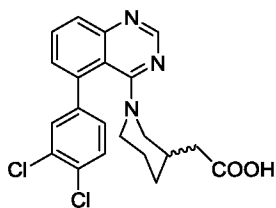
Compound 136: 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-N-hydroxypiperidine-3-carboxamide

A mixture of 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (200 mg, 0.49 mmol), hydroxylamine.HCl (240 mg, 3.49 mmol), HATU (280 mg, 0.74 mmol), and DIPEA (0.44 mL, 2.49 mmol) in 10 mL of DMF was stirred at rt for 16 hours. The reaction mixture was diluted with water and the resulting solid was isolated by filtration and dried to afford 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-N-hydroxypiperidine-3-carboxamide (130 mg, 65%, AUC-HPLC 95.84%) as an off-white solid. mp: 215-220 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 10.45–10.35 (m, 1H), 8.72–8.58 (m, 2H), 7.84–7.80 (m, 2H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 6.4 Hz, 1H), 7.40 (bs, 1H), 3.98–3.85 (m, 1H), 3.76 (bs, 1H), 2.49–2.39 (m, 2H), 2.15–2.08 (m, 1H), 1.59 (bs, 1H), 1.47–1.30 (m, 2H), 1.23–1.16 (m, 1H); MS (ESI) *m/z*: 417.18 [C₂₀H₁₈Cl₂N₄O₂+H]⁺.

Compound 137: (Racemic)2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)acetic acid

Compound 138: (enantiomer 1) (S)-2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)acetic acid

Compound 139: (enantiomer 2) (R)-2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)acetic acid



The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)quinazoline (1.0 g, 3.257 mmol) and 2-(piperidin-3-yl)acetic acid (1.17 g, 6.514 mmol). The crude product was purified by Prep-HPLC afford racemic 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)acetic acid as white solid (400 mg, 30%, LC-MS 94%) mp: 142-155 °C. Chiral resolution of the racemic compound gave 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)acetic acid peak 1 (enantiomer-1) (130 mg, 10%, HPLC 99% & Chiral-HPLC 99%) and peak 2 (enantiomer-2) (160 mg, 12%, HPLC 95% & Chiral-HPLC 96%)

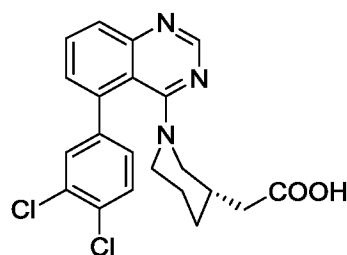
Enantiomer-1: White solid. mp: 180 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 12.10 (s, 1H), 8.63 (s, 1H), 7.87–7.76 (m, 2H), 7.69 (d, *J* = 7.6 Hz, 2H), 7.54–7.38 (m, 2H), 3.97–3.60 (m, 2H), 2.67–2.50 (m, 1H), 2.36–2.33 (m, 1H), 2.20–2.15 (m, 1H), 2.0–1.93 (m, 2H), 1.68–1.57 (m, 1H),

1.45–1.20 (m, 1H), 1.19–0.90 (m, 1H), 0.89–0.75 (m, 1H). MS (ESI) m/z : 416.21 $[\text{C}_{21}\text{H}_{19}\text{Cl}_2\text{N}_3\text{O}_2+\text{H}]^+$.

Enantiomer-2: White solid. mp:185 °C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 11.99 (s, 1H), 8.64–8.54 (m, 1H), 7.87–7.78 (m, 2H), 7.70–7.66 (m, 2H), 7.57–7.37 (m, 2H), 3.75–3.59 (m, 2H), 2.60–2.49 (m, 1H), 2.33–2.13 (m, 1H), 2.10–1.92 (m, 2H), 1.75–1.51 (m, 1H), 1.50–1.35 (m, 1H), 1.34–1.23 (m, 1H), 1.22–0.90 (m, 1H), 0.89–0.72 (m, 1H). MS (ESI) m/z : 416.21 $[\text{C}_{21}\text{H}_{19}\text{Cl}_2\text{N}_3\text{O}_2+\text{H}]^+$.

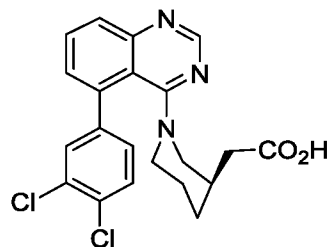
Chiral synthesis of Compounds 138 and 139

Compound 138: (S)-2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)acetic acid



The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)quinazoline (250 mg, 1.028 mmol) and (S)-2-(piperidin-3-yl)acetic acid (200 mg, 0.651 mmol). The crude was purified by Preparative HPLC to afford (S)-2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)acetic acid (90 mg, 21%, HPLC 96% & Chiral-HPLC 99%) as a white solid. mp:134–154 °C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 12.10 (s, 1H), 8.70–8.42 (m, 1H), 7.90–7.76 (m, 2H), 7.70 (d, $J = 8.0$ Hz, 2H), 7.54–7.38 (m, 2H), 3.97–3.55 (m, 2H), 2.67–2.50 (m, 1H), 2.36–2.33 (m, 1H), 2.20–2.11 (m, 1H), 2.09–1.80 (m, 2H), 1.69–1.33 (m, 2H), 1.32–0.70 (m, 2H); MS (ESI) m/z : 416.17 $[\text{C}_{21}\text{H}_{19}\text{Cl}_2\text{N}_3\text{O}_2+\text{H}]^+$.

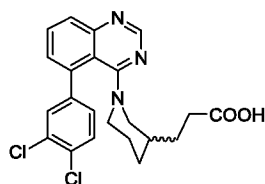
Compound 139: (R)-2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)acetic acid



The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)quinazoline (160 mg, 0.521 mmol) and (R)-2-(piperidin-3-yl)acetic acid (119 mg, 0.832 mmol). The crude compound was purified by preparative HPLC to afford (R)-2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)acetic acid (50 mg, 23%, AUC-HPLC 91.93%) as an off-white solid. mp: 160–170 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 8.61–8.51 (m, 1H), 7.95–7.75 (m, 2H), 7.75–7.6 (m, 2H), 7.6–7.5 (m, 2H), 3.75–3.6 (m, 2H), 2.65 (m, 1H),

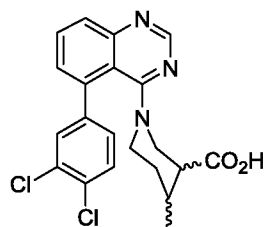
2.18 (m, 1H), 2.1-1.91 (m, 2H), 1.25-1.52 (m, 2H), 1.30-0.81 (m, 3H); MS (ESI) m/z : 416.30 [$C_{21}H_{19}Cl_2N_3O_2+H$] $^+$.

Compound 140: 3-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)propanoic acid



The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)quinazoline (200 mg, 1.68 mmol) and 3-(piperidin-3-yl)propanoic acid (129 mg, 0.821 mmol). The residue was purified by preparative HPLC to afford 3-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)propanoic acid (100 mg, 29%, LC-MS 98%, HPLC 98%) as a white solid, mp: 110-142 °C. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.70-8.49 (m, 1H), 7.93-7.78 (m, 2H), 7.77-7.68 (m, 2H), 7.62-7.37 (m, 2H), 3.90-3.65 (m, 1H), 3.32 (bs, 1H), 2.69-2.45 (m, 1H), 2.27-2.01 (m, 4H), 1.59-1.38 (m, 2H), 1.30-0.78 (m, 3H), 0.76-0.62 (m, 1H); MS (ESI) m/z : 430.29 [$C_{22}H_{21}Cl_2N_3O_2+H$] $^+$.

Compound 141: 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-4-methylpiperidine-3-carboxylic acid



Step 1: Preparation of methyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-4-methylpiperidine-3-carboxylate:

The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)quinazoline (300 mg, 0.97 mmol) and methyl 4-methylpiperidine-3-carboxylate (280 mg, 1.46 mmol). The crude compound was purified by column chromatography (silica gel, eluent pet-ether/EtOAc 80:20) to afford methyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-4-methylpiperidine-3-carboxylate (120 mg, 29%, LC-MS 89%) as a semi solid. MS (ESI) m/z : 430.24 [$C_{22}H_{21}Cl_2N_3O_2+H$] $^+$.

Step 2: Preparation of 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-4-methylpiperidine-3-carboxylic acid:

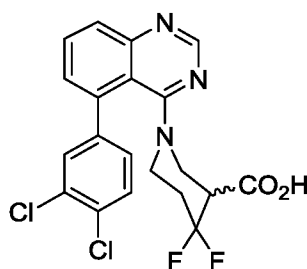
The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-4-methylpiperidine-3-carboxylate (100 mg, 0.23 mmol). The crude compound was purified by preparative HPLC to afford 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-4-methylpiperidine-3-carboxylic acid (20 mg, 20%, AUC-HPLC 96.10%) as an off-white solid, mp: 218-222 °C; ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.63-8.54

(m, 1H), 8.42 (bs, 1H), 7.87–7.70 (m, 3H), 7.54 (d, $J = 6.4$ Hz, 1H), 7.45 (bs, 1H), 3.02–2.89 (m, 2H), 2.30–2.10 (m, 1H), 2.06 (bs, 1H), 1.50–1.35 (m, 2H), 1.14 (bs, 1H), 0.88–0.83 (m, 1H), 0.74 (d, $J = 7.2$ Hz, 3H); MS (ESI) m/z : 416.23 [$C_{21}H_{19}Cl_2N_3O_2+H$] $^+$.

Compound 142: (racemic) 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-4,4-difluoropiperidine-3-carboxylic acid

Compound 143: (enantiomer 1) 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-4,4-difluoropiperidine-3-carboxylic acid

Compound 144: (enantiomer 2) 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-4,4-difluoropiperidine-3-carboxylic acid

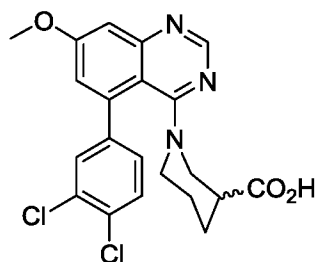


The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)quinazoline (200 mg, 0.651 mmol) in IPA (10 mL) and 4,4-difluoropiperidine-3-carboxylic acid (156 mg, 0.781 mmol). The residue was purified by column chromatography (silica gel, eluent 0.5% HCOOH in ACN) to afford the racemic 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-4,4-difluoropiperidine-3-carboxylic acid (60 mg, 18%, AUC-HPLC 98%) as an off-white solid. mp: 266–269 °C; ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.73–8.69 (m, 1H), 7.89–7.32 (m, 4H), 7.62 (bs, 1H), 7.51–7.41 (m, 1H), 4.15–3.70 (m, 1H), 3.50 (bs, 1H), 3.13–3.10 (m, 2H), 2.07–1.79 (m, 2H), 1.25–1.0 (m, 1H); MS (ESI) m/z : 438.15 [$C_{20}H_{15}Cl_2F_2N_3O_2+H$] $^+$.

50 mg of racemic 1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)-4,4-difluoropiperidine-3-carboxylic acid was resolved by chiral chromatography to afford peak 1 and peak 2.

Peak 1: (5 mg, AUC HPLC 95.4%, chiral HPLC 98.6%) as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.69–8.65 (m, 1H), 7.86–7.70 (m, 4H), 7.59 (bs, 1H), 7.48–7.39 (m, 1H), 4.18–3.71 (m, 1H), 3.44 (bs, 1H), 3.13–2.70 (m, 2H), 2.03–1.96 (m, 1H), 1.74–1.60 (m, 1H), 1.16–1.02 (m, 1H); MS (ESI) m/z : 438.15 [$C_{20}H_{15}Cl_2F_2N_3O_2+H$] $^+$ and

Peak 2: (4 mg, AUC HPLC 97.5%, chiral HPLC 94.32%) as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.72–8.68 (m, 1H), 7.89–7.72 (m, 4H), 7.62 (bs, 1H), 7.49–7.41 (m, 1H), 4.14–3.99 (m, 1H), 3.78–3.71 (m, 1H), 3.15–2.99 (m, 2H), 2.07–1.97 (m, 1H), 1.82–1.78 (m, 1H), 1.17–1.03 (m, 1H); MS (ESI) m/z : 438.19 [$C_{20}H_{15}Cl_2F_2N_3O_2+H$] $^+$.

Compound 145: 1-(5-(3,4-dichlorophenyl)-7-methoxyquinazolin-4-yl)piperidine-3-carboxylic acid**Step 1: 5-(3,4-dichlorophenyl)-7-methoxyquinazolin-4(3H)-one**

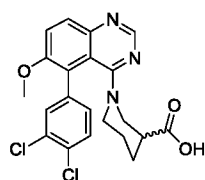
The title compound was prepared in a similar fashion as described in general procedure E starting from 5-bromo-7-methoxyquinazolin-4(3H)-one (400 mg, ~0.84 mmol) and 3,4-dichlorophenylboronic acid (540 mg, 2.84 mmol). The crude compound was purified by column chromatography (silica gel, eluent DCM/MeOH 98/2) to afford 5-(3,4-dichlorophenyl)-7-methoxyquinazolin-4(3H)-one (300 mg, 45.6%, LC-MS 73%) as a yellow solid. MS (ESI) m/z : 321.24 [$C_{15}H_{10}Cl_2N_2O_2+H$]⁺.

Step 2: methyl 1-(5-(3,4-dichlorophenyl)-7-methoxyquinazolin-4-yl)piperidine-3-carboxylate

To a solution of 5-(3,4-dichlorophenyl)-7-methoxyquinazolin-4(3H)-one (250 mg, ~0.41 mmol) in acetonitrile (30 mL) were added PyBop and DBU. The mixture was stirred at rt for 30 minutes, prior to the addition of methyl piperidine-3-carboxylate (172 mg, 1.20 mmol). The reaction mixture was stirred at rt for an additional 16 h, then was diluted with water and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and concentrated. The crude compound was purified by column chromatography (silica gel column, eluent pet-ether/EtOAc 60:40) afford methyl 1-(5-(3,4-dichlorophenyl)-7-methoxyquinazolin-4-yl)piperidine-3-carboxylate (250 mg, 93%, LC-MS 80%) as a yellow solid. MS (ESI) m/z : 446.38 [$C_{22}H_{21}Cl_2O_3+H$]⁺.

Step 3: 1-(5-(3,4-dichlorophenyl)-7-methoxyquinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(3,4-dichlorophenyl)-7-methoxyquinazolin-4-yl)piperidine-3-carboxylate (250 mg, 0.560 mmol). The crude compound was purified by preparative HPLC to afford 1-(5-(3,4-dichlorophenyl)-7-methoxyquinazolin-4-yl)piperidine-3-carboxylic acid (58 mg, 24%, AUC-HPLC 98.77 %) as a white solid. m.p. 252-263 °C; ^1H NMR (400 MHz, $DMSO-d_6$) δ (ppm): 8.59–8.51 (m, 1H), 7.71 (d, J = 8.8 Hz, 2H), 7.47–7.25 (m, 1H), 7.25–7.17 (m, 2H), 3.94 (s, 3H), 3.61–3.48 (m, 2H), 2.59 (s, 2H), 2.16 (bs, 1H), 1.73 (bs, 1H), 1.45–1.35 (m, 2H), 1.23 (bs, 1H); MS (ESI) m/z : 432.18 [$C_{21}H_{19}Cl_2N_3O_3+H$]⁺.

Compound 146: 1-(5-(3,4-dichlorophenyl)-6-methoxyquinazolin-4-yl)piperidine-3-carboxylic acid

Step 1: Preparation of 5-bromo-6-methoxyquinazolin-4(3H)-one:

A solution of 6-amino-2-bromo-3-methoxybenzoic acid (1.5 g, 6.09 mmol) and formamidine acetate (2.0 g, 13.41 mmol) in 2-methoxyethanol (30 mL) was stirred at 130 °C for 16 hours and was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent DCM/MeOH 95:5) to afford 5-bromo-6-methoxyquinazolin-4(3H)-one (700 mg, 45%, LC-MS 79%) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 12.18 (s, 1H), 7.95 (d, *J* = 3.6 Hz, 1H), 7.65 (q, *J* = 8.8 Hz, 2H), 3.93 (s, 3H); MS (ESI) *m/z*: 255.14 [C₉H₇BrN₂O₂ + H]⁺.

Step 2: Preparation of 5-(3,4-dichlorophenyl)-6-methoxyquinazolin-4(3H)-one:

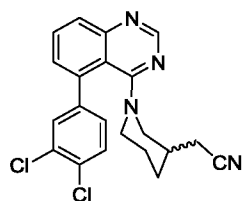
The title compound was prepared in a similar fashion as described in general procedure E starting from 5-bromo-6-methoxyquinazolin-4(3H)-one (770 mg, 3.03 mmol) and 3,4-dichlorophenylboronic acid (1 g, 5.45 mmol). The crude compound was purified by column chromatography (silica gel, eluent pet-ether/EtOAc 1:1) to afford 5-(3,4-dichlorophenyl)-6-methoxyquinazolin-4(3H)-one (700 mg, 72%, LC-MS 78%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 11.84 (s, 1H), 7.91 (d, *J* = 3.2 Hz, 1H), 7.76–7.70 (m, 1H), 7.67–7.65 (m, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 2.0 Hz, 1H), 7.12 (dd, *J* = 1.6 Hz, 8.4 Hz, 1H), 3.77 (s, 3H); MS (ESI) *m/z*: 321.20 [C₁₅H₁₀Cl₂N₂O₂ + H]⁺.

Step 3: Preparation of methyl 1-(5-(3,4-dichlorophenyl)-6-methoxyquinazolin-4-yl)piperidine-3-carboxylate:

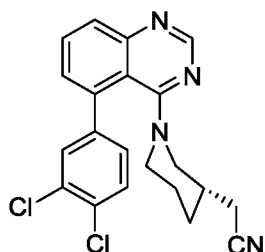
To a solution of 5-(3,4-dichlorophenyl)-6-methoxyquinazolin-4(3H)-one (200 mg, 0.625 mmol) in ACN (20 mL) were added PyBOP (480 mg, 0.93 mmol) and DBU (0.19 mL, 1.25 mmol) at rt and stirred for 30 minutes prior to the addition of methyl piperidine-3-carboxylate (160 mg, 1.125 mmol) and the mixture was stirred at rt for 16 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The extracts were dried over Na₂SO₄, filtered and concentrated. The crude compound was purified by column chromatography (silica gel, eluent pet-ether/EtOAc 70:30) to afford methyl 1-(5-(3,4-dichlorophenyl)-6-methoxyquinazolin-4-yl)piperidine-3-carboxylate (230 mg, 85%, LC-MS 88%) as a colourless liquid. MS (ESI) *m/z*: 446.21 [C₂₂H₂₁Cl₂N₃O₃ + H].

Step 4: Preparation of 1-(5-(3,4-dichlorophenyl)-6-methoxyquinazolin-4-yl)piperidine-3-carboxylic acid:

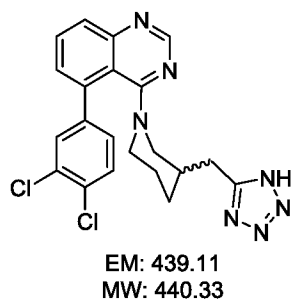
The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(3,4-dichlorophenyl)-6-methoxyquinazolin-4-yl)piperidine-3-carboxylate (230 mg, 0.51 mmol). The crude compound was purified by preparative HPLC to afford 1-(5-(3,4-dichlorophenyl)-6-methoxyquinazolin-4-yl)piperidine-3-carboxylic acid (70 mg, 31%, AUC-HPLC 99.23%) as an off-white solid. mp: 246–248 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 12.30 (bs, 1H), 8.58–8.49 (m, 1H), 7.95–7.83 (m, 2H), 7.63 (bs, 2H), 7.39–7.31 (m, 1H), 3.04 (s, 3H), 3.62–3.41 (m, 2H), 3.10–2.80 (m, 1H), 2.50–2.41 (m, 1H), 1.71 (bs, 1H), 1.49 (bs, 1H), 1.30–1.09 (m, 2H), 0.51 (bs, 1H); MS (ESI) *m/z*: 432.18 [C₂₁H₁₉Cl₂N₃O₃ + H]⁺.

Compound 147: 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)acetonitrile

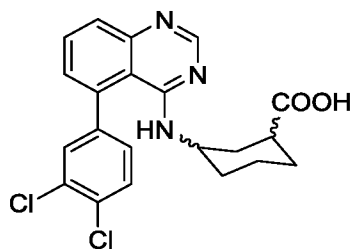
A solution of 4-chloro-5-(3,4-dichlorophenyl)quinazoline (300 mg, 0.977 mmol, 2-(piperidin-3-yl)acetonitrile (220 mg, 1.758 mmol) and TEA (0.7 mL, 4.88 mmol) in IPA (30 mL) was heated at 85 °C for 16 hours. The reaction mixture was concentrated and the residue was diluted with water. The aqueous phase was extracted with ethyl acetate. The organic phase was dried over Na₂SO₄, filtered and concentrated. The crude compound was purified by column chromatography (silica gel, pet-ether/EtOAc 70:30) to afford 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)acetonitrile (340 mg, 88%, LC-MS 99.64%, AUC-HPLC 99%) as an off-white solid. m.p: 71-85 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.63 (s, 1H), 7.86–7.72 (m, 4H), 7.57–7.53 (m, 2H), 3.65 (bs, 2H), 3.17 (d, *J* = 5.6 Hz, 1H), 2.39–2.32 (m, 3H), 1.76–1.47 (m, 2H), 1.41 (bs, 1H), 1.25 (s, 1H), 0.98–0.89 (s, 1H); MS (ESI) *m/z*: 397.21 [C₂₁H₁₈Cl₂N₄+H]⁺.

Compound 148: (S)-2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)acetonitrile

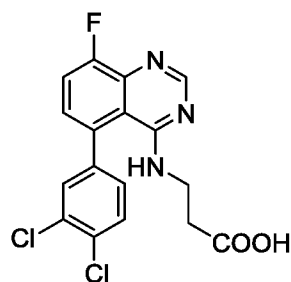
The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)-3,4-dihydroquinazoline and (S)-2-(piperidin-3-yl)acetonitrile. The crude compound was purified by preparative HPLC to afford (S)-2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)acetonitrile as an off-white solid. (5 mg, , HPLC 98.74%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.69–8.58 (m, 1H), 7.86–7.72 (m, 4H), 7.57–7.53 (m, 2H), 3.65 (brs, 2H), 2.39–2.32 (m, 3H), 1.59 (d, *J* = 12.4 Hz, 1H), 1.47 (brs, 1H), 1.23 (s, 1H), 1.22 (s, 1H), 1.14 (brs, 1H), 0.94 (d, *J* = 10.4 Hz, 1H); MS (ESI) *m/z*: 397.25 [C₂₁H₁₈Cl₂N₄+H]⁺.

Compound 149: 4-(3-((1*H*-tetrazol-5-yl)methyl)piperidin-1-yl)-5-(3,4-dichlorophenyl)quinazoline

The title compound was prepared in a similar fashion as described in general procedure F starting from 2-(1-(5-(3,4-dichlorophenyl)quinazolin-4-yl)piperidin-3-yl)acetonitrile (250 mg, 0.63 mmol). The residue was purified by preparative HPLC to afford racemic 4-(3-((1*H*-tetrazol-5-yl)methyl)piperidin-1-yl)-5-(3,4-dichlorophenyl)quinazoline (28 mg, 10%, AUC-HPLC 97.84%) as a solid, mp: 120–167 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.70 (bs, 1H), 7.94–7.90 (m, 1H), 7.84–7.75 (m, 4H), 7.37 (bs, 1H), 2.75–2.67 (m, 3H), 2.32 (bs, 1H), 1.84 (bs, 1H), 1.53–1.35 (m, 2H), 1.28–1.23 (m, 3H), 0.98 (bs, 1H); MS (ESI) *m/z*: 440.20 [C₂₁H₁₉Cl₂N₇+H]⁺.

Compound 150: 3-(5-(3,4-dichlorophenyl)quinazolin-4-ylamino)cyclohexanecarboxylic acid

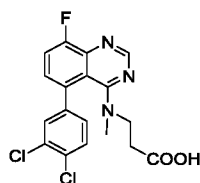
To a solution of 4-chloro-5-(3,4-dichlorophenyl)quinazoline (200 mg, 0.65 mmol) in *t*-butanol (25 mL) was added 3-aminocyclohexanecarboxylic acid (186 mg, 1.30 mmol) and KF (113 mg, 1.95 mmol) at rt. The reaction mixture was heated at 80 °C for 16 h, and filtered. The filtrate was concentrated and the residue was purified by preparative HPLC to afford 3-(5-(3,4-dichlorophenyl)quinazolin-4-ylamino)cyclohexanecarboxylic acid (20 mg, 19%, AUC-HPLC 92.38) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.49 (t, *J* = 3.6 Hz, 1H), 7.85–7.73 (m, 4H), 7.46 (d, *J* = 11.6 Hz, 1H), 7.36–7.32 (m, 1H), 5.11 (d, *J* = 7.6 Hz, 1H), 3.96–3.94 (m, 1H), 2.17 (bs, 1H), 2.02 (d, *J* = 12 Hz, 1H), 1.78–1.64 (m, 2H), 1.30–1.23 (m, 2H), 1.08–1.05 (m, 1H), 0.78 (d, *J* = 11.6 Hz, 1H), 0.64–0.61 (m, 1H); MS (ESI) *m/z*: 416.17 [C₂₁H₁₉Cl₂N₃O₂+H]⁺.

Compound 151: 3-((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)amino)propanoic acid**Step 1: Preparation of methyl 3-((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)amino)propanoate**

The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)-8-fluoroquinazoline (100 mg, 0.30 mmol) and methyl-3-aminopropanoate hydrochloride (42.6 mg, 0.30 mmol). The crude product was purified by column chromatography (Silica gel (230-400 mesh), eluent Petroleum ether/EtOAc 55/45) to afford methyl 3-((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)amino)propanoate (108 mg, yield 89.5%) as colorless thick oil. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.67 (s, 1H), 7.59 (d, $J = 8.0$ Hz, 1H), 7.48 (d, $J = 2.0$ Hz, 1H), 7.45-7.38 (dd, $J = 9.1, 8.3$, 1H), 7.24 (dd, $J = 8.0, 2.1$ Hz, 1H), 7.18 (dd, $J = 8.1, 5.1$ Hz, 1H), 5.6-5.7 (m, 1H), 3.90-3.70 (m, 1H), 3.65 (s, 3H), 3.65-3.55 (m, 1H), 2.5 (t, $J = 6.2$ Hz, 2H). LC-MS: 91.06%; m/z : 394.1 [$\text{C}_{18}\text{H}_{14}\text{Cl}_2\text{FN}_3\text{O}_2 + \text{H}$] $^+$.

Step 2: Preparation of 3-((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)amino)propanoic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 3-((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)amino)propanoate (105 mg, 0.26 mmol). The aqueous work-up yielded a precipitate that was washed with pentane, dried under vacuum to afford 3-((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)amino)propanoic acid (32 mg, yield 36%, HPLC 97.68%); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 12.60-12.00 (bs, 1H), 8.56 (s, 1H), 7.80-7.60 (m, 3H), 7.45-7.25 (m, 2H), 6.00-5.80 (m, 1H), 3.60-3.50 (m, 2H), 2.40-2.30 (m, 2H); m/z : 380.1 [$\text{C}_{17}\text{H}_{12}\text{Cl}_2\text{FN}_3\text{O}_2 + \text{H}$] $^+$.

Compound 152: 3-((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)(methyl)amino)propanoic acid**Step 1: Preparation of methyl 3-((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)(methyl)amino)propanoate**

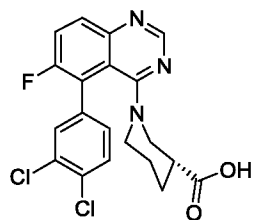
The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)-8-fluoroquinazoline (100 mg, 0.30 mmol) and methyl-3-aminopropanoate hydrochloride (46.9 mg, 0.30 mmol). The crude product was purified by column chromatography (silica gel (230-400 mesh), eluent petroleum ether/EtOAc 1/1) to afford methyl 3-((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)(methyl)amino)propanoate.

((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)(methylamino)propanoate (80 mg, 64.0%) as pale yellow thick oil. ^1H NMR(400 MHz, CDCl_3) δ (ppm): 8.67 (bs, 1H), 7.55-7.45 (m, 3H), 7.40-7.30 (m, 1H), 7.25-7.18 (m, 1H), 3.65 (s, 3H), 3.65-3.50 (m, 2H), 2.52 (s, 3H), 1.35-1.20 (m, 2H); LCMS: 90.71%; m/z : 408.1 $[\text{C}_{19}\text{H}_{16}\text{Cl}_2\text{FN}_3\text{O}_2+\text{H}]^+$.

Step 2: Preparation of 3-((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)(methylamino)propanoic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 3-((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)(methyl) amino) propanoate (80 mg, 0.19 mmol, 1eq). The aqueous work-up yielded a precipitate that was washed with pentane and dried under vacuum to afford 3-((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)(methylamino)propanoic acid (22 mg, yield 28.4%, AUC HPLC 94.66%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 8.52 (s, 1H), 7.74-7.60 (m, 3H), 7.55-7.46 (m, 1H), 7.34 (bs, 1H), 3.41-3.32 (m, 2H), 2.44 (s, 3H), 2.41-2.25 (m, 2H); LC-MS 94.85 %; m/z : 394.1 $[\text{C}_{18}\text{H}_{14}\text{Cl}_2\text{FN}_3\text{O}_2+\text{H}]^+$.

Compound 153: (R)-1-(5-(3,4-dichlorophenyl)-6-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid



Step 1: Preparation of 2-bromo-3-fluoro-6-nitrobenzoic acid

To a solution of 2-bromo-3-fluorobenzoic acid (2 g, 9.17 mmol) in H_2SO_4 (8 mL) was added HNO_3 (0.8 mL, 9.17 mmol) at 0 °C. The reaction mixture was stirred for 16 hours at room temperature and was poured onto ice. The solid was isolated by filtration and purified by column chromatography to afford 2-bromo-3-fluoro-6-nitrobenzoic acid (500 mg, 20%, LC-MS 92%) as a pale yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 8.35 (dd, $J = 5.2$ Hz, 9.6 Hz, 1H), 7.74–7.66 (m, 1H); MS (ESI) m/z : 263.9 $[\text{C}_7\text{H}_3\text{BrFNO}_4-\text{H}]^+$.

Step 2: Preparation of 6-amino-2-bromo-3-fluorobenzoic acid

A slurry of 2-bromo-3-fluoro-6-nitrobenzoic acid (500 mg, 1.9 mmol) and Raney-Ni (50 mg, 10%) in methanol (50 mL) was stirred for 16 hours at room temperature under H_2 (balloon pressure). The reaction mixture was filtered through a short pad of celite bed. The filtrate was concentrated under reduced pressure to afford 6-amino-2-bromo-3-fluorobenzoic acid (300 mg, 67%, LC-MS 99%) as an off-white solid. MS (ESI) m/z : 234.09 $[\text{C}_7\text{H}_5\text{BrFNO}_2+\text{H}]^+$.

Step 3: Preparation of 5-bromo-6-fluoroquinazolin-4(3H)-one:

A solution of 6-amino-2-bromo-3-fluorobenzoic acid (300 mg, 1.28 mmol) and formamidine acetate (266 mg, 2.56 mmol) in 2-methoxy ethanol (10 mL) was heated at 120 °C for 16 hours. The reaction mixture was concentrated under reduced pressure and suspended in water. The precipitate was

isolated by filtration and dried to afford 5-bromo-6-fluoroquinazolin-4(3*H*)-one (300 mg, 67%, LC-MS 92%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 7.96 (s, 1H), 7.71 (dd, 4.8 Hz, 8.8 Hz, 1H), 7.53 (t, 8.4 Hz, 1H); MS (ESI) *m/z*: 243.13 [C₈H₄BrFN₂O+H]⁺.

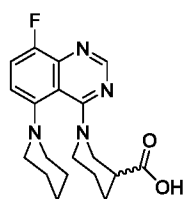
Step 4: Preparation of 5-(3,4-dichlorophenyl)-6-fluoroquinazolin-4(3*H*)-one:

The title compound was prepared in a similar fashion as described in general procedure E starting from 5-bromo-6-fluoroquinazolin-4(3*H*)-one (300 mg, 1.23 mmol) and 4-chlorophenylboronic acid (282 mg, 1.48 mmol). The crude product was purified by column chromatography (silica gel, eluent dichloromethane/methanol 98:2) to afford 5-(3,4-dichlorophenyl)-6-fluoroquinazolin-4(3*H*)-one (100 mg, 26%, LC-MS 85%). MS (ESI) *m/z*: 309.26 [C₁₄H₇Cl₂FN₂O+H]⁺.

Step 5: (R)-1-(5-(3,4-dichlorophenyl)-6-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid

To a solution of 5-(3,4-dichlorophenyl)-6-fluoroquinazolin-4(3*H*)-one (400 mg, 0.129 mmol) in acetonitrile was added PyBOP (1.34 gm, 2.59 mmol) and DBU (394 mg, 2.596 mmol). The reaction mixture was stirred for 30 min, prior to the addition of (R)-piperidine-3-carboxylic acid (251 mg, 1.94 mmol). The reaction mixture was stirred for 16 hours at room temperature. Reaction mixture was concentrated under reduced pressure, added to water and extracted with dichloromethane (2 x 20 mL), dried over Na₂SO₄, filtered and concentrated. Crude was purified by prep-HPLC to afford (R)-1-(5-(3,4-dichlorophenyl)-6-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid (75 mg, 77%, AUC-HPLC 97%) as an off-white solid. mp: 210–221 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.75–8.55 (m, 1H), 8.05–7.65 (m, 4H), 7.46 (s, 1H), 3.70–3.40 (m, 2H), 2.67 (s, 2H), 1.72 (s, 1H), 1.57–1.27 (m, 2H), 1.23 (s, 1H), 1.10 (bs, 1H). MS (ESI) *m/z*: 420.26 [C₂₀H₁₆Cl₂FN₃O₂+H]⁺.

Compound 154: 1-(8-fluoro-5-(piperidin-1-yl)quinazolin-4-yl)piperidine-3-carboxylic acid



Step 1: 8-fluoro-5-(piperidin-1-yl)quinazolin-4(3*H*)-one

The title compound was prepared in a similar fashion as described in general procedure A starting from 5-bromo-8-fluoroquinazolin-4(3*H*)-one (300 mg, 1.23 mmol) and piperidine (210.22 mg, 2.46 mmol). The residue was purified using column chromatography (silica gel, Hex to DCM to DCM/MeOH 92:8) to afford 8-fluoro-5-(piperidin-1-yl)quinazolin-4(3*H*)-one (183 mg, 0.74 mmol, 60.2 %) as yellow solid; ¹H NMR (400 MHz, MeOD-*d*₄) δ (ppm): 8.00 (s, 1H), 7.46 (t, *J* = 9.4 Hz, 1H), 7.07 (bs, 1H), 3.01 (m, 3H), 2.65 (s, 2H), 1.75 (bs, 4H), 1.61 (bs, 2H); MS (ESI) *m/z* 248.1 [C₁₃H₁₄FN₃O+H]⁺.

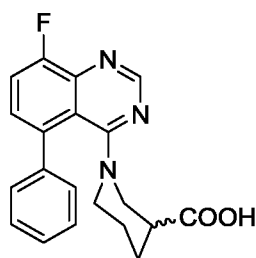
Step 2: methyl 1-(8-fluoro-5-(piperidin-1-yl)-3,4-dihydroquinazolin-4-yl)piperidine-3-carboxylate

The title compound was prepared in a similar fashion as described in general procedure D starting from 8-fluoro-5-(piperidin-1-yl)quinazolin-4(3H)-one (180 mg, 0.73 mmol) and methyl piperidine-3-carboxylate (209.07 mg, 1.46 mmol) to afford the crude methyl 1-(8-fluoro-5-(piperidin-1-yl)-3,4-dihydroquinazolin-4-yl)piperidine-3-carboxylate (220 mg, 0.59 mmol) as an off-white solid; MS (ESI) m/z 373.00 [$C_{20}H_{25}FN_4O_2 + H$] $^+$. The reaction crude product was carried forth to the next step without further purification.

Step 3: 1-(8-fluoro-5-(piperidin-1-yl)quinazolin-4-yl)piperidine-3-carboxylic acid

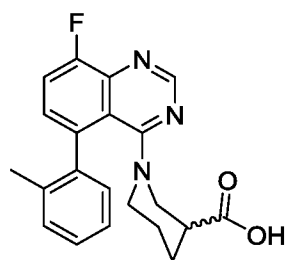
The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(8-fluoro-5-(piperidin-1-yl)quinazolin-4-yl)piperidine-3-carboxylate (~ 0.73 mmol). The residue was purified by preparative HPLC (C18: 10-60 % ACN in water) to afford 1-(8-fluoro-5-(piperidin-1-yl)quinazolin-4-yl)piperidine-3-carboxylic acid (58.2 mg, 0.16 mmol, 22.2 %, AUC HPLC 99.51 %) as yellow solid; ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.49 (s, 1H), 8.13 & 7.95 (2s, 1H), 7.64-7.55 (t, $J = 8.2$ Hz, 1H), 7.10-6.95 (m, 1H), 3.17 (s, 2H), 3.15-2.95 (m, 2H), 2.76 (s, 2H), 2.73 (s, 2H), 2.05-1.90 (m, 1H), 1.85-1.50 (m, 8H), 1.40-0.20 (m, 2H); MS (ESI) m/z 359.10 [$C_{19}H_{23}FN_4O_2 + H$] $^+$.

Compound 155: 1-(8-fluoro-5-phenylquinazolin-4-yl)piperidine-3-carboxylic acid



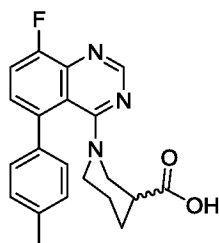
The title compound was prepared in a similar fashion as described in general procedure B starting from methyl 1-(5-bromo-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (96 mg, 0.26 mmol) and phenylboronic acid (48 mg, 0.39 mmol). The residue was purified by preparative HPLC (C18, eluent $CH_3CN/H_2O/HCOOH$ 0.01%) to afford 1-(8-fluoro-5-phenylquinazolin-4-yl)piperidine-3-carboxylic acid (52 mg, 57%, AUC HPLC 99.14%) as white solid; ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.73-8.54 (m, 1H), 7.90-7.10 (m, 7H), 4.14-3.55 (m, 2H), 2.87-2.62 (m, 1H), 2.38-2.02 (m, 1H), 1.85-0.46 (m, 5H); MS (ESI) m/z 352.1 [$C_{20}H_{18}FN_3O_2 + H$] $^+$.

Compound 156: 1-(8-fluoro-5-(o-tolyl)quinazolin-4-yl)piperidine-3-carboxylic acid



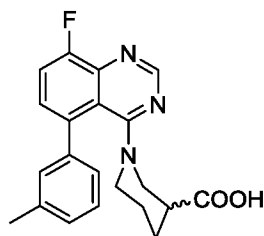
The title compound was prepared in a similar fashion as described in general procedure B starting from methyl 1-(5-bromo-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (95 mg, 0.258 mmol) and *o*-tolylboronic acid (70.70 mg, 0.52 mmol). The residue was purified by preparative HPLC (C18 10-70 % ACN in water) to afford 1-(8-fluoro-5-(*o*-tolyl)quinazolin-4-yl)piperidine-3-carboxylic acid (36.23 mg, 0.099 mmol, 38.4 %, AUC HPLC 97.68 %) as off-white solid; ^1H NMR (400 MHz, MeOD) δ (ppm): 8.59 (s, 1H), 7.65-7.55 (m, 1H), 7.45-7.35 (m, 2H), 7.34-7.28 (m, 2H), 7.27-7.20 (m, 1H), 4.80-4.40 (m, 1H), 3.75-3.65 (m, 2H), 3.25-3.10 (m, 1H), 2.80-2.60 (m, 1H), 2.14 (s, 2H), 1.93 (s, 2H), 1.85-1.70 (m, 1H), 1.50-1.20 (m, 2H); MS (ESI) m/z 366.10 [$\text{C}_{21}\text{H}_{20}\text{FN}_3\text{O}_2 + \text{H}$] $^+$.

Compound 157: 1-(8-fluoro-5-(*p*-tolyl)quinazolin-4-yl)piperidine-3-carboxylic acid

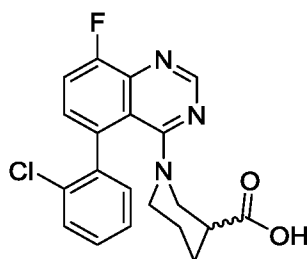


The title compound was prepared in a similar fashion as described in general procedure E starting from methyl 1-(5-bromo-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (95 mg, 0.258 mmol) and *p*-tolylboronic acid (70.70 mg, 0.52 mmol). The residue was purified by preparative HPLC (C18, 10-70 % ACN in water) to afford 1-(8-fluoro-5-(*p*-tolyl)quinazolin-4-yl)piperidine-3-carboxylic acid (32.8 mg, 0.086 mmol, 34.82 %, AUC HPLC 99.66 %) as an off-white solid; ^1H NMR (400 MHz, MeOD- d_4) δ (ppm): 8.53 (s, 1H), 7.57 (2d, $J = 9.6, 8.4$ Hz, 1H), 7.52-7.43 (m, 2H), 7.33-7.25 (bs, 3H), 7.16 (d, $J = 7.6$ Hz, 1H), 3.80-3.70 (m, 1H), 3.69-3.50 (m, 2H), 3.10-2.70 (m, 1H), 2.42 (s, 3H), 2.32 (s, 1H), 1.90-1.70 (m, 1H), 1.60-1.30 (m, 2H), 1.29-1.15 (m, 1H); MS (ESI) m/z 366.10 [$\text{C}_{21}\text{H}_{20}\text{FN}_3\text{O}_2 + \text{H}$] $^+$.

Compound 158: 1-(8-fluoro-5-(*m*-tolyl)quinazolin-4-yl)piperidine-3-carboxylic acid



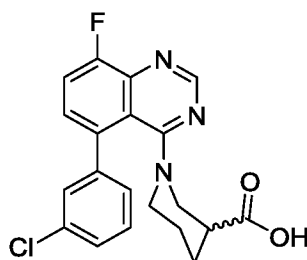
The title compound was prepared in a similar fashion as described in general procedure B starting from methyl 1-(5-bromo-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (96 mg, 0.26 mmol) and *m*-tolylboronic acid (53 mg, 0.39 mmol). The residue was purified by preparative HPLC (C18, eluent $\text{CH}_3\text{CN}/\text{H}_2\text{O}/\text{HCOOH}$ 0.01%) to afford 1-(8-fluoro-5-(*m*-tolyl)quinazolin-4-yl)piperidine-3-carboxylic acid (32 mg, 34%, AUC HPLC 99.14%) as white solid; ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.71-8.53 (m, 1H), 7.81-7.66 (m, 1H), 7.51-7.44 (m, 1H), 7.40-7.01 (m, 4H), 4.22-3.58 (m, 2H), 2.84-2.57 (m, 1H), 2.37 (s, 3H), 2.34-1.98 (m, 1H), 1.81-0.59 (m, 5H); MS (ESI) m/z 366.1 [$\text{C}_{21}\text{H}_{20}\text{FN}_3\text{O}_2 + \text{H}$] $^+$.

Compound 159: Methyl 1-(5-(2-chlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate**Step 1: methyl 1-(5-(2-chlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate**

The title compound was prepared in a similar fashion as described in general procedure E starting from methyl 1-(5-bromo-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (95 mg, 0.258 mmol) and (2-chlorophenyl)boronic acid (81.31 mg, 0.52 mmol). After an aqueous work-up, the combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford methyl 1-(5-(2-chlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate as off-white solid; MS (ESI) m/z 400.10 [$C_{21}H_{19}FN_3O_2 + H$] $^+$. The crude product was carried forth to the next step without further purification.

Step 2: 1-(5-(2-chlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid

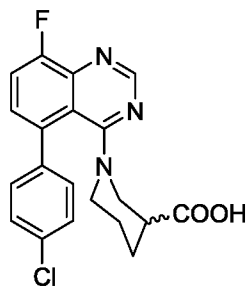
The title compound was prepared in a similar fashion as described in general procedure B starting from methyl 1-(5-(2-chlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (~ 0.258 mmol). The residue was purified by preparative HPLC (C18: 10-70 % ACN in water) to afford 1-(5-(2-chlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid (15.74 mg, 0.041 mmol, 15.8 % over 2 steps, AUC HPLC 96.36 %) as off-white solid; ^1H NMR (400 MHz, DMSO) δ (ppm): 12.30 (bs, 1H), 8.72 (bs, 1H), 7.75 (t, $J = 8.6$ Hz, 1H), 7.70-7.51 (m, 2H), 7.50-7.45 (m, 2H), 7.12 (t, $J = 51.0$ Hz, 1H), 3.85-3.70 (m, 1H), 3.60-3.45 (m, 1H), 3.00-2.70 (m, 1H), 2.65-2.55 (m, 1H), 1.90-1.55 (m, 2H), 1.49-1.05 (m, 2H), 1.00-0.80 (m, 1H); MS (ESI) m/z 386.10 [$C_{20}H_{17}ClFN_3O_2 + H$] $^+$.

Compound 160: 1-(5-(3-chlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure B starting from methyl 1-(5-bromo-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (96 mg, 0.26 mmol) and (3-chlorophenyl)boronic acid (61 mg, 0.39 mmol). The residue was purified by preparative HPLC (C18, eluent $CH_3CN/H_2O/HCOOH$ 0.01%) to 1-(5-(3-chlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid (11 mg, 11%, AUC HPLC 92.32%) as white solid; ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.73-8.56 (m, 1H), 7.78-7.66 (m, 1H), 7.65-7.19 (m, 5H), 4.30-3.55 (m,

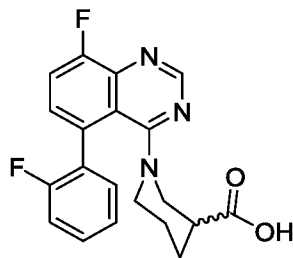
2H), 2.84-2.63 (m, 1H), 2.37-2.00 (m, 1H), 1.86-1.64 (m, 1H), 1.54-1.18 (m, 3H), 1.15-0.42 (m, 1H); MS (ESI) m/z 386.0 $[\text{C}_{20}\text{H}_{17}\text{ClFN}_3\text{O}_2 + \text{H}]^+$.

Compound 161: 1-(5-(4-chlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid



The title compound was prepared in a similar fashion as described in general procedure B starting from methyl 1-(5-bromo-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (96 mg, 0.26 mmol) and (4-chlorophenyl)boronic acid (61 mg, 0.39 mmol). The residue was purified by preparative HPLC (C18, eluent $\text{CH}_3\text{CN}/\text{H}_2\text{O}/\text{HCOOH}$ 0.01%) to afford 1-(5-(4-chlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid (8 mg, AUC HPLC 94.60%) as white solid; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 8.72-8.57 (m, 1H), 7.79-7.68 (m, 1H), 7.67-7.20 (m, 5H), 4.12-3.47 (m, 2H), 2.94-2.71 (m, 1H), 2.39-2.14 (m, 1H), 1.83-1.62 (m, 1H), 1.56-0.49 (m, 4H); MS (ESI) m/z 386.1 $[\text{C}_{20}\text{H}_{17}\text{ClFN}_3\text{O}_2 + \text{H}]^+$.

Compound 162: 1-(8-fluoro-5-(2-fluorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



Step 1: methyl 1-(8-fluoro-5-(2-fluorophenyl)quinazolin-4-yl)piperidine-3-carboxylate

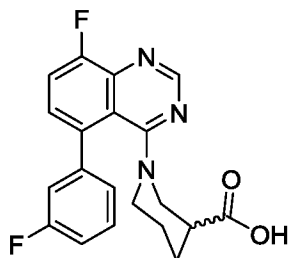
The title compound was prepared in a similar fashion as described in general procedure E starting from methyl 1-(5-bromo-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (95 mg, 0.258 mmol) and (2-chlorophenyl)boronic acid (81.31 mg, 0.52 mmol). After an aqueous work-up, the combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford methyl 1-(8-fluoro-5-(2-fluorophenyl)quinazolin-4-yl)piperidine-3-carboxylate as off-white solid; MS (ESI) m/z 384.10 $[\text{C}_{21}\text{H}_{19}\text{F}_2\text{N}_3\text{O}_2 + \text{H}]^+$. The crude product was carried forth to the next step without further purification.

Step 2: 1-(8-fluoro-5-(2-fluorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(8-fluoro-5-(2-fluorophenyl)quinazolin-4-yl)piperidine-3-carboxylate (~ 0.258 mmol).

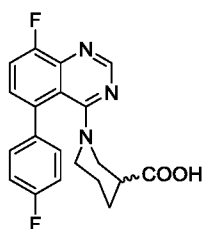
The residue was purified using reverse phase column chromatography (varian preparative HPLC: 10-70 % ACN in water) to afford 1-(8-fluoro-5-(2-fluorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (53.57 mg, 0.14 mmol, 56.1 % over 2 steps, AUC HPLC 95.56 %) as off-white solid; ^1H NMR (400 MHz, DMSO) δ (ppm): 8.75-8.60 (m, 1H), 7.82-7.60 (m, 2H), 7.50 (bs, 2H), 7.42-7.20 (m, 2H), 4.00-3.55 (m, 2H), 3.00-2.60 (m, 1H), 2.30-1.90 (m, 1H), 1.80-1.55 (m, 2H), 1.40-0.80 (m, 3H); MS (ESI) m/z 370.10 [$\text{C}_{20}\text{H}_{17}\text{F}_2\text{N}_3\text{O}_2 + \text{H}$] $^+$.

Compound 163: 1-(8-fluoro-5-(3-fluorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid

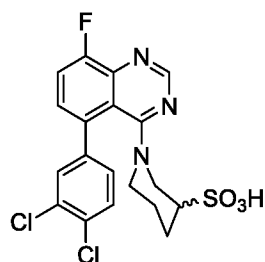


The title compound was prepared in a similar fashion as described in general procedure E starting from methyl 1-(5-bromo-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (95 mg, 0.258 mmol) and (3-fluorophenyl)boronic acid (72.75 mg, 0.52 mmol). The residue was purified by preparative HPLC (10-70 % ACN in water) to afford 1-(8-fluoro-5-(3-fluorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (27.04 mg, 0.073 mmol, 28.4 %, AUC HPLC 95.07 %) as off-white solid; ^1H NMR (400 MHz, MeOD- d_4) δ (ppm): 8.57 (s, 1H), 7.60 (2d, $J = 9.6, 8.4$ Hz, 1H), 7.55-7.43 (m, 2H), 7.28-7.13 (m, 3H), 4.60-4.20 (m, 1H), 3.90-3.50 (m, 2H), 3.10-2.60 (m, 1H), 2.00-1.75 (m, 1H), 1.70-1.25 (m, 3H), 1.00-0.80 (m, 1H); MS (ESI) m/z 370.10 [$\text{C}_{20}\text{H}_{17}\text{F}_2\text{N}_3\text{O}_2 + \text{H}$] $^+$.

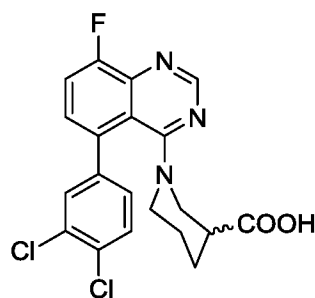
Compound 164: 1-(8-fluoro-5-(4-fluorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



The title compound was prepared in a similar fashion as described in general procedure B starting from methyl 1-(5-bromo-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (96 mg, 0.26 mmol) and (4-fluorophenyl)boronic acid (55 mg, 0.39 mmol). The residue was purified by preparative HPLC (C18, eluent $\text{CH}_3\text{CN}/\text{H}_2\text{O}/\text{HCOOH}$ 0.01%) to afford 1-(8-fluoro-5-(4-fluorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (47 mg, 49%, AUC HPLC 97.47%) as white solid; ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.74-8.58 (m, 1H), 7.78-7.67 (m, 1H), 7.65-7.23 (m, 5H), 4.12-3.50 (m, 2H), 2.92-2.68 (m, 1H), 2.41-2.13 (m, 1H), 1.85-1.21 (m, 4H), 1.17-0.52 (m, 1H); MS (ESI) m/z 370.1 [$\text{C}_{20}\text{H}_{17}\text{F}_2\text{N}_3\text{O}_2 + \text{H}$] $^+$.

Compound 165: 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-sulfonic acid

The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)-8-fluoroquinazoline (100 mg, 0.30 mmol) and piperidine-3-sulfonic acid (50.6 mg, 0.30 mmol, 1eq). The aqueous work-up yielded a precipitate that was washed in turn with water (10 mL) and pentane (10 mL), then dried under vacuum to afford 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-sulfonic acid, (29 mg, 20.26 %, HPLC 98.77%) as a white solid. ^1H NMR(400 MHz, DMSO d_6) δ (ppm): 8.77 (m, 1H), 8.10-7.84 (m, 1H), 7.84-7.58 (m, 3H), 7.57-7.27 (m, 1H), 4.90-4.50 (m, 1H), 4.15-3.90 (m, 1H), 3.70-3.30 (m, 1H), 3.30-3.10 (m, 1H), 2.35-2.10 (m, 1H), 2.00-1.80 (m, 1H), 1.70-1.60 (m, 1H), 1.60-1.50 (m, 1H), 1.50-1.20 (m, 1H); LC-MS (ESI) m/z : 456.2 [$\text{C}_{19}\text{H}_{16}\text{Cl}_2\text{FN}_3\text{O}_3\text{S}+\text{H}$] $^+$.

Compound 166: 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid**Step 1: Preparation of methyl 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate**

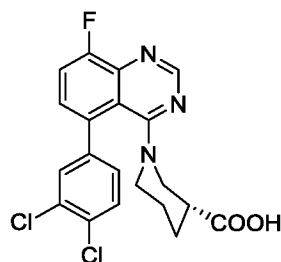
The title compound was prepared in a similar fashion as described in general procedure B starting from 5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4(3H)-one (100 mg, 0.32 mmol) and methyl piperidine-3-carboxylate (137 mg, 0.96 mmol). The residue was purified by column chromatography (silica gel, eluent $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 100:0 to 90:10) to afford methyl 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (138 mg, 99.9%).

Step 2: Preparation of 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (138 mg, 0.32 mmol) in MeOH (2 mL). The residue was purified by preparative HPLC (C18, eluents ACN/ $\text{H}_2\text{O}/\text{HCOOH}$ 0.01%) to afford 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid (22

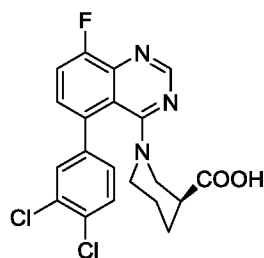
mg, 16 %, AUC HPLC 98.91%) as white solid; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 12.33 (bs, 1H), 8.73-8.60 (m, 1H), 7.82-7.64 (m, 3H), 7.60-7.28 (m, 2H), 4.20-3.46 (m, 2H), 3.00-2.71 (m, 1H), 2.44-2.13 (m, 1H), 1.83-1.65 (m, 1H), 1.61-0.55 (m, 4H); MS (ESI) m/z 420.0 $[\text{C}_{20}\text{H}_{16}\text{Cl}_2\text{FN}_3\text{O}_2 + \text{H}]^+$.

Compound 167: (R)-1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid



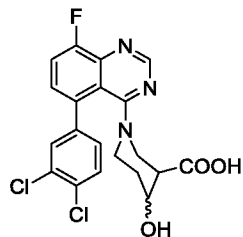
The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)-8-fluoro-3,4-dihydroquinazoline (300 mg, 0.30 mmol) and (R)-piperidine-3-carboxylic acid (182 mg, 0.48 mmol). The crude compound was purified by Preparative HPLC to afford (R)-1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid (72 mg, 15%, HPLC 99%) as an off-white solid. m.p: 238-245 °C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 12.28 (bs, 1H), 8.66-8.60 (m, 1H), 7.69 (d, $J = 8.4$ Hz, 3H), 7.51 (d, $J = 6.4$ Hz, 1H), 7.43 (s, 1H), 3.48 (d, $J = 11.2$ Hz, 2H), 2.88 (bs, 1H), 2.75-2.64 (m, 1H), 2.35-2.18 (m, 1H), 1.70 (d, $J = 11.6$ Hz, 1H), 1.46-1.17 (m, 3H); MS (ESI) m/z : 420.16 $[\text{C}_{20}\text{H}_{16}\text{Cl}_2\text{FN}_3\text{O}_2 + \text{H}]^+$.

Compound 168: (S)-1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid.



The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)-8-fluoro-3,4-dihydroquinazoline (100 mg, 0.30 mmol) and (S)-piperidine-3-carboxylic acid (62 mg, 0.48 mmol). The crude compound was purified by Preparative HPLC to afford (S)-1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid (20 mg, 15%, AUC-HPLC 99.33%) as an off-white solid. m.p: 215-226 °C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 8.67-8.61 (m, 1H), 7.71 (d, $J = 8.4$ Hz, 3H), 7.54-7.46 (m, 1H), 7.34 (bs, 1H), 3.52 (bs, 2H), 2.86 (bs, 1H), 2.70-2.67 (m, 1H), 2.60 (s, 1H), 2.12 (bs, 1H), 1.72 (bs, 1H), 1.50-1.39 (m, 2H); MS (ESI) m/z : 420.16 $[\text{C}_{20}\text{H}_{16}\text{Cl}_2\text{FN}_3\text{O}_2 + \text{H}]^+$.

Compound 169: *1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-4-hydroxypiperidine-3-carboxylic acid*



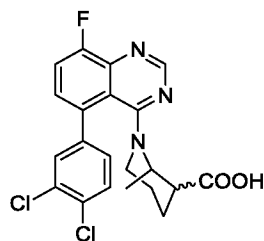
Step 1: Preparation of ethyl 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-4-hydroxypiperidine-3-carboxylate

The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)-8-fluoroquinazoline (100 mg, 0.30 mmol) and ethyl 4-hydroxypiperidine-3-carboxylate hydrochloride (83.1 mg, 0.39 mmol). The crude compound was purified by column chromatography (Silica gel (230-400 mesh), eluent $\text{CHCl}_3/\text{MeOH}$ 97.5/2.5) to afford ethyl 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-4-hydroxypiperidine-3-carboxylate (122 mg, yield 85%) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 8.72-8.56 (m, 1H), 7.79-7.63 (m, 3H), 7.60-7.50 (m, 1H), 7.45-7.31 (m, 1H), 4.95-4.80 (m, 1H), 4.20-3.85 (m, 3H), 3.70-3.40 (m, 2H), 3.1-2.90 (m, 1H), 2.85-2.60 (m, 1H), 1.70-1.30 (m, 2H), 1.30-1.10 (m, 4H).

Step 2: Preparation 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-4-hydroxypiperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from ethyl 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-4-hydroxypiperidine-3-carboxylate (110 mg, 0.23 mmol, 1eq). The aqueous work-up yielded a precipitate that was washed with pentane and dried under vacuum to afford 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-4-hydroxypiperidine-3-carboxylic acid (40.1 mg, 38.79%, AUC HPLC 88.72%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 8.78-8.48 (m, 1H), 7.88-7.60 (m, 3H), 7.60-7.20 (m, 2H), 4.28-3.80 (m, 1H), 3.70-3.45 (m, 2H), 3.05-2.90 (m, 1H), 2.9-2.70 (m, 1H), 1.65-1.10 (m, 3H), 0.95-0.55 (m, 1H); LC-MS 95.29%; m/z : 436.1 $[\text{C}_{20}\text{H}_{16}\text{Cl}_2\text{FN}_3\text{O}_3+\text{H}]^+$.

Compound 170: *1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-2-methylpiperidine-3-carboxylic acid*



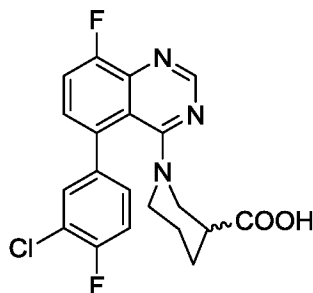
Step 1: Preparation of methyl 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-2-methylpiperidine-3-carboxylate

To a solution of 5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4(3*H*)-one (200 mg, 0.65 mmol) in acetonitrile (10 mL) was added PyBOP (670 mg, 1.30 mmol), DBU (197 mg, 1.30 mmol) and methyl 2-methylpiperidine-3-carboxylate (153 mg, 0.98 mmol). The resulting mixture was stirred at room temperature for 2 days and then diluted with water (15 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent CH₂Cl₂/MeOH 100:0 to 90:10) to afford methyl 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-2-methylpiperidine-3-carboxylate (80 mg, 27 %) as white solid.

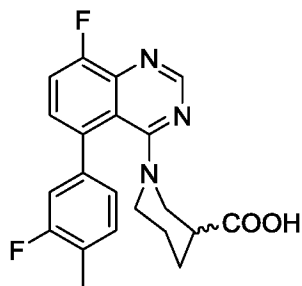
Step 2: Preparation of 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-2-methylpiperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-2-methylpiperidine-3-carboxylate (80 mg, 0.18 mmol). The residue was purified by preparative HPLC (C18, eluents ACN/H₂O/HCOOH 0.01%) to afford 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-2-methylpiperidine-3-carboxylic acid (32 mg, 41 %, AUC HPLC 96.08%) as white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 12.41 (bs, 1H), 8.73-8.62 (m, 1H), 7.82-7.64 (m, 3H), 7.63-7.36 (m, 2H), 5.44-4.25 (m, 1H), 3.63-3.15 (m, 1H), 2.96-2.58 (m, 1H), 2.27-1.40 (m, 3H), 1.32-1.18 (m, 1H), 1.00-0.61 (m, 4H); MS (ESI) *m/z* 434.0 [C₂₁H₁₈Cl₂FN₃O₂ + H]⁺.

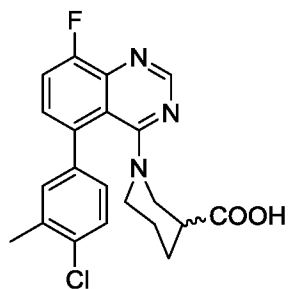
Compound 171: *1-(5-(3-chloro-4-fluorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid*



The title compound was prepared in a similar fashion as described in general procedure B starting from methyl 1-(5-bromo-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (96 mg, 0.26 mmol) and (3-chloro-4-fluorophenyl)boronic acid (68 mg, 0.39 mmol). The residue was purified by preparative HPLC (C18, eluent CH₃CN/H₂O/HCOOH 0.01%) to afford 1-(5-(3-chloro-4-fluorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid (47 mg, 45%, AUC HPLC 95.61%) as white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.72-8.56 (m, 1H), 7.78-7.61 (m, 2H), 7.57-7.28 (m, 3H), 4.21-3.49 (m, 2H), 2.97-2.65 (m, 2H), 2.43-2.12 (m, 1H), 1.84-1.66 (m, 1H), 1.60-1.34 (m, 2H), 1.21-0.55 (m, 1H); MS (ESI) *m/z* 404.0 [C₂₀H₁₆ClF₂N₃O₂ + H]⁺.

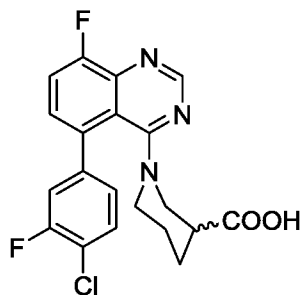
Compound 172: *1-(8-fluoro-5-(3-fluoro-4-methylphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid*

The title compound was prepared in a similar fashion as described in general procedure B starting from methyl 1-(5-bromo-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (96 mg, 0.26 mmol) and (3-fluoro-4-methylphenyl)boronic acid (60 mg, 0.39 mmol). The residue was purified by preparative HPLC (C18, eluent CH₃CN/H₂O/HCOOH 0.01%) to afford 1-(8-fluoro-5-(3-fluoro-4-methylphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (62 mg, 62%, AUC HPLC 92.24%) as white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.67-8.53 (m, 1H), 7.69 (t, *J* = 8.9, 1H), 7.53-7.41 (m, 1H), 7.40-7.30 (m, 1H), 7.29-6.99 (m, 2H), 4.19-3.50 (m, 2H), 2.96-2.66 (m, 1H), 2.42-2.07 (m, 4H), 1.87-1.62 (m, 1H), 1.52-0.56 (m, 4H); MS (ESI) *m/z* 384.1 [C₂₁H₁₉F₂N₃O₂ + H]⁺.

Compound 173: *1-(5-(4-chloro-3-methylphenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid*

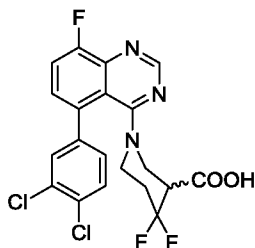
The title compound was prepared in a similar fashion as described in general procedure B starting from methyl 1-(5-bromo-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (96 mg, 0.26 mmol) and (4-chloro-3-methylphenyl)boronic acid (66 mg, 0.39 mmol). The residue was purified by preparative HPLC (C18, eluent CH₃CN/H₂O/HCOOH 0.01%) to afford 1-(5-(4-chloro-3-methylphenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid (37 mg, 36%, AUC HPLC 99.14%) as white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.69-8.56 (m, 1H), 7.75-7.65 (m, 1H), 7.64-7.08 (m, 4H), 4.21-3.58 (m, 2H), 2.90-2.62 (m, 1H), 2.44-2.10 (m, 4H), 1.82-1.64 (m, 1H), 1.54-0.60 (m, 4H); MS (ESI) *m/z* 400.1 [C₂₁H₁₉ClFN₃O₂ + H]⁺.

Compound 174: *1-(5-(4-chloro-3-fluorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid*



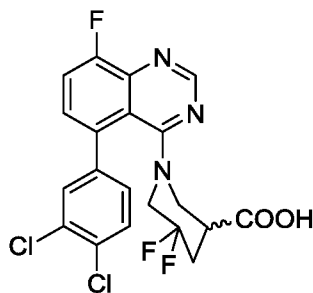
The title compound was prepared in a similar fashion as described in general procedure B starting from methyl 1-(5-bromo-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (96 mg, 0.26 mmol) and (3-chloro-4-fluorophenyl)boronic acid (68 mg, 0.39 mmol). The residue was purified by preparative HPLC (C18, eluent CH₃CN/H₂O/HCOOH 0.01%) to afford 1-(5-(3-fluorophenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (22 mg, 21%, AUC HPLC 98.60%) as white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 12.31 (s, 1H), 8.70-8.59 (m, 1H), 7.78-7.46 (m, 4H), 7.35-7.13 (m, 1H), 4.17-3.44 (m, 2H), 3.06-2.73 (m, 1H), 2.43-2.17 (m, 1H), 1.83-1.64 (m, 1H), 1.59-0.54 (m, 4H); MS (ESI) *m/z* 404.0 [C₂₀H₁₆ClF₂N₃O₂ + H]⁺.

Compound 175: *1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-4,4-difluoropiperidine-3-carboxylic acid*



The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)-8-fluoro-3,4-dihydroquinazoline (70 mg, 0.21 mmol) and 4,4-difluoropiperidine-3-carboxylic acid (85 mg, 0.42 mmol). The crude compound was purified by preparative HPLC to afford the racemic 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-4,4-difluoropiperidine-3-carboxylic acid (15 mg, 8%, LC-MS 99.43%, AUC-HPLC 95.04%) as an off-white solid mp. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.71 (s, 1H), 7.74 (q, *J* = 8.8 Hz, 3H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.40 (bs, 1H), 3.16 (bs, 1H), 2.32-2.14 (m, 1H), 1.90 (bs, 1H), 1.77 (bs, 1H), 1.23 (s, 1H), 1.14 (bs, 1H), 0.84 (d, *J* = 7.6 Hz, 1H); MS (ESI) *m/z*: 456.17 [C₂₀H₁₄Cl₂F₃N₃O₂+H]⁺.

Compound 176: 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-5,5-difluoropiperidine-3-carboxylic acid



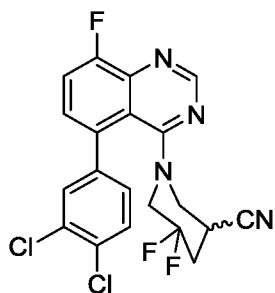
Step 1: Preparation of methyl 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-5,5-difluoropiperidine-3-carboxylate

The title compound was prepared in a similar fashion as described in general procedure D starting from 5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4(3*H*)-one (130 mg, 0.42 mmol) and methyl 5,5-difluoropiperidine-3-carboxylate hydrochloride (181 mg, 0.84 mmol). The residue was purified by column chromatography (silica gel, eluent CH₂Cl₂/MeOH 100:0 to 90:10) to afford methyl 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-5,5-difluoropiperidine-3-carboxylate (70 mg, 35%).

Step 2: Preparation of 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-5,5-difluoropiperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-5,5-difluoropiperidine-3-carboxylate (70 mg, 0.15 mmol). The residue was purified by preparative HPLC (C18, eluents ACN/H₂O/HCOOH 0.01%) to afford 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-5,5-difluoropiperidine-3-carboxylic acid (19 mg, 28%, AUC HPLC 97.23%) as white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.84-8.70 (m, 1H), 8.18-7.03 (m, 5H), 4.65-4.07 (m, 1H), 3.00-2.67 (m, 2H), 2.28-0.84 (m, 4H); MS (ESI) *m/z* 456.0 [C₂₀H₁₄Cl₂F₃N₃O₂ + H]⁺.

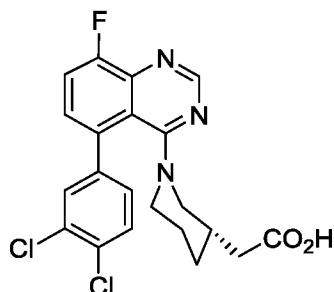
Compound 177: 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-5,5-difluoropiperidine-3-carbonitrile



The title compound was prepared in a similar fashion as described in general procedure D starting from 5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4(3*H*)-one (227 mg, 0.73 mmol) and 5,5-difluoropiperidine-3-carbonitrile hydrochloride (400 mg, 2.19 mmol). The residue was purified by

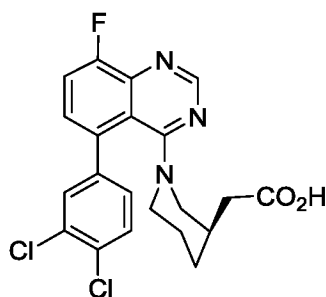
column chromatography (silica gel, eluent $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 100:0 to 90:10) and preparative HPLC (C18, eluent $\text{CH}_3\text{CN}/\text{H}_2\text{O}/\text{HCOOH}$ 0.01%) to afford 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-5,5-difluoropiperidine-3-carbonitrile (4 mg, AUC HPLC 98.77%) as white solid; ^1H NMR (400 MHz, $\text{MeOD}-d_4$) δ (ppm): 8.76 (s, 1H), 8.06-7.18 (m, 5H), 4.78-3.79 (m, 1H), 3.72-3.36 (m, 2H), 3.19-2.94 (m, 1H), 2.71-1.52 (m, 3H); MS (ESI) m/z 437.0 [$\text{C}_{20}\text{H}_{13}\text{Cl}_2\text{F}_3\text{N}_4 + \text{H}$] $^+$.

Compound 178: (S)-2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetic acid



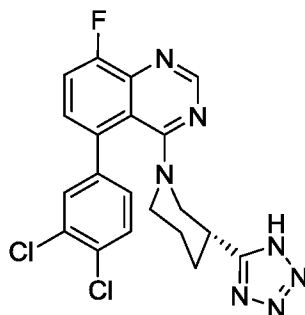
The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)-8-fluoroquinazoline (350 mg, 1.067 mmol) and (S)-2-(piperidin-3-yl)acetic acid (244 mg, 1.70 mmol). The crude compound was purified by preparative HPLC to afford (S)-2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetic acid (60 mg, AUC-HPLC 95.61%) as an off-white solid. mp: 152-161 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 8.67-8.59 (m, 1H), 7.75-7.68 (m, 3H), 7.52-7.36 (m, 2H), 4.02 (m, 1H), 3.72-3.52 (m, 1H), 2.65-2.60 (m, 1H), 2.25-1.90 (m, 3H), 1.80-1.55 (m, 2H), 1.45-1.50 (m, 1H), 1.20-1.0 (m, 1H), 1.01-0.82 (m, 1H); MS (ESI) m/z : 434.29 [$\text{C}_{21}\text{H}_{18}\text{Cl}_2\text{FN}_3\text{O}_2 + \text{H}$] $^+$

Compound 179: (R)-2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetic acid



The title compound was prepared in a similar fashion as described in general procedure B starting from 4-chloro-5-(3,4-dichlorophenyl)-8-fluoroquinazoline (160 mg, 0.487 mmol) and (R)-2-(piperidin-3-yl)acetic acid (111 mg, 0.780 mmol). The crude compound was purified by preparative HPLC to afford (R)-2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetic acid (25 mg, 12%, AUC-HPLC 95.23%) as an off-white solid. mp: 151-164 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 8.67-8.59 (m, 1H), 7.75-7.68 (m, 3H), 7.52-7.37 (m, 2H), 4.02 (m, 1H), 3.7-3.52 (m, 1H), 2.65-2.6 (m, 1H), 2.25-1.9 (m, 3H), 1.8-1.55 (m, 2H), 1.45-1.5 (m, 1H), 1.20-1.0 (m, 1H), 1.0-0.80 (m, 1H); MS (ESI) m/z : 434.29 [$\text{C}_{21}\text{H}_{18}\text{Cl}_2\text{FN}_3\text{O}_2 + \text{H}$] $^+$

Compound 180: (R)-4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(3,4-dichlorophenyl)-8-fluoroquinazoline



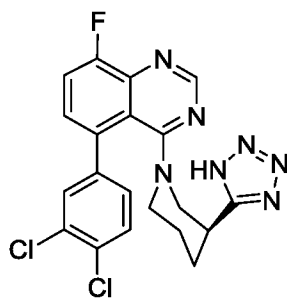
Step 1: (R)-2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetonitrile:

The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)-8-fluoro-3,4-dihydroquinazoline (250 mg, 0.762 mmol) and (R)-piperidine-3-carbonitrile (150 mg, 1.37 mmol). The crude compound was purified by column chromatography (silica gel, eluent pet-ether/EtOAc 70:30) to afford (R)-1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carbonitrile (100 mg, 32%, LC-MS 71%) as a viscous liquid. MS (ESI) m/z : 401.21 [$C_{20}H_{15}Cl_2FN_4+3$]⁺.

Step-2: (R)-4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(3,4-dichlorophenyl)-8-fluoroquinazoline

The title compound was prepared in a similar fashion as described in general procedure B starting from (R)-1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carbonitrile (100 mg, 0.250 mmol). The crude compound was purified by preparative HPLC to afford (R)-4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(3,4-dichlorophenyl)-8-fluoroquinazoline (32 mg, 28%, AUC-HPLC 99.43%) as an off-white solid. m.p: 220–272 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 16.2 (bs, 1H), 8.69 (d, J = 13.2 Hz, 1H), 7.75 (d, J = 11.2 Hz, 3H), 7.55 (bs, 1H), 7.49 (d, J = 7.2 Hz, 1H), 3.98 (bs, 1H), 3.65 (bs, 1H), 3.10 (bs, 1H), 2.91–2.77 (m, 2H), 2.32–2.10 (m, 1H), 1.94 (d, J = 11.2 Hz, 1H), 1.57 (bs, 1H), 1.43–1.27 (m, 1H); MS (ESI) m/z : 444.19 [$C_{20}H_{16}Cl_2FN_7+H$]⁺.

Compound 181: (S)-4-(3-(1H-tetrazol-5-yl)piperidin-1-yl)-5-(3,4-dichlorophenyl)-8-fluoroquinazoline



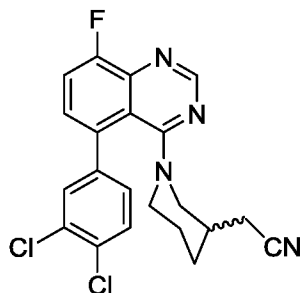
Step 1: *(S)*-1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carbonitrile:

The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)-8-fluoro-3,4-dihydroquinazoline (200 mg, 0.609 mmol) and *(S)*-piperidine-3-carbonitrile (107 mg, 0.975 mmol). The crude compound was purified by column chromatography (silica gel, eluent pet-ether/EtOAc 60:40) to afford *(S)*-1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carbonitrile (185 mg, 76%, LC-MS 82%) as a yellow solid. MS (ESI) m/z : 401.21 $[\text{C}_{20}\text{H}_{15}\text{Cl}_2\text{FN}_4+\text{H}]^+$.

Step-2: *(S)*-4-(3-(1*H*-tetrazol-5-yl)piperidin-1-yl)-5-(3,4-dichlorophenyl)-8-fluoroquinazoline

The title compound was prepared in a similar fashion as described in general procedure F starting from *(S)*-1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carbonitrile (180 mg, 0.450 mmol). The crude compound was purified by preparative HPLC to afford *(S)*-4-(3-(1*H*-tetrazol-5-yl)piperidin-1-yl)-5-(3,4-dichlorophenyl)-8-fluoroquinazoline (56 mg, 28%, AUC-HPLC 90.28%) as an off-white solid. m.p: 275–283 °C. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 16.2 (bs, 1H), 8.67 (d, $J = 11.2$ Hz, 1H), 7.71 (t, $J = 11.2$ Hz, 3H), 7.53–7.45 (m, 2H), 3.96 (d, $J = 12$ Hz, 1H), 3.61 (d, $J = 12.8$ Hz, 1H), 2.89 (t, $J = 10.8$ Hz, 2H), 2.30–2.05 (m, 1H), 1.93 (d, $J = 10.8$ Hz, 1H), 1.56–1.53 (m, 1H), 1.42–1.21 (m, 2H); MS (ESI) m/z : 444.16 $[\text{C}_{20}\text{H}_{16}\text{Cl}_2\text{FN}_7+\text{H}]^+$.

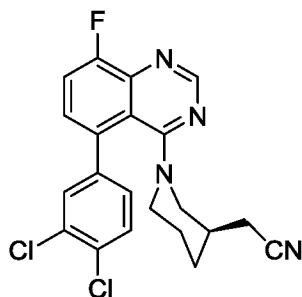
Compound 182: 2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetonitrile



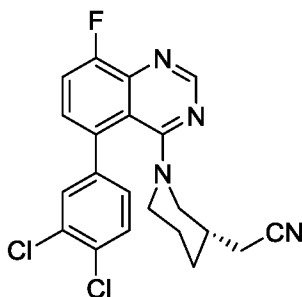
The title compound was prepared in a similar fashion as described in general procedure D starting from 5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4(3*H*)-one (100 mg, 0.32 mmol) and 2-(piperidin-3-yl)acetonitrile (79.48 mg, 0.64 mmol). The residue was purified using combiflash (silica gel, 100% DCM to DCM: MeOH 90:10) to afford racemic 2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetonitrile (12.65 mg, 0.03 mmol, 9.5 %, AUC HPLC 99.35 %) as white solid; ^1H NMR (400 MHz, MeOD- d_4) δ (ppm): 8.67 & 8.57 (2s, 1H), 7.70-7.43 (m, 4H), 8.53-8.44 & 7.42-7.35 (2m, 1H), 4.30-4.15 & 3.90-3.65 (2m, 2H), 2.73 & 2.55 (2t, $J = 11.4$ Hz, 1H), 2.30 (d, $J = 13.2$ Hz, 3H), 1.90-1.70 (m, 1H), 1.69-1.40 (m, 1H), 1.39-1.00 (m, 2H), 0.95-0.70 (m, 1H); MS (ESI) m/z 415.00 $[\text{C}_{21}\text{H}_{17}\text{Cl}_2\text{FN}_4 + \text{H}]^+$.

Compound 183: *(R)*-2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetonitrile and

Compound 184: *(S)*-2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetonitrile



Example 183



Example 184

Racemic 2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetonitrile (1.05 g) was resolved by SFC chiral HPLC (Chiralpack-IC (250 x 4.6) mm, 5 μ , column) to afford Compound 183 enantiomer-1 (*R*, isomer, 360 mg, retention time 10.15 min, AUC- HPLC 95.24%, AUC-chiral HPLC 99.58%) and Compound 184 enantiomer-2 (*S* isomer, 375 mg, retention time 16.84 min, AUC-HPLC 89.0%, AUC-chiral HPLC 99.92%)

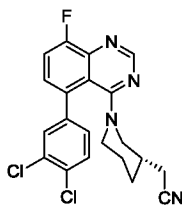
(R)-2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetonitrile;

An analytical sample of *R*-enantiomer (~50 mg) was re-purified by preparative HPLC to yield a pure isomer (22 mg, AUC HPLC: 99.90%). ¹H NMR(400 MHz, CDCl₃) δ (ppm): 8.85-8.65 (m, 1H), 7.60-7.44 (m, 3H), 7.44-7.31 (m, 2H), 4.40-4.20 (m, 0.5H), 3.85-3.50 (m, 1.5H), 2.80-2.50 (m, 1.5H), 1.95-1.80 (m, 0.5H), 2.30-2.10 (m, 2H), 2.10-1.80 (m, 1H), 1.80-1.70 (m, 1H), 1.65-1.50 (m, 2H), 1.50-1.30 (m, 1H). MS (ESI) m/z : 415.2 [C₂₁H₁₇Cl₂FN₄+H]⁺. [α]²⁰ = +152.39 (c= 0.104 , chloroform)

(S)-2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetonitrile

An analytical sample of *S*-enantiomer of approximately (~50 mg) was re-purified by preparative HPLC to yield 20 mg a pure isomer (20 mg, AUC HPLC: 99.89 %). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.85-8.65 (m, 1 H), 7.65-7.44 (m, 3 H), 7.44-7.30 (m, 2H), 4.40-4.20 (m, 0.5H), 3.85-3.90 (m, 1.5H), 2.80-2.45 (m, 1.5H), 2.45-2.30 (m, 0.5H), 2.30-2.05 (m, 2H), 2.05-1.90(m, 1H), 1.90-1.80 (m, 0.5 H), 1.80-1.70 (m, 0.5 H), 1.65-1.50 (m, 2H), 1.50-1.30 (m, 1H). MS (ESI) m/z : 415.2 [C₂₁H₁₇Cl₂FN₄+H]⁺. [α]²⁰ = -123.19 (c= 0.103 , chloroform)

Compound 184: *(S)*-2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetonitrile

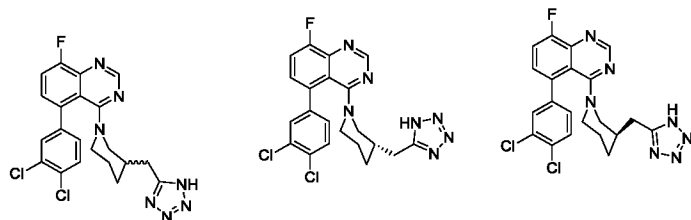


The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)-8-fluoro-3,4-dihydroquinazoline (150 mg, 0.457 mmol) and (S)-2-(piperidin-3-yl)acetonitrile (102 mg, 0.823 mmol). The crude compound was purified by preparative HPLC to afford (S)-2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetonitrile (15 mg, HPLC 95.04%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.72–8.62 (m, 1H), 7.74 (t, *J* = 8.4 Hz, 3H), 7.55–7.40 (m, 2H), 3.65 (d, *J* = 10 Hz, 2H), 2.40–2.32 (m, 3H), 2.27–2.15 (m, 1H), 1.75–1.47 (m, 2H), 1.29–1.23 (m, 1H), 1.14 (bs, 1H), 0.95 (d, *J* = 11.6 Hz, 1H); MS (ESI) *m/z*: 415.20 [C₂₁H₁₇Cl₂FN₄+H]⁺.

Compound 185: (racemic)-4-(3-((1*H*-tetrazol-5-yl)methyl)piperidin-1-yl)-5-(3,4-dichlorophenyl)-8-fluoroquinazoline

Compound 186: (S)-4-(3-((1*H*-tetrazol-5-yl)methyl)piperidin-1-yl)-5-(3,4-dichlorophenyl)-8-fluoroquinazoline and

Compound 187: (R)-4-(3-((1*H*-tetrazol-5-yl)methyl)piperidin-1-yl)-5-(3,4-dichlorophenyl)-8-fluoroquinazoline



Step 1: 2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetonitrile:

The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)-8-fluoro-3,4-dihydroquinazoline (700 mg, 2.13 mmol) and 2-(piperidin-3-yl)acetonitrile (476 mg, 3.84 mmol). The residue was purified by column chromatography (silica gel, eluent pet-ether/EtOAc 70/30) to afford racemic 2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetonitrile (650 mg, 73%, LC-MS 84%) as a white solid. MS (ESI) *m/z*: 415.42 [C₂₁H₁₇Cl₂FN₄+H]⁺.

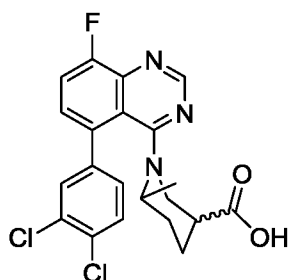
Step 2: (R) and (S)-4-(3-((1*H*-tetrazol-5-yl)methyl)piperidin-1-yl)-5-(3,4-dichlorophenyl)-8-fluoroquinazoline

The title compound was prepared in a similar fashion as described in general procedure F starting from racemic 2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetonitrile (300 mg, 0.72 mmol). The crude compound was purified by preparative HPLC to afford racemic 4-(3-((1*H*-tetrazol-5-yl)methyl)piperidin-1-yl)-5-(3,4-dichlorophenyl)-8-fluoroquinazoline (250 mg, 54%, HPLC-97%) as an off-white solid. Further purification by chiral prep-HPLC gave (S)-4-(3-((1*H*-tetrazol-5-yl)methyl)piperidin-1-yl)-5-(3,4-dichlorophenyl)-8-fluoroquinazoline (29 mg, AUC-HPLC 98%) and (R)-4-(3-((1*H*-tetrazol-5-yl)methyl)piperidin-1-yl)-5-(3,4-dichlorophenyl)-8-fluoroquinazoline (45 mg, AUC-HPLC 99.05%).

(S)-4-(3-((1*H*-tetrazol-5-yl)methyl)piperidin-1-yl)-5-(3,4-dichlorophenyl)-8-fluoroquinazoline: off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.68–8.57 (m, 1H), 7.75–7.68 (m, 3H), 7.50 (t, *J* = 6.8 Hz, 1H), 7.34 (bs, 1H), 3.76–3.50 (m, 2H), 2.72–2.64 (m, 3H), 2.21 (d, *J* = 11.2 Hz, 1H), 1.51 (bs, 2H), 1.30 (bs, 1H), 1.11 (bs, 1H), 0.94–0.85 (m, 1H); MS (ESI) *m/z*: 458.19 [C₂₁H₁₈Cl₂FN₇ + H]⁺

(R)-4-(3-((1*H*-tetrazol-5-yl)methyl)piperidin-1-yl)-5-(3,4-dichlorophenyl)-8-fluoroquinazoline: off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.68–8.57 (m, 1H), 7.75–7.33 (m, 5H), 4.01–3.97 (m, 1H), 3.73–3.57 (m, 2H), 2.73–2.66 (m, 3H), 2.21 (d, *J* = 11.2 Hz, 1H), 1.51 (bs, 2H), 1.29 (bs, 1H), 1.11 (bs, 1H); MS (ESI) *m/z*: 458.22 [C₂₁H₁₈Cl₂FN₇ + H]⁺.

Compound 188: *Cis-1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-methylpiperidine-3-carboxylic acid*

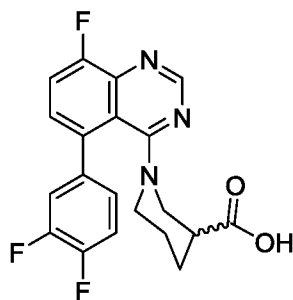


Step 1: *methyl cis-1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-methylpiperidine-3-carboxylate*

The title compound was prepared in a similar fashion as described in general procedure D starting from 5-(3,4-dichlorophenyl)quinazolin-4(3*H*)-one (80 mg, 0.259 mmol) and methyl *cis*-6-methylpiperidine-3-carboxylate (81.37 mg, 0.518 mmol). The residue was purified by column chromatography (silica gel, 100% DCM to DCM: MeOH 90:10) to afford methyl *cis*-1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-methylpiperidine-3-carboxylate (5 mg, 0.011 mmol) as a yellow thick gel; MS (ESI) *m/z* 448.10 [C₂₂H₂₀Cl₂FN₃O₂ + H]⁺.

Step 2: *cis-1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-methylpiperidine-3-carboxylic acid*

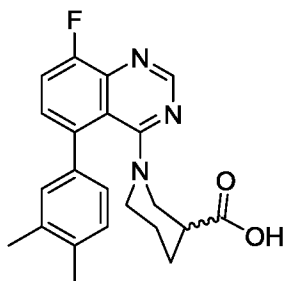
The title compound was prepared in a similar fashion as described in general procedure C starting from methyl *cis*-1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-methylpiperidine-3-carboxylate (5 mg, 0.011 mmol). The residue was purified by preparative HPLC to afford *Cis*-1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-methylpiperidine-3-carboxylic acid (0.70 mg, 1.61 μmol, 14.7 %, AUC HPLC 99.19 %) as white solid; ¹H NMR (400 MHz, MeOD-*d*₄) δ (ppm): 8.60 & 8.53 (2s, 1H), 7.70–7.55 (m, 3H), 7.54–7.40 (m, 2H), 5.15–5.05 & 4.35–4.25 (2m, 1H), 4.56 (s, 1H), 4.00–3.85 & 3.75–3.60 (m, 1H), 3.55–3.50 & 3.10–2.95 (m, 1H), 2.60–2.45 & 2.40–2.30 (m, 1H), 1.70–1.40 (m, 3H), 1.05–0.95 (m, 1H), 0.94–0.80 (m, 2H); MS (ESI) *m/z* 434.00 [C₂₁H₁₈Cl₂FN₃O₂ + H]⁺.

Compound 189: 1-(5-(3,4-difluorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid**Step 1: 1 methyl 1-(5-(3,4-difluorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate**

The title compound was prepared in a similar fashion as described in general procedure E starting from methyl 1-(5-bromo-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (95 mg, 0.258 mmol) and (3,4-difluorophenyl)boronic acid (82.11 mg, 0.52 mmol), Pd(dppf)Cl₂.CH₂Cl₂ (21.07 mg, 0.0258 mmol). The crude methyl 1-(5-(3,4-difluorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate as off-white solid; MS (ESI) *m/z* 402.10 [C₂₁H₁₈F₃N₃O₂ + H]⁺, was used without further purification in the next step.

Step 2: 1-(5-(3,4-difluorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(3,4-difluorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (~ 0.258 mmol). The residue was purified by preparative HPLC to afford 1-(5-(3,4-difluorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid (59.17 mg, 0.15 mmol, 59.2 % over 2 steps, AUC HPLC 98.10 %) as off-white solid; ¹H NMR (400 MHz, MeOD-*d*₄) δ (ppm): 8.58 (s, 1H), 7.60 (2d, *J* = 8.4 Hz, 1H), 7.50 (2d, *J* = 5.4 Hz, 1H), 7.35 (bs, 2H), 7.20 (bs, 1H), 4.75-4.40 (m, 2H), 3.80-3.50 (m, 2H), 3.00-2.75 (m, 1H), 2.50-2.30 & 1.10-0.80 (2m, 1H), 1.95-1.65 (m, 1H), 1.64-1.10 (m, 2H); MS (ESI) *m/z* 388.10 [C₂₀H₁₆F₃N₃O₂ + H]⁺.

Compound 190: 1-(5-(3,4-dimethylphenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid**Step 1: methyl 1-(5-(3,4-dimethylphenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate**

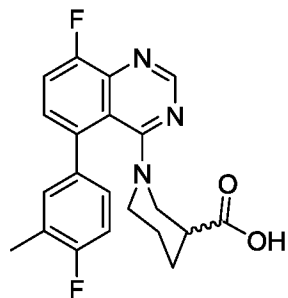
The title compound was prepared in a similar fashion as described in general procedure E starting from methyl 1-(5-bromo-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (95 mg, 0.258 mmol) and (3,4-dimethylphenyl)boronic acid (77.44 mg, 0.52 mmol), Pd(dppf)Cl₂.CH₂Cl₂ (21.07 mg, 0.0258 mmol). The combined organic layers were dried over sodium sulfate, filtered and concentrated under

reduced pressure to afford methyl 1-(5-(3,4-dimethylphenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate as off-white solid; MS (ESI) m/z 394.10 [$C_{23}H_{24}FN_3O_2 + H$] $^+$. The crude product was used without further purification in the next step.

Step 2: 1-(5-(3,4-dimethylphenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(3,4-dimethylphenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (~ 0.258 mmol). The residue was purified using reverse phase column chromatography (Varian preparative HPLC: 10-70 % ACN in water) to afford 1-(5-(3,4-dimethylphenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid (70.84 mg, 0.187 mmol, 72.4 % over 2 steps, AUC HPLC 99.37 %) as white solid; ^1H NMR (400 MHz, MeOD- d_4) δ (ppm): 8.53 (s, 1H), 7.57 (2d, $J = 8.4$ Hz, 1H), 7.45 (2d, $J = 5.4$ Hz, 1H), 7.21 (d, $J = 7.6$ Hz, 2H), 7.16-7.02 (m, 1H), 4.80-4.60 (m, 1H), 4.00-3.70 (m, 1H), 3.69-3.50 (m, 1H), 3.00-2.70 (m, 1H), 2.34 (s, 6H), 2.25 (s, 1H), 2.00-1.75 (m, 1H), 1.70-1.30 (m, 2H), 1.29-0.80 (m, 1H); MS (ESI) m/z 380.10 [$C_{22}H_{22}FN_3O_2 + H$] $^+$.

Compound 191: 1-(8-fluoro-5-(4-fluoro-3-methylphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid



Step 1: methyl 1-(8-fluoro-5-(4-fluoro-3-methylphenyl)quinazolin-4-yl)piperidine-3-carboxylate

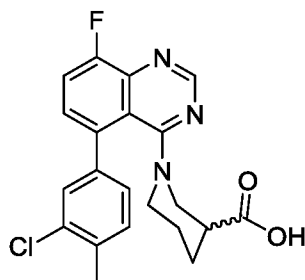
The title compound was prepared in a similar fashion as described in general procedure E starting from methyl 1-(5-bromo-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (95 mg, 0.258 mmol) and (4-fluoro-3-methylphenyl)boronic acid (80.05 mg, 0.52 mmol). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford methyl 1-(8-fluoro-5-(4-fluoro-3-methylphenyl)quinazolin-4-yl)piperidine-3-carboxylate as off-white solid; MS (ESI) m/z 398.10 [$C_{22}H_{21}F_2N_3O_2 + H$] $^+$. The crude product was carried forth to the next step without further purification.

Step 2: 1-(8-fluoro-5-(4-fluoro-3-methylphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(8-fluoro-5-(4-fluoro-3-methylphenyl)quinazolin-4-yl)piperidine-3-carboxylate (~ 0.258 mmol). The residue was purified using preparative HPLC (C18, 10-70 % ACN in water) to afford 1-(8-fluoro-5-(4-fluoro-3-methylphenyl)quinazolin-4-yl)piperidine-3-carboxylic acid (60.02 mg, 0.16 mmol, 60.67 % over 2 steps, AUC HPLC 98.53 %) as white solid; ^1H NMR (400 MHz, MeOD- d_4) δ (ppm): 8.56 (s, 1H), 7.58 (2d, $J = 8.4, 8.0$ Hz, 1H), 7.48 (d, $J = 5.2$ Hz, 1H), 7.46 (d, $J =$

5.2 Hz, 1H), 7.15-7.10 (m, 1H), 7.03-6.90 (m, 1H), 3.90-3.50 (m, 2H), 3.10-2.70 (m, 1H), 2.34 (s, 3H), 2.26 (s, 3H), 1.90-1.60 (m, 1H), 1.50-1.20 (m, 2H); MS (ESI) m/z 384.10 [$C_{21}H_{19}ClF_2N_3O_2 + H$] $^+$.

Compound 192: methyl 1-(5-(3-chloro-4-methylphenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate



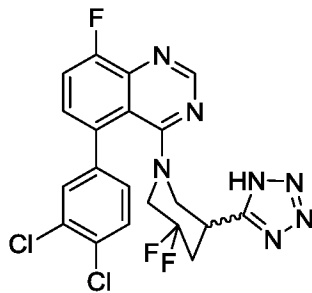
Step 1: methyl 1-(5-(3-chloro-4-methylphenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate

The title compound was prepared in a similar fashion as described in general procedure E starting from methyl 1-(5-bromo-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (95 mg, 0.258 mmol) and (3-chloro-4-methylphenyl)boronic acid (88.61 mg, 0.52 mmol). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford methyl 1-(5-(3-chloro-4-methylphenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate as an off-white solid; MS (ESI) m/z 414.10 [$C_{22}H_{21}FN_3O_2 + H$] $^+$. The crude product was carried forth to the next step without further purification.

Step 2: 1-(5-(3-chloro-4-methylphenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid

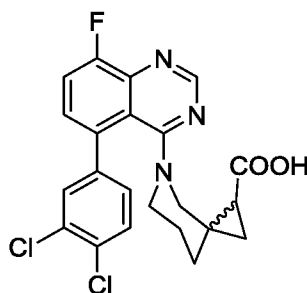
The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(3-chloro-4-methylphenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylate (~0.258 mmol). The residue was purified by preparative HPLC (C18: 10-70 % ACN in water) to afford 1-(5-(3-chloro-4-methylphenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid (29.7 mg, 0.074 mmol, 28.8 % over 2 steps, AUC HPLC 97.09 %) as white solid; ^1H NMR (400 MHz, MeOD) δ (ppm): 8.57 (s, 1H), 7.59 (2d, $J = 10.0$, 8.4 Hz, 1H), 7.49 (2d, $J = 5.4$ Hz, 1H), 7.45-7.37 (m, 2H), 7.35-7.20 (m, 1H), 3.80-3.55 (m, 2H), 3.10-2.95 (m, 1H), 2.90-2.60 (m, 1H), 2.40-2.20 (m, 1H), 2.00-1.70 (m, 1H), 1.69-1.40 (m, 3H), 1.39-1.20 (m, 2H), 1.00-0.85 (m, 1H); MS (ESI) m/z 400.10 [$C_{21}H_{19}ClFN_3O_2 + H$] $^+$.

Compound 193: 5-(3,4-dichlorophenyl)-4-(3,3-difluoro-5-(1H-tetrazol-5-yl)piperidin-1-yl)-8-fluoroquinazoline



The title compound was prepared in a similar fashion as described in general procedure F starting from 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-5,5-difluoropiperidine-3-carbonitrile (113 mg, 0.26 mmol). The residue was purified by preparative HPLC (C18, eluents ACN/H₂O/HCOOH 0.01%) to afford 5-(3,4-dichlorophenyl)-4-(3,3-difluoro-5-(1H-tetrazol-5-yl)piperidin-1-yl)-8-fluoroquinazoline (31 mg, 25 %, AUC HPLC 99.94%) as white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.94-8.69 (m, 1H), 8.09-7.22 (m, 5H), 4.81-4.20 (m, 1H), 3.92-3.50 (m, 2H), 3.06-2.58 (m, 3H), 2.45-2.10 (m, 1H); (ESI) *m/z* 480.0 [C₂₀H₁₄Cl₂F₃N₇+ H]⁺.

Compound 194: 5-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-5-azaspiro[2.5]octane-1-carboxylic acid



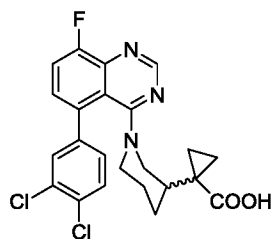
Step 1: Preparation of methyl 5-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-5-azaspiro[2.5]octane-1-carboxylate

To a solution of 5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4(3H)-one (200 mg, 0.65 mmol) in acetonitrile (10 mL) was added PyBOP (670 mg, 1.30 mmol), DBU (197 mg, 1.30 mmol) and methyl 5-azaspiro[2.5]octane-1-carboxylate (166 mg, 0.98 mmol). The resulting mixture was stirred at room temperature for 3 days and then diluted with water (15 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent CH₂Cl₂/MeOH 100:0 to 90:10) to afford methyl 5-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-5-azaspiro[2.5]octane-1-carboxylate (65 mg, 22 %) as white solid.

Step 2: Preparation of 5-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-5-azaspiro[2.5]octane-1-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 5-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-5-azaspiro[2.5]octane-1-carboxylate (65 mg, 0.14 mmol). The residue was purified by preparative HPLC (C18, eluents ACN/H₂O/HCOOH 0.01%) to afford 5-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-5-azaspiro[2.5]octane-1-carboxylic acid (5 mg, 8%, AUC HPLC 96.46%) as white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.67-8.53 (m, 1H), 7.80-7.65 (m, 3H), 7.59-7.53 (m, 1H), 7.51-7.34 (m, 1H), 3.57-3.46 (m, 1H), 3.07-2.73 (m, 1H), 2.47-1.94 (m, 3H), 1.77-0.96 (m, 4H), 0.84-0.12 (m, 2H); MS (ESI) *m/z* 446.0 [C₂₂H₁₈Cl₂FN₃O₂ + H]⁺.

Compound 195: 1-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)cyclopropane-1-carboxylic acid



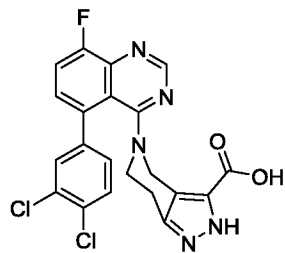
Step 1: Preparation of methyl 1-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)cyclopropane-1-carboxylate

The title compound was prepared in a similar fashion as described in general procedure D starting from 5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4(3*H*)-one (200 mg, 0.64 mmol) and methyl 1-(piperidin-3-yl)cyclopropane-1-carboxylate hydrochloride (211 mg, 0.96 mmol). The residue was purified by flash column (silica gel, 100% DCM to DCM: MeOH 90:10) to afford methyl 1-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)cyclopropane-1-carboxylate (108 mg, 36%) as yellow solid.

Step 2: Preparation of 1-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)cyclopropane-1-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)cyclopropane-1-carboxylate (108 mg, 0.23 mmol). The residue was purified by preparative HPLC (C18, eluents ACN/H₂O/HCOOH 0.01%) to afford 1-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)cyclopropane-1-carboxylic acid (16 mg, 15%, AUC HPLC 98.73%) as white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.75-8.50 (m, 1H), 7.92-7.28 (m, 5H), 4.01-3.49 (m, 2H), 2.47-2.06 (m, 2H), 1.63-1.08 (m, 5H), 1.07-0.88 (m, 2H), 0.83-0.44 (m, 2H); MS (ESI) *m/z* 460.1 [C₂₃H₂₀Cl₂FN₃O₂ + H]⁺.

Compound 196: 5-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-3-carboxylic acid



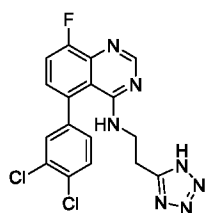
Step 1: methyl 5-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine-3-carboxylate

To a solution of 5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4(3H)-one (250 mg, 0.81 mmol) in acetonitrile (4 mL) was added methyl 4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-3-carboxylate dihydrochloride (411 mg, 1.62 mmol), DBU (246 mg, 1.62 mmol) and PyBOP (843 mg, 1.62 mmol). The reaction mixture was stirred at room temperature overnight under nitrogen, was then diluted with water (15 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers was dried over sodium sulfate, filtered and concentrated under reduced pressure to afford methyl 5-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine-3-carboxylate as off-white solid, MS (ESI) m/z 472.00 [$C_{22}H_{16}Cl_2FN_5O_2 + H$] $^+$.

Step 2: 5-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 5-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-3-carboxylate (~ 0.81 mmol). The residue was purified by preparative HPLC to afford 5-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-3-carboxylic acid (3.25 mg, 8.76 μ mol, AUC HPLC 96.94 %) as white solid; ^1H NMR (400 MHz, MeOD- d_4) δ (ppm): 8.67 (s, 1H), 7.77-7.68 (m, 2H), 7.65-7.59 (m, 1H), 7.58-7.53 & 7.52-7.45 (2m, 1H), 7.41 (d, J = 7.6 Hz, 1H), 4.27-4.10 (m, 2H), 3.25-3.10 (m, 4H), 2.95-2.85 (m, 1H), 2.75-2.65 (m, 1H); MS (ESI) m/z 458.00 [$C_{21}H_{14}Cl_2FN_5O_2 + H$] $^+$.

Compound 197: N-(2-(1H-tetrazol-5-yl)ethyl)-5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-amine.



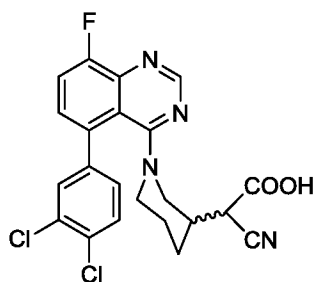
Step-1: Preparation of 3-((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)amino)propanenitrile

The title compound was prepared in a similar fashion as described in general procedure B starting from 4-chloro-5-(3,4-dichlorophenyl)-8-fluoroquinazoline (100 mg, 0.306 mmol) and 3-aminopropanenitrile (23.6 mg, 0.337 mmol, 1.1 eq). The residue was purified by column chromatography (silica-gel, eluent Pet ether/EtOAc 1:1) to afford 3-((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)amino)propanenitrile (81 mg, yield 73.3%,) as a thick oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.72 (s, 1H), 7.65 (d, *J* = 6.8 Hz, 1H), 7.56 (bs, 1H), 7.54-7.42 (m, 1H), 7.36-7.28 (m, 1H), 7.23-7.17 (m, 1H), 5.58-5.45 (bs, 1H), 3.85-3.70 (m, 1H), 3.65-3.50 (m, 1H), 2.91-2.72 (m, 1H), 2.65-2.50 (m, 1H).

Step-2: Preparation of *N*-(2-(1*H*-tetrazol-5-yl)ethyl)-5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-amine

The title compound was prepared in a similar fashion as described in general procedure F starting from 3-((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)amino)propanenitrile (80 mg, 0.222 mmol). The residue was purified by preparative TLC (eluent CHCl₃/MeOH 90:10) to afford *N*-(2-(1*H*-tetrazol-5-yl)ethyl)-5-(3,4-dichlorophenyl)-8-fluoro-*N*-methylquinazolin-4-amine (13 mg, yield 14.4 %, AUC-HPLC 96.8%), as off-white solid. ¹H NMR(400 MHz, DMSO-*d*₆) δ (ppm): 8.57 (s, 1H), 7.74 (s, 1H), 7.70-7.65 (m, 1H), 7.54 (d, *J* = 6.4 Hz, 1H), 7.35-7.26 (m, 2H), 6.11-6.05 (m, 1H), 3.85-3.71(m, 2H), 3.1-3.0 (m, 2H). MS, *m/z*: 404.2 [C₁₇H₁₂Cl₂FN₇ + H]⁺*z*.

Compound 198: 2-cyano-2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetic acid



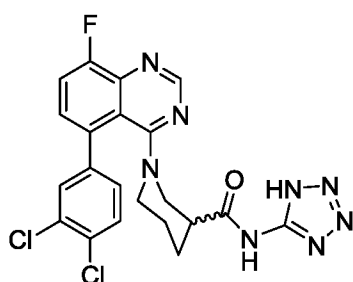
Step 1: Preparation of ethyl-2-cyano-2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetate

The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)quinazoline (129 mg, 0.395 mmol) and ethyl-2-cyano-2-(piperidin-3-yl)acetate (230 mg, 1.19 mmol). The residue was purified by column chromatography (silica gel, eluent Petroleum ether/EtOAc 8:2) to afford ethyl-2-cyano-2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetate as a mixture of diastereoisomers as white solid (50 mg, 26% yield). ¹H NMR(400 MHz, CDCl₃) δ (ppm): 8.90-8.70 (m, 1H), 7.65-7.55 (m, 3H), 7.50-7.30 (m, 2H), 4.40-4.20 (m, 2H), 3.80-3.60 (m, 2H), 3.45-3.30 (m, 1H), 3.00-2.85 (m, 1H), 2.80-2.50 (m, 2H), 1.90-1.50 (m, 4H), 0.95-0.75 (m, 3H). MS (ESI); *m/z*: 487.2 [C₂₄H₂₁Cl₂FN₄O₂+H]⁺.

Step 2: 2-cyano-2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetic acid

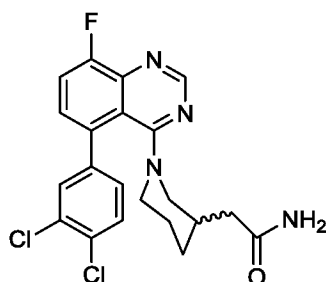
The title compound was prepared in a similar fashion as described in general procedure C starting from ethyl 2-cyano-2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetate (15 mg, 0.03 mmol). The residue was purified by preparative HPLC (C18, eluents ACN/H₂O/HCOOH 0.01%) to afford 2-cyano-2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetic acid as a mixture of diastereoisomers (8.0 mg, 58%, AUC HPLC 94.89%) as yellow solid; ¹H NMR (400 MHz, MeOD-*d*₄) δ (ppm): 8.84-8.50 (m, 1H), 8.29-7.22 (m, 6H), 4.43-3.49 (m, 2H), 2.85-2.70 (m, 1H), 2.50-2.28 (m, 1H), 2.21-0.49 (m, 6H); MS (ESI) *m/z* 459.0 [C₂₂H₁₇Cl₂FN₄O₂ + H]⁺.

Compound 199: 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-N-(1H-tetrazol-5-yl)piperidine-3-carboxamide



To a solution of 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carboxylic acid (100 mg, 0.238 mmol) and diisopropylethylamine (92.4 mg, 0.714 mmol) in DCM (10 mL), was added HATU (99.5 mg, 0.261 mmol) and 10 minutes later 1H-tetrazol-5-amine (24.3 mg, 0.286 mmol). The reaction mixture was stirred at room temperature for 20 hours and was diluted with water (10 mL), then extracted with DCM (40 mL). The organic layer was washed with brine (10 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by preparative HPLC (C18, eluents ACN/H₂O/HCOOH 0.01%) to afford racemic 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-N-(1H-tetrazol-5-yl)piperidine-3-carboxamide (2.6 mg, AUC HPLC 94.07%) as yellow solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.66 (s, 1H), 7.80-7.64 (m, 3H), 7.60-7.36 (m, 2H), 4.14-3.82 (m, 2H), 3.10-2.69 (m, 1H), 2.62-2.75 (m, 1H), 2.48-2.41 (m, 1H), 2.32-2.05 (m, 1H), 1.91-1.75 (m, 1H), 1.63-1.37 (m, 2H), 1.19-0.76 (m, 1H); MS (ESI) *m/z* 487.0 [C₂₁H₁₇Cl₂FN₈O + H]⁺.

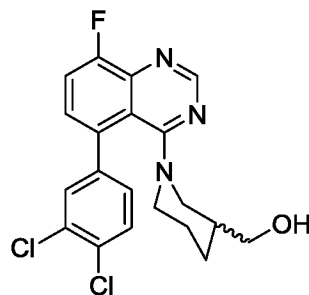
Compound 200: 2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetamide



The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)-8-fluoroquinazoline (100 mg, 0.306 mmol) and 2-(piperidin-3-

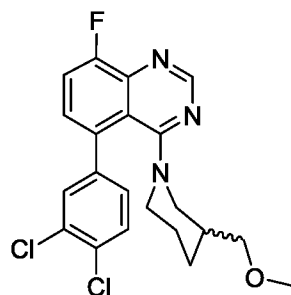
yl)acetamide hydrochloride (82.1 mg, 0.459 mmol). The residue was purified by column chromatography (silica gel, eluent $\text{CHCl}_3/\text{MeOH}$ 97:3) to afford 2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)acetamide (92 mg, 70% yield, AUC-HPLC 94.6%) as a white solid. ^1H NMR(400 MHz, CDCl_3) δ (ppm): 8.60-8.80 (m, 1H), 7.70-7.45 (m, 3H), 7.44-7.30 (m, 1H), 7.25-7.15 (m, 1H), 6.15-5.80 (m, 1H), 5.60-5.22 (m, 1H), 4.35-4.15 (m, 0.5H), 3.90-3.65 (m, 0.5H), 3.50-3.30 (m, 0.5H), 3.25-2.90 (m, 1.5 H), 2.40-2.15 (m, 2H), 2.15-1.90 (m, 2H), 1.85-1.60 (m, 1H), 1.59-1.30 (m, 1H), 1.30-1.10 (m, 1H), 1.00-0.80 (m, 1H). MS (ESI) m/z : 433.2 $[\text{C}_{21}\text{H}_{19}\text{Cl}_2\text{FN}_4\text{O} + \text{H}]^+$.

Compound 201: (1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)methanol.



The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)-8-fluoroquinazoline (100 mg, 0.306 mmol) and piperidin-3-ylmethanol hydrochloride (55.5 mg, 0.368 mmol). The reaction crude product was purified column chromatography (silica-gel, eluent using $\text{CHCl}_3/\text{MeOH}$ 97:3) to afford (1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)methanol (70 mg, yield 56.3%, HPLC: 98.98%) as pale yellow solid. ^1H NMR(400 MHz, CDCl_3) δ (ppm): 8.75-8.65 (s, 1H), 7.56-7.47 (m, 2H), 7.42-7.34 (m, 1H), 7.28-7.24 (m, 2H), 4.5-4.30 (m, 0.5H), 4.15-3.90 (m, 0.5H), 3.85-3.70 (m, 1H), 3.60-3.15 (m, 3H), 3.20-3.10 (m, 1H), 2.75-2.55 (m, 1H), 2.30-2.10 (m, 1H), 1.75-1.65 (m, 1H), 1.65-1.45 (m, 2H), 1.20-1.42 (m, 1H). MS (ESI) m/z : 406 $[\text{C}_{20}\text{H}_{18}\text{Cl}_2\text{FN}_3\text{O} + \text{H}]^+$.

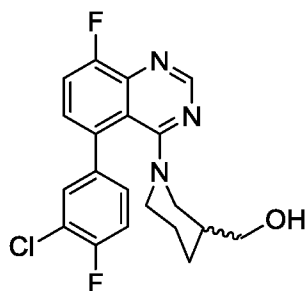
Compound 202: 5-(3,4-dichlorophenyl)-8-fluoro-4-(3-(methoxymethyl)piperidin-1-yl)quinazoline.



The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)-8-fluoroquinazoline (100 mg, 0.306 mmol) and 3-(methoxymethyl)piperidine hydrochloride (60.7 mg, 0.368 mmol). The reaction crude product was purified by column chromatography (silica gel, eluent Pet ether/EtOAc 7:3) to afford 5-(3,4-dichlorophenyl)-8-fluoro-4-(3-(methoxymethyl)piperidin-1-yl)quinazoline (53 mg, yield 41.3%, AUC-HPLC: 99.55%) as colorless gummy liquid. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.8-8.60 (m, 1H), 7.60-7.40 (m, 3H), 7.37-7.28 (m, 1H), 7.25-7.24 (m, 1H), 4.3-4.05 (m, 0.5H), 3.85-3.72 (m,

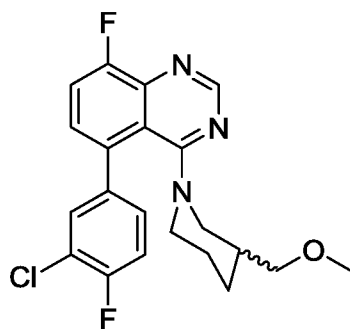
0.5H), 3.70-3.50 (m, 1H), 3.35-3.15 (m, 3H), 3.15-3.00 (m, 1H), 2.9-2.7 (m, 1H), 2.60-2.45 (m, 0.5H), 2.25-2.05 (m, 2H), 1.85-1.7 (m, 0.5H), 1.6-1.35 (m, 2H), 1.80-1.70 (m, 1H), 1.15-0.95 (m, 1H); MS (ESI): m/z : 420 $[\text{C}_{21}\text{H}_{20}\text{Cl}_2\text{FN}_3\text{O}+\text{H}]^+$.

Compound 203: (1-(5-(3-chloro-4-fluorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)methanol.



The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3-chloro-4-fluorophenyl)-8-fluoroquinazoline (200 mg, 0.647 mmol) and piperidin-3-ylmethanol (78.8 mg, 0.684 mmol). The reaction crude product was purified by column chromatography (silica gel, eluent $\text{CHCl}_3/\text{MeOH}$ 97:3) to afford (1-(5-(3-chloro-4-fluorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)methanol (150 mg, 59.5%, AUC-HPLC: 97.59%) as an off-white solid. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.70 (s, 1H), 7.55-7.39 (m, 2H), 7.38-7.29 (m, 1H), 7.28-7.16 (m, 2H), 4.40-4.20 (m, 0.5H), 3.90-3.70 (m, 1H), 3.60-3.30 (m, 1.5H), 3.31-3.15 (m, 1H), 3.10-2.90 (m, 1H), 2.70-2.50 (m, 1H), 2.25-2.10 (m, 0.5H), 1.75-1.5 (m, 1.5H), 1.40-1.10 (m, 3H); MS (ESI) m/z : 390.2 $[\text{C}_{20}\text{H}_{18}\text{ClF}_2\text{N}_3\text{O}+\text{H}]^+$.

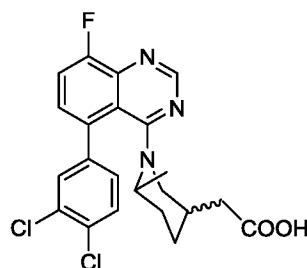
Compound 204: 5-(3-chloro-4-fluorophenyl)-8-fluoro-4-(3-(methoxymethyl)piperidin-1-yl)quinazoline



The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3-chloro-4-fluorophenyl)-8-fluoroquinazoline (50 mg, 0.161 mmol, 1eq) and 3-(methoxymethyl)piperidine hydrochloride (34.5 mg, 0.209 mmol). The reaction crude product was purified by column chromatography (silica-gel, eluent pet ether/EtOAc 7/3) to afford 5-(3-chloro-4-fluorophenyl)-8-fluoro-4-(3-(methoxymethyl)piperidin-1-yl)quinazoline (42 mg, 60.86%, AUC-HPLC 98.75%) as colorless thick oil. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.80- 8.61 (m, 1H), 7.62-7.45 (m, 2H), 7.45-7.11 (m, 3H), 4.35-4.12 (m, 0.5H), 3.93-3.72 (m, 0.5H), 3.70-3.55 (m, 1H), 3.33-3.11 (m, 3H), 3.10-3.05 (m, 1H), 3.01-2.92 (m, 1H), 2.91-2.65 (m, 1H), 2.62-2.42 (m, 1H), 2.25-2.02

(m, 1H), 1.85-1.70 (m, 1H), 1.60-1.45 (m, 1H), 1.35-1.20 (m, 1H), 1.11-0.90 (m, 1H). MS (ESI): m/z : 404.2 $[\text{C}_{21}\text{H}_{20}\text{ClF}_2\text{N}_3\text{O}+\text{H}]^+$.

Compound 205: 2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-methylpiperidine-3-yl)acetic acid



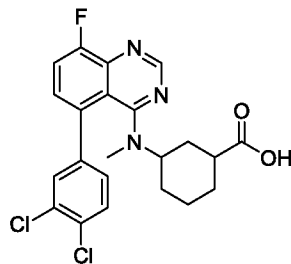
Step 1: Preparation of Methyl-2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-methylpiperidin-3-yl)acetate

The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)quinazoline (80 mg, 0.245 mmol) and methyl 2-(6-methylpiperidin-3-yl)acetate hydrochloride (76 mg, 0.367 mmol). The residue was purified by column chromatography (silica gel, eluent petroleum ether/EtOAc 9:1) to afford methyl-2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-methylpiperidin-3-yl)acetate as a mixture of diastereoisomers and as a white solid (70 mg, in 62% yield). ^1H NMR(400 MHz, CDCl_3) δ (ppm): 8.80-8.62 (m, 1H), 7.60-7.50 (m, 2H), 7.49-7.39 (m, 2H), 7.29-7.20 (m, 1H), 5.20-5.04 (m, 1H), 3.70 (s, 3H), 3.69-3.60 (m, 1H), 3.55-3.40 (m, 2H), 2.25-2.05 (m, 2H), 1.90-1.85 (m, 1H), 1.60-1.40 (m, 2H), 1.00-0.90 (m, 1H), 0.81 (d, $J = 7.5$ Hz, 3H).

Step 2: Preparation of 2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-methylpiperidine-3-yl)acetic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from chlorophenyl)-8-fluoroquinazolin-4-yl)-6-methylpiperidin-3-yl)acetate (60 mg, 0.713 mmol, 1.0 eq). The solid obtained after aqueous work-up, was washed with pentane, dried under vacuum to afford 2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-methylpiperidine-3-yl)acetic acid as a mixture of diastereoisomer (35mg, 36%, AUC HPLC 92.09 %) as a white solid. ^1H NMR(400 MHz, $\text{DMSO}-d_6$) δ (ppm): 12.01 (bs, 1H), 8.65-8.58 (m, 1H), 7.84-7.60 (m, 3H), 7.60-7.40 (m, 2H), 5.15-5.00 (m, 1H), 4.20-4.00 (m, 1H), 3.75-3.55 (m, 1H), 2.20-1.90 (m, 2H), 1.50-1.25 (m, 3H), 1.24-1.05 (m, 2H), 0.95-0.70 (m, 3H). MS (ESI); m/z : 448.2 $[\text{C}_{22}\text{H}_{20}\text{Cl}_2\text{FN}_3\text{O}_2 + \text{H}]^+$.

Compound 206: 3-((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)(methylamino)cyclohexane-1-carboxylic acid



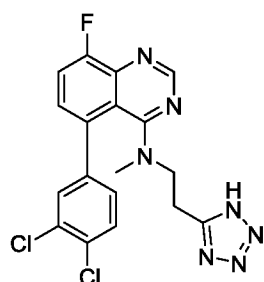
Step-1: Preparation of methyl 3-((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)(methylamino)cyclohexane-1-carboxylate

The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)-8-fluoroquinazoline (100 mg, 0.306 mmol) and methyl 3-(methylamino) cyclohexane-1-carboxylate hydrochloride (69.5 mg, 0.336 mmol). The reaction crude product was purified by column chromatography (silica gel, eluent Pet ether/EtOAc 65:35) to afford methyl 3-((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)(methylamino)cyclohexane-1-carboxylate (60 mg, yield 42.4%) as a thick oil. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.77-8.67 (m, 1H), 7.6-7.5(m, 3H), 7.40-7.20 (m, 2H), 3.80-3.60 (m, 3H), 2.50-2.30 (m, 3H), 2.00-1.80 (m, 2H), 1.70-1.50 (m, 3H), 1.51-1.40 (m, 3H), 1.30-1.10 (m, 2H). MS (ESI): m/z : 462.2 $[\text{C}_{23}\text{H}_{22}\text{Cl}_2\text{FN}_3\text{O}_2+\text{H}]^+$.

Step-2: Preparation of 3-((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)(methylamino)cyclohexane-1-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 3-((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)(methylamino)cyclohexane-1-carboxylate (55 mg, 0.119 mmol, 1eq). The solid obtained after aqueous work-up was washed with pentane, dried under vacuum to afford 3-((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)(methylamino)cyclohexane-1-carboxylic acid (15 mg, 28.1%, AUC-HPLC 92.19%), as off-white solid. ^1H NMR(400 MHz, DMSO-d_6) δ (ppm): ^1H NMR (400 MHz, CDCl_3) δ (ppm): 12.1-12.05 (s,1H), 7.8-7.65 (m, 3H), 7.55-7.45 (m, 2H), 4.3-4.05 (m, 1H), 2.40-2.30 (m, 3H), 2.30-2.20 (m, 1H),1.80-1.60 (m, 3H), 1.40-1.20 (m, 4H), 1.15-1.05 (m, 1H). MS (ESI): m/z : 448.2 $[\text{C}_{22}\text{H}_{20}\text{Cl}_2\text{FN}_3\text{O}_2+\text{H}]^+$.

Compound 207: N-(2-(1H-tetrazol-5-yl)ethyl)-5-(3,4-dichlorophenyl)-8-fluoro-N-methylquinazolin-4-amine



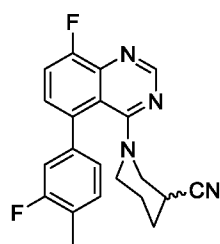
Step-1: Preparation of 3-((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)(methyl)amino)propanenitrile;

The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)-8-fluoroquinazoline (100 mg, 0.306 mmol) and 3-(methylamino)propanenitrile (25.8 mg, 0.306 mmol). The reaction crude product was purified by column chromatography (silica gel, eluent Pet ether/EtOAc 65/35) to afford 3-((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)(methyl)amino)propanenitrile (100 mg, 87.1%, AUC-HPLC: 98.03%) as an off-white solid. ¹H NMR(400 MHz, CDCl₃) δ (ppm): 8.70 (s, 1H), 7.58-7.47 (m, 3H), 7.46-7.35 (m, 2H), 3.80-3.62 (m, 2H), 2.80-2.70 (m, 2H), 2.46 (s, 3H). MS (ESI) *m/z*: 375 [C₁₈H₁₃Cl₂FN₄+H]⁺.

Step-2: Preparation of N-(2-(1H-tetrazol-5-yl)ethyl)-5-(3,4-dichlorophenyl)-8-fluoro-N-methylquinazolin-4-amine

The title compound was prepared in a similar fashion as described in general procedure F starting from 3-((5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)(methyl)amino)propanenitrile (70 mg, 0.1871 mmol). The residue was purified by preparative TLC using CHCl₃/MeOH 90:10 to afford N-(2-(1H-tetrazol-5-yl)ethyl)-5-(3,4-dichlorophenyl)-8-fluoro-N-methylquinazolin-4-amine (5 mg, AUC HPLC 90.49%), as an off-white solid. ¹H-NMR (400 MHz, CDCl₃) δ (ppm): 8.86 (s, 1H), 7.6-7.40 (m, 4H), 7.29-7.25 (m, 1H), 4.31-4.05 (bs, 1H), 3.95-3.51 (m, 2H), 3.51-3.32 (m, 2H), 2.6-2.5 (s, 3H); MS (ESI): *m/z*: 418 [C₁₈H₁₄Cl₂FN₇ + H]⁺

Compound 208: 1-(8-fluoro-5-(3-fluoro-4-methylphenyl)quinazolin-4-yl)piperidine-3-carbonitrile



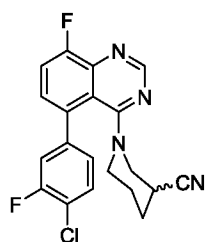
Step 1: 8-fluoro-5-(3-fluoro-4-methylphenyl)quinazolin-4(3H)-one

The title compound was prepared in a similar fashion as described in general procedure E starting from 5-bromo-8-fluoroquinazolin-4(3H)-one (200 mg, 0.82 mmol) and (3-fluoro-4-methylphenyl)boronic acid (253.38 mg, 1.54 mmol) to afford 8-fluoro-5-(3-fluoro-4-methylphenyl)quinazolin-4(3H)-one (379.7 mg, 1.39 mmol) as an off-white solid ; MS (ESI) *m/z* 273.00 [C₁₅H₁₀F₂N₂O + H]⁺. The reaction crude product was used in the next step without further purification.

Step 2: *1-(8-fluoro-5-(3-fluoro-4-methylphenyl)quinazolin-4-yl)piperidine-3-carbonitrile*

The title compound was prepared in a similar fashion as described in general procedure D starting from 8-fluoro-5-(3-fluoro-4-methylphenyl)quinazolin-4(3*H*)-one (~ 0.82 mmol) and piperidine-3-carbonitrile (360 mg, 2.46 mmol). The reaction crude product was purified by column chromatography (silica gel, 100% DCM to DCM/MeOH 90:10) and by preparative HPLC to afford 1-(8-fluoro-5-(3-fluoro-4-methylphenyl)quinazolin-4-yl)piperidine-3-carbonitrile (50.82 mg, 0.139 mmol, 16.9 % over 2 steps, AUC HPLC 98.24 %) as white solid; ¹H NMR (400 MHz, DMSO) δ (ppm): 8.68 (s, 1H), 7.73 (t, *J* = 8.4 Hz, 1H), 7.55-7.45 (m, 1H), 7.38-7.18 (m, 3H), 2.33 (s, 4H), 2.15-2.00 (m, 1H), 1.90-1.50 (m, 5H), 1.10-0.80 (m, 2H); MS (ESI) *m/z* 365.10 [C₂₁H₁₈F₂N₄ + H]⁺.

Compound 209: 1-(5-(4-chloro-3-fluorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carbonitrile



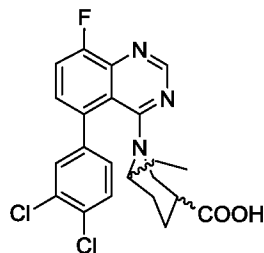
Step 1: *5-(4-chloro-3-fluorophenyl)-8-fluoroquinazolin-4(3H)-one*

The title compound was prepared in a similar fashion as described in general procedure E starting from 5-bromo-8-fluoroquinazolin-4(3*H*)-one (183 mg, 0.75 mmol) and (3-fluoro-4-chlorophenyl)boronic acid (263.28 mg, 1.51 mmol) to afford 5-(4-chloro-3-fluorophenyl)-8-fluoroquinazolin-4(3*H*)-one (287.97 mg, 0.98 mmol) as off-white solid ; MS (ESI) *m/z* 293.00 [C₁₄H₇F₂N₂O + H]⁺. The reaction crude product was used in the next step without further purification.

Step 2: *1-(5-(4-chloro-3-fluorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carbonitrile*

The title compound was prepared in a similar fashion as described in general procedure D starting from 5-(4-chloro-3-fluorophenyl)-8-fluoroquinazolin-4(3*H*)-one (~ 0.75 mmol) and piperidine-3-carbonitrile (330 mg, 2.25 mmol). The residue was purified column chromatography (silica gel, 100% DCM to DCM/MeOH 95:5) and by preparative HPLC to afford 1-(5-(4-chloro-3-fluorophenyl)-8-fluoroquinazolin-4-yl)piperidine-3-carbonitrile (36.0 mg, 0.093 mmol, 12.4 % over 2 steps, AUC HPLC 99.0 %) as white solid; ¹H NMR (400 MHz, DMSO) δ (ppm): 8.69 (s, 1H), 7.75 (t, *J* = 9.0 Hz, 1H), 7.70-7.50 (m, 3H), 7.35-7.30 (m, 1H), 3.50-3.30 (m, 1H), 3.15-2.85 (m, 2H), 2.70-2.50 & 2.45-2.30 (2m, 1H), 1.90-1.50 (m, 3H), 1.30-0.90 (m, 2H); MS (ESI) *m/z* 385.00 [C₂₀H₁₅ClF₂N₄ + H]⁺.

Compound 210: 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-ethylpiperidine-3-carboxylic acid



Diastereoisomer-1

Step 1: Preparation of methyl 6-ethylpiperidine-3-carboxylate hydrochloride

Following a procedure similar to that described in published literature (PCT Int. Appl., 2011026911; PCT Int. Appl., 2012101064; PCT Int. Appl., 2011026904; PCT Int. Appl., 2011026917, 10 Mar 2011) procedure two diastereoisomers of methyl 6-ethylpiperidine-3-carboxylate were isolated, diastereoisomer 1 (peak-1) and diastereoisomer 2 (peak-2).

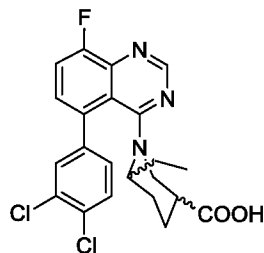
Step-1: Preparation of methyl 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-ethylpiperidine-3-carboxylate

The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)-8-fluoroquinazoline (150 mg, 0.460 mmol) and methyl 6-ethylpiperidine-3-carboxylate hydrochloride (diastereoisomer 1) 142.8 mg, 0.690 mmol). The residue was purified by column chromatography (silica gel, eluent Pet ether/EtOAc 80:20) to afford methyl 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-ethylpiperidine-3-carboxylate (non-polar spot: 70 mg, yield 33%) as gummy liquid. MS (ESI) m/z : 462.0 [$C_{23}H_{22}Cl_2FN_3O_2 + H$]⁺. The reaction crude product was used without further purification in the next step.

Step-2: Preparation of 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-ethylpiperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-ethylpiperidine-3-carboxylate (70 mg, 0.151 mmol). The residue was purified by preparative TLC with $CHCl_3/MeOH$ 95:5 as eluent to afford 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-ethylpiperidine-3-carboxylic acid (diastereoisomer 1, 57.5 mg, yield 85% over 2 steps, AUC HPLC 94.95%) as an off-white solid. ¹H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.85-8.65 (m, 1H), 7.70-7.42 (m, 3H), 7.40-7.20 (m, 2H), 4.75-4.55 (m, 0.5H), 4.30-4.05 (m, 1H), 3.90-3.70 (m, 1H), 3.15-2.90 (m, 0.5H), 2.62-2.15 (m, 1H), 1.95-1.61 (m, 2H), 1.47-1.20 (m, 3H), 0.91-0.78 (m, 2H), 0.52-0.35 (m, 2H). MS (ESI) m/z : 448.2 [$C_{22}H_{20}Cl_2FN_3O_2 + H$]⁺.

Compound 211: 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-ethylpiperidine-3-carboxylic acid



Diastereoisomer-2

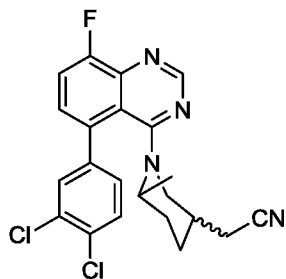
Step-1: Preparation of methyl 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-ethylpiperidine-3-carboxylate

The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)-8-fluoroquinazoline (150 mg, 0.460 mmol) and methyl 6-ethylpiperidine-3-carboxylate hydrochloride (diastereoisomer 2, step 1 of Compound 210, 69.8 mg, 0.337 mmol). The crude product was purified by column chromatography (silica gel, pet ether/EtOAc 4:1) to afford diastereoisomer-1 methyl 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-ethylpiperidine-3-carboxylate (60 mg, impure methyl 6-ethylpiperidine-3-carboxylate hydrochloride; 37.7% purity by LCMS). MS: (ESI) m/z : 462.2 [$C_{23}H_{22}Cl_2FN_3O_2 + H$] $^+$. The reaction crude product was used without further purification in the next step.

Step-2: Preparation of 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-ethylpiperidine-3-carboxylic acid

The title compound was prepared in a similar fashion as described in general procedure C starting from methyl 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-ethylpiperidine-3-carboxylate. The reaction crude product was purified by preparative TLC to afford 1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-ethylpiperidine-3-carboxylic acid (diastereoisomer 2, 8.0 mg, yield 36.5% over 2 steps, AUC-HPLC 93.90%), as off-white solid. ^1H NMR(400 MHz, DMSO- d_6) δ (ppm): 12.40-11.62 (bs, 1H), 8.70-8.45 (m, 1H), 8.10-7.60 (m, 3H), 7.59-7.46 (m, 1H), 7.45-7.35 (m, 1H), 4.90-4.60 (m, 1H), 3.55-3.45 (m, 1H), 2.72-2.55 (m, 1H), 2.40-2.28 (m, 1H), 2.18-2.02 (m, 1H), 1.80-1.58 (m, 2H), 1.57-1.30 (m, 3H), 0.85 (t, $J = 7.4$ Hz, 3H). MS (ESI): m/z : 448.2 [$C_{22}H_{20}Cl_2FN_3O_2 + H$] $^+$.

Compound 212: 2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-methylpiperidin-3-yl)acetonitrile (diastereoisomer 1)



**Diastereomer-1 (Cis
relative configuration)**

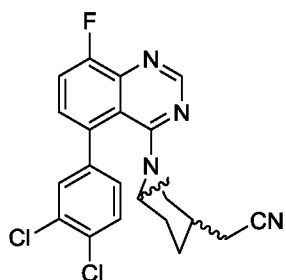
Step 1: Preparation of 2-(6-methylpiperidin-3-yl)acetonitrile

Following literature procedure two diastereoisomers of 2-(6-methylpiperidin-3-yl)acetonitrile were isolated, diastereoisomer 1 (peak-1) and diastereoisomer 2 (peak-2)

Step 2 Preparation of 2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-methylpiperidin-3-yl)acetonitrile

The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3,4-dichlorophenyl)quinazoline (100 mg, 0.306 mmol) and 2-(6-methylpiperidin-3-yl)acetonitrile hydrochloride (diastereomer-1, 106 mg, 0.609 mmol). The reaction crude product was purified by column chromatography (silica gel, eluent Petroleum ether/EtOAc 8:2) to afford 2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-methylpiperidin-3-yl)acetonitrile as white solid (diastereomer-1; 20 mg, 15.2%, AUC HPLC: 95.39). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.96-8.75 (m, 1H), 7.80-7.66 (m, 1H), 7.65-7.45 (m, 3H), 7.44-7.30 (m, 1H), 4.40-4.15 (m, 1H), 3.80-3.55 (m, 0.5H), 3.30-3.10 (m, 0.5H), 2.90-2.75 (m, 0.5H), 2.70-2.50 (m, 0.5H), 2.40-2.10 (m, 2H), 2.00-1.80 (m, 1H), 1.80-1.50 (m, 4H), 0.95-0.75 (m, 3H). MS (ESI): *m/z*: 429.2 [C₂₂H₁₉Cl₂FN₄+H]⁺.

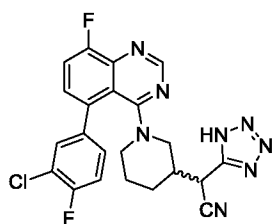
Compound 213: 2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-methylpiperidin-3-yl)acetonitrile



**Diastereoisomer-2
(Trans relative
configuration)**

The title compound was prepared in a similar fashion as described in general procedure G starting from 4-chloro-5-(3, 4-dichlorophenyl)quinazoline (100 mg, 0.306 mmol) and 2-(6-methylpiperidin-3-yl)acetonitrile hydrochloride (diastereomer-2, 106 mg, 0.609 mmol). The reaction crude product was purified by column chromatography (silica gel, eluent petroleum ether/EtOAc 8:2) to afford 2-(1-(5-(3,4-dichlorophenyl)-8-fluoroquinazolin-4-yl)-6-methylpiperidin-3-yl)acetonitrile, as white solid, (80 mg, 60.9%, AUC HPLC: 95.69%). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.85-8.66 (m, 1H), 7.65-7.45 (m, 3H), 7.44-7.28 (m, 2H), 4.95-4.80 (m, 1H), 4.25-4.00 (m, 1H), 3.90-3.65 (m, 1H), 2.90-2.70 (m, 1H), 2.35-2.05 (m, 2H), 1.55-1.20 (m, 4H), 0.95-0.70 (m, 3H). MS (ESI): *m/z*: 429.2 [C₂₂H₁₉Cl₂FN₄+H]⁺.

Compound 214: 2-(1-(5-(3-chloro-4-fluorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)-2-(1H-tetrazol-5-yl)acetonitrile



Step 1: Synthesis of benzyl (Z)-3-(1-cyano-2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate

A mixture of benzyl 3-oxopiperidine-1-carboxylate (25 g, 0.107 mmol, 1.0 eq), ethyl cyanoacetate (14.54 g, 0.129 mmol, 1.2 eq), NH₄OAc (2.09 g, 0.026 mmol, 0.25 eq) and acetic acid (5 mL) in toluene (250 mL) was refluxed at 130 °C for 16 h. After the completion of reaction (TLC: *R_f*: 0.5 (30% ethyl acetate in hexane)), the reaction mixture was cooled to room temperature, quenched with a saturated aqueous solution of NaHCO₃ (500 mL) and extracted with EtOAc (2 x 300 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford crude product. The crude was purified by column chromatography (200-400 mesh silica-gel, eluent hexanes/EtOAc 90:10 to 80:10,) to afford benzyl (E)-3-(1-cyano-2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate (24 g, yield: 68%) as a thick liquid. LCMS: 89%; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 7.46 – 7.33 (m, 4H), 7.10 (d, *J* = 12.7 Hz, 1H), 5.19 – 5.15 (d, *J* = 13.4 Hz, 3H), 4.19 (dq, *J* = 14.2, 7.1 Hz, 2H), 3.59 – 3.50 (m, 2H), 2.10 (dt, *J* = 16.7, 6.3 Hz, 1H), 2.03 – 1.90 (m, 1H), 1.82 (d, *J* = 8.5 Hz, 2H), 1.22 (dq, *J* = 10.8, 6.1, 4.3 Hz, 4H). MS (ESI) *m/z* 329 [C₁₈H₂₀N₂O₄ + H]⁺

Step 2: Synthesis of benzyl 3-(1-cyano-2-ethoxy-2-oxoethyl)piperidine-1-carboxylate

A mixture of benzyl (E)-3-(1-cyano-2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate (10 g, 0.030 mmol, 1 eq), and 10% Pd/C (50% wet) (2.0 g) in ethanol (100 mL) was stirred under H₂ atmosphere (50 psi) for 48 h. The reaction mixture was filtered through celite and concentrated under reduced pressure to afford ethyl 2-cyano-2-(piperidin-3-yl) acetate. The crude was purified by column chromatography (200-400 mesh silica-gel, eluent hexanes/EtOAc 90:10 to 85:15, TLC: *R_f*: 0.4 (50% ethyl acetate in hexane)) to afford benzyl 3-(1-cyano-2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (7.1 g, yield: 69.3%) as thick yellow liquid. LCMS: 94%, ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 7.39 – 7.31 (m, 5H), 5.13 – 5.03 (m, 2H), 4.34 (dd, *J* = 25.4, 5.5 Hz, 1H), 4.28 – 4.11 (m, 2H), 4.07 –

3.89 (m, 2H), 2.90 – 2.65 (m, 2H), 2.11 – 2.02 (m, 1H), 1.90 – 1.75 (d, $J = 12.6$ Hz, 1H), 1.72 – 1.61 (m, 1H), 1.47 – 1.35 (m, 2H), 1.30 – 1.21 (m, 3H).

Step 3: Synthesis of benzyl 3-(2-amino-1-cyano-2-oxoethyl)piperidine-1-carboxylate

To a mixture of benzyl 3-(1-cyano-2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (23 g, 1 eq) and 7N NH_3 in methanol (575 mL) stirred at 0 °C for 30 min was added aq. ammonia (28%, 185 ml) was added to the reaction mixture and allowed to stir for further 4 h at rt. The reaction mixture was concentrated under vacuum and triturated with pentanes to afford benzyl 3-(2-amino-1-cyano-2-oxoethyl) piperidine-1-carboxylate (12.0 g, yield 57%) as a yellow solid. TLC: R_f : 0.5 (10% MeOH in DCM), LCMS: 95.87%; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 7.84 (d, $J = 17.8$ Hz, 1H), 7.58 (d, $J = 9.4$ Hz, 1H), 7.36 (s, 3H), 7.42–7.28 (m, 2H), 5.08 (d, $J = 5.3$ Hz, 2H), 4.05 (q, $J = 18.6, 17.4$ Hz, 1H), 3.87 (s, 1H), 3.70 (dd, $J = 19.7, 7.4$ Hz, 1H), 2.87 (dt, $J = 27.6, 11.7$ Hz, 1H), 2.07 – 2.00 (m, 1H), 1.86 (d, $J = 12.5$ Hz, 1H), 1.68 (d, $J = 12.5$ Hz, 1H), 1.34 (s, 3H). MS (ESI) m/z 302 [$\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}_3 + \text{H}$] $^+$

Step 4: Synthesis of benzyl 3-(2-amino-2-oxo-1-(1H-tetrazol-5-yl)ethyl)piperidine-1-carboxylate

A mixture of benzyl 3-(2-amino-1-cyano-2-oxoethyl)piperidine-1-carboxylate (7 g, 0.023 mmol, 1 eq), sodium azide (9.0 g, 0.302 mmol, 6.0 eq), and TEA.HCl (19.8 g, 0.144 mmol, 6.2 eq) in toluene (105 mL) was refluxed at 130 °C for 16 h. The solvent was decanted from the reaction mixture and the obtained solid was washed with ethyl acetate and methanol. The organic layer was concentrated under reduced pressure to afford crude benzyl (E)-3-(1-cyano-2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate (8.0 g, crude) as semi solid. The crude material was used directly in next step. LCMS: 72%; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 16.33 (s, 1H), 7.90 (s, 1H), 7.37 (dq, $J = 14.1, 7.2$ Hz, 6H), 5.09 (d, 2H), 4.07 (s, 1H), 3.92 (d, $J = 10.5$ Hz, 1H), 2.83 (t, 1H), 2.20 (m, 1H), 1.87–1.57 (s, 1H), 1.57 (d, 1H), 1.24 (m, 3H), 1.00 (m, 1H). MS (ESI) m/z 345 [$\text{C}_{16}\text{H}_{20}\text{N}_6\text{O}_3 + \text{H}$] $^+$

Step 5: Synthesis of benzyl 3-(cyano(1H-tetrazol-5-yl)methyl)piperidine-1-carboxylate

To a mixture of benzyl (E)-3-(1-cyano-2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate (17.0 g, 0.049 mmol, 1 eq) in DCM (170 mL) under N_2 atmosphere at 0 °C were added TEA (20 mL, 0.148 mmol, 3.0 eq) and TFAA (8.22 mL, 0.059 mmol, 1.2 eq). The reaction mixture was stirred for 3 h while warming from 0 °C to 5 °C. TLC : R_f : 0.2 (10% MeOH in DCM). The reaction was quenched with water (300 mL) and extracted with DCM (2 x 300 mL). The combined organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford benzyl (E)-3-(1-cyano-2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate (6.2 g, yield: 38.6%) as a dark brown liquid. LCMS: 96.3%; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 7.39–7.30 (m, 6H), 5.06 (d, $J = 8.7$ Hz, 2H), 4.33 (dd, $J = 13.6, 6.9$ Hz, 1H), 4.01 (d, 1H), 3.96 (dt, $J = 29.6, 13.7$ Hz, 1H), 2.73 – 2.69 (s, 2H), 2.00 (s, 1H), 1.94 – 1.85 (m, 1H), 1.72 – 1.59 (m, 1H), 1.33 (dt, $J = 19.0, 9.7$ Hz, 2H). MS (ESI) m/z 327 [$\text{C}_{16}\text{H}_{18}\text{N}_6\text{O}_2 + \text{H}$] $^+$

Step 6: Synthesis of 2-(piperidin-3-yl)-2-(1H-tetrazol-5-yl)acetonitrile

A mixture of benzyl 3-(cyano(1H-tetrazol-5-yl)methyl)piperidine-1-carboxylate (1.0 g, 1 eq), and 10% Pd/C (50% wet) (1.0 g) in methanol (10 mL) was stirred under H_2 (1atm) for 16 h. The reaction

mixture was filtered through celite and concentrated to afford 2-(piperidin-3-yl)-2-(1H-tetrazol-5-yl)acetonitrile (0.6 g, crude) as a brown solid. LCMS: 75%. MS (ESI) m/z 193 [$C_8H_{12}N_6 + H$]⁺.

Step 7: *Synthesis of 5-bromo-8-fluoroquinazolin-4(3H)-one*

A mixture of 2-amino-6-bromo-3-fluorobenzoic acid (2 g, 0.009 mmol, 1 eq) and formamidine acetate (1.067 gm, 0.012 mmol, 1.2 eq) was heated at 120 °C for 16 h. The cooled reaction mixture was washed with *n*-pentane and diethyl ether to afford 5-bromo-8-fluoroquinazolin-4(3H)-one (1.6 g, yield: 76%) as a yellow solid. LCMS: 95%; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 10.59 (s, 1H), 8.17 (s, 1H), 7.74 (dd, *J* = 8.7, 4.7 Hz, 1H), 7.61 (t, *J* = 9.3 Hz, 1H). MS (ESI) m/z 244 [$C_8H_4BrFN_2O + H$]⁺.

Step 8: *5-(3-chloro-4-fluorophenyl)-8-fluoroquinazolin-4(3H)-one*

A mixture of 5-bromo-8-fluoroquinazolin-4(3H)-one (0.9 g, 0.004 mmol, 1.0 eq), (3-chloro-4-fluorophenyl)boronic acid (0.71 g, 0.004 mol, 1.1 eq) and K₃PO₄ (1.5 g, 0.007 mol, 2.0 eq), in dioxane (9.0 mL) and water (0.9 mL) was degassed with N₂ for 30 min. Pd(dppf)Cl₂•DCM (0.303 g, 0.0004 mol, 0.1 eq) was added and stirred under N₂ at 100 °C for 16 h. The reaction mixture was cooled to room temperature and poured in water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was separated, washed with brine, dried over Na₂SO₄ and concentrated in vacuum. The crude was purified by column chromatography (200-400 mesh silica-gel, eluent hexanes/EtOAc 90:10 to 45:55, TLC : *R_f*: 0.3 (5% MeOH in DCM) to afford 5-(3-chloro-4-fluorophenyl)-8-fluoroquinazolin-4(3H)-one (0.5 g, yield: 46%) as yellow solid. LCMS: 92%; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 12.33 (s, 1H), 8.17 (s, 1H), 7.73 (dd, *J* = 10.1, 8.3 Hz, 1H), 7.53 (dd, *J* = 7.2, 2.2 Hz, 1H), 7.41 (t, *J* = 9.0 Hz, 1H), 7.35 – 7.25 (m, 2H). MS (ESI) m/z 293 [$C_{14}H_7ClF_2N_2O + H$]⁺.

Step 9: *Synthesis of 4-chloro-5-(3-chloro-4-fluorophenyl)-8-fluoroquinazoline*

A mixture of 5-(3-chloro-4-fluorophenyl)-8-fluoroquinazolin-4(3H)-one (1.0 g, 0.003 mmol, 1.0 eq) and PCl₅ (6.41 g, 0.030 mmol, 9.0 eq) in POCl₃ (10 mL) was heated at 125 °C for 16 h. After completion of the reaction the reaction mixture was cooled to room temperature and poured in saturated aq NaHCO₃ solution (100 mL) and extracted with ethyl acetate (3 x 50 mL). The organic layer was separated, washed with brine, dried over Na₂SO₄ and concentrated in vacuum. The crude was purified by column chromatography (200-400 mesh silica-gel, eluent hexanes/EtOAc 90:10 to 60:40, TLC: *R_f*: 0.3 (5% MeOH in DCM) to afford 4-chloro-5-(3-chloro-4-fluorophenyl)-8-fluoroquinazoline (0.25 g, yield: 23 %) as yellow solid. LCMS: 91.8%; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 9.20 (s, 1H), 8.04 (t, *J* = 8.9 Hz, 1H), 7.74 (d, *J* = 7.0 Hz, 2H), 7.60 – 7.45 (m, 2H). MS (ESI) m/z 312 [$C_{14}H_6Cl_2F_2N_2 + H$]⁺.

Step 10: *Synthesis of 2-(1-(5-(3-chloro-4-fluorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)-2-(1H-tetrazol-5-yl)acetonitrile*

A mixture of 2-(piperidin-3-yl)-2-(1H-tetrazol-5-yl)acetonitrile (0.6 g, 0.003 mmol, 1.0 eq), 4-chloro-5-(3-chloro-4-fluorophenyl)-8-fluoroquinazoline (0.17 g, 0.002 mmol, 0.5 eq) and TEA (1.0 mL, 5.0 eq) in *i*-PrOH (15 mL) was heated at 85 °C for 6 h. The reaction mixture was concentrated in vacuum

and the residue was purified by prep-HPLC to afford 2-(1-(5-(3-chloro-4-fluorophenyl)-8-fluoroquinazolin-4-yl)piperidin-3-yl)-2-(1*H*-tetrazol-5-yl)acetonitrile as a mixture of diastereoisomers (0.10 g, AUC HPLC 90%, yield: 23.5%) as semi solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.72–8.57 (m, 1H), 7.71 (d, *J* = 9.4 Hz, 2H), 7.59 (s, 1H), 7.49 (s, 2H), 4.23 (m, 2H), 3.17 (s, 1H), 2.93 (q, *J* = 7.3 Hz, 3H), 1.75 (s, 1H), 1.68 (s, 2H), 0.86 (dt, *J* = 11.3, 6.2 Hz, 2H). MS (ESI) *m/z* 467 [C₂₂H₁₇ClF₂N₈ + H]⁺. The mixture of diastereoisomer was purified by chiral SFC HPLC: column: CHIRALPAK IC 250 mm x 4.6 mm, 5μ; eluent: CO₂/(0.1% DEA, IPA/MEOH 50:50), to afford diastereoisomer 1, rt: 5.01 min and diastereoisomer 2, rt 8.37 min.

Example 5

Table 1. Enzymatic activities

Compound	IC50 (μM)	Compound	IC50 (μM)	Compound	IC50 (μM)
001	>10	017	<10	033	<10
002	>10	018	<10	034	>10
003	>10	019	>10	035	>10
004	>10	020	<10	036	>10
005	<2.5	021	<0.5	037	<10
006	>10	022	<0.5	038	>10
007	>10	023	<10	039	<2.5
008	<10	024	<2.5	040	>10
009	>10	025	>10	041	<10
010	>10	026	>10	042	<2.5
011	<2.5	027	>10	043	>10
012	>10	028	>10	044	>10
013	>10	029	>10	045	>10
014	>10	030	>10	046	>10
015	<2.5	031	>10	047	>10
016	<2.5	032	<10	048	<10

Compound	IC50 (μM)
049	>10
050	>10
051	>10
052	>10
053	>10
054	>10
055	<10
056	<2.5
057	<2.5
058	<10
059	>10
060	>10
061	>10
062	>10
063	>10
064	<2.5
065	>10
066	<2.5
067	>10
068	>10
069	>10
070	>10
071	<2.5

Compound	IC50 (μM)
072	<10
073	>10
074	<2.5
075	>10
076	>10
077	>10
078	<0.1
079	<0.5
080	<0.5
081	<2.5
082	<10
083	>10
084	>10
085	<2.5
086	>10
087	>10
088	<2.5
089	<10
090	>10
091	>10
092	<10
093	<10
094	<0.5

Compound	IC50 (μM)
095	<0.5
096	<10
097	<10
098	<10
099	<10
100	>10
101	>10
102	>10
103	<0.5
104	<0.5
105	>10
106	>10
107	>10
108	>10
109	>10
110	<10
111	>10
112	>10
113	>10
114	>10
115	<2.5
116	>10
117	>10

Compound	IC50 (μM)
118	<10
119	<2.5
120	>10
121	>10
122	<2.5
123	>10
124	<10
125	<10
126	>10
127	<0.5
128	<2.5
129	<0.5
130	<0.5
131	<2.5
132	<10
133	<0.5
134	>10
135	<0.5
136	<10
137	<0.5
138	<0.5
139	<2.5
140	<2.5

Compound	IC50 (μM)
141	<10
142	<0.5
143	<0.5
144	<10
145	>10
146	>10
147	<0.5
148	<2.5
149	<0.5
150	>10
151	>10
152	<0.5
153	<0.5
154	>10
155	<0.5
156	<2.5
157	<2.5
158	<0.5
159	<2.5
160	<0.5
161	<0.5
162	<2.5
163	<2.5

Compound	IC50 (μM)
164	<2.5
165	<0.5
166	<0.1
167	<0.1
168	<0.1
169	<2.5
170	<0.1
171	<0.1
172	<0.1
173	<0.1
174	<0.1
175	<0.5
176	<0.1
177	<10
178	<0.1
179	<0.1
180	<0.1
181	<0.5
182	<0.5
183	<0.1
184	<0.5
185	<0.5
186	<0.5

Compound	IC50 (μM)
187	<0.1
188	<0.1
189	<2.5
190	<0.5
191	<0.5
192	<0.5
193	<2.5
194	<2.5
195	<0.5
196	<0.5

Compound	IC50 (μM)
197	<0.5
198	<0.1
199	<10
200	<1
201	<0.5
202	<2.5
203	<0.1
204	<0.5
205	<0.5
206	<2.5

Compound	IC50 (μM)
207	<10
208	<2.5
209	<2.5
210	<0.5
211	<2.5
212	<0.1
213	>10

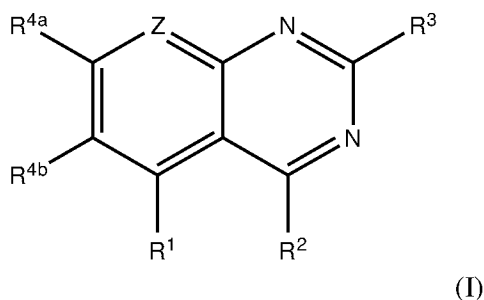
Industrial Applicability

The compounds as defined above may find a multiple number of applications in which their ability to modulate serine and glycine metabolism. The compounds may also be used in treating or preventing a condition or disorder in a mammal in which the modulation of serine and glycine metabolism prevents, inhibits or ameliorates a pathology or a symptomology of the condition. The condition or disorder may be cancer, inflammation, Alzheimer's disease, metabolic disorders, neurological disorders and central nervous system disorders.

It will be apparent that various other modifications and adaptations of the invention will be apparent to the person skilled in the art after reading the foregoing disclosure without departing from the spirit and scope of the invention and it is intended that all such modifications and adaptations come within the scope of the appended claims.

Claims

1. A compound of general formula (I) and/or its solvates, hydrates and pharmaceutically acceptable salts



wherein

Z represents N or C-R^{4c};

R¹ represents -Q¹-R⁶;

Q¹ represents a direct bond, -NH-, -C(O)-NH-, -C(O)-, alkynyl, alkenyl, or alkyl;

R² represents a group -Q³-R¹⁹, -N(R¹⁸)-Q²-COOH, -N(R¹⁸)-Q²-CN or -N(R¹⁸)-Q²-tetrazolyl;

Q³ represents a direct bond, -NH-, -N(R²⁰)- or -N(R²⁰)-alkyl-;

R¹⁹ represents optionally substituted cycloalkyl or optionally substituted non-aromatic heterocyclyl which has in each case 6 to 7 ring members and 1 to 3 heteroatoms selected from N, O or S and may be optionally benzo- or heteroaromatic-fused or may be optionally spirocyclic extended;

R²⁰ represents optionally substituted alkyl;

wherein R¹⁸ represents hydrogen, alkyl or cycloalkyl;

Q² represents a direct bond, alkyl, cycloalkyl, alkylcycloalkyl or cycloalkylalkyl;

R³ represents hydrogen, amino, alkyl, alkylthio, haloalkyl, nitro, alkylamino, dialkylamino, acyl or cyano;

R^{4a} and R^{4c} independently of each other represent hydrogen, amino, alkyl, alkoxy, alkylthio, halogen, haloalkyl, nitro, alkylamino, dialkylamino, acyl or cyano;

R^{4b} represents hydrogen, amino, alkyl, alkoxy, alkylthio, halogen, haloalkyl, nitro, alkylamino, dialkylamino, or acyl;

R⁶ represents an optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl or optionally substituted aromatic or non-aromatic heterocyclyl which is optionally heteroaryl- or aryl-fused.

2. A compound of claim 1 and/or its solvates, hydrates and pharmaceutically acceptable salts wherein in formula (I)

R¹ represents -Q¹-R⁶;

R² represents -Q³-R¹⁹;

Q³ represents a direct bond, -NH-, -N(R²⁰)- or -N(R²⁰)-C₁-C₃-alkyl;

R¹⁹ represents optionally substituted C₃-C₈-cycloalkyl or optionally substituted non-aromatic heterocyclyl which has in each case 6 to 7 ring members and 1 to 3 heteroatoms selected from N, O or S and may be optionally benzo- or heteroaromatic-fused or may be optionally spirocyclic extended;

and wherein R¹⁹ is unsubstituted or substituted by at least one substituent selected from cyano, C₁-C₆-alkyl-cyano, halo-C₁-C₃-alkyl-cyano, C₃-C₈-cycloalkyl-cyano, halo-C₁-C₃-alkyl-, -COOH, -C₁-C₃-alkyl-C(O)-NH₂, C₃-C₈-cycloalkyl-COOH, halo-C₃-C₈-cycloalkyl-COOH, piperidinyl-COOH, cyano-C₃-C₈-cycloalkyl-COOH, -SO₂H, -SO₃H, hydroxyl (OH), hydroxy-C₁-C₆-alkyl, =O (Oxo), -COCO₂H, -CH(OH)-COOH, =CH-COOH, C₁-C₆-alkyl-COOH, halo-C₁-C₆-alkyl-COOH, cyano-C₁-C₆-alkyl-COOH, amino-C₁-C₆-alkyl-COOH, C₂-C₆-alkenyl-COOH, C₂-C₆-alkinyl-COOH, C₁-C₆-alkyl-OH, C₁-C₆-alkoxy-C₁-C₆-alkyl, C₂-C₆-alkenyl-OH, C₁-C₆-alkyl-SH, C₂-C₆-alkenyl-SH, -C(O)-NH-OH, -C(O)-NH-NH₂, -C(O)-NH-S(O)₂-C₁-C₃-alkyl, tetrazolyl, triazolyl, imidazolyl, oxadiazolonyl, oxadiazolyl, C₁-C₃-alkyl-tetrazolyl, C₁-C₃-alkyl-triazolyl, C₁-C₃-alkyl-imidazolyl, C₁-C₃-alkyl-oxadiazolonyl, C₁-C₃-alkyl-oxadiazolyl, halo-C₁-C₃-alkyl-tetrazolyl, halo-C₁-C₃-alkyl-triazolyl, halo-C₁-C₃-alkyl-imidazolyl, halo-C₁-C₃-alkyl-oxadiazolonyl, halo-C₁-C₃-alkyl-oxadiazolyl, C₃-C₈-cycloalkyl-tetrazolyl, -C₃-C₈-cycloalkyl-triazolyl, C₃-C₈-cycloalkyl-imidazolyl, C₃-C₈-cycloalkyl-oxadiazolonyl, C₃-C₈-cycloalkyl-oxadiazolyl, -C(O)-NH-tetrazolyl, -C(O)-NH-triazolyl, -C(O)-NH-imidazolyl, -C(O)-NH-oxadiazolonyl, -C(O)-NH-oxadiazolyl, -N(C₁-C₃-alkyl)-C₁-C₃-alkyl-tetrazolyl, C₂-C₆-alkenyl-cyano, C₂-C₆-alkinyl-cyano, C₃-C₆-cycloalkyl-tetrazolyl, C₃-C₆-cycloalkyl-triazolyl, C₃-C₆-cycloalkyl-imidazolyl, C₃-C₆-cycloalkylalkyl-oxadiazolonyl, C₃-C₆-cycloalkyl-oxadiazolyl, -CO-NH-tetrazolyl, -CO-NH-triazolyl, -CO-NH-imidazolyl, -CO-NH-oxadiazolonyl, -CO-NH-oxadiazolyl, cyano-C₁-C₃-alkyl-tetrazolyl, cyano-C₁-C₃-alkyl-triazolyl, cyano-C₁-C₃-alkyl-imidazolyl, cyano-C₁-C₃-alkyl-oxadiazolonyl, cyano-C₁-C₃-alkyl-oxadiazolyl, heterocyclyl substituted C₁-C₃-alkyl-tetrazolyl, heterocyclyl substituted C₁-C₃-alkyl-triazolyl, heterocyclyl substituted C₁-C₃-alkyl-imidazolyl, heterocyclyl substituted C₁-C₃-alkyl-oxadiazolonyl, heterocyclyl substituted C₁-C₃-alkyl-oxadiazolyl, heterocyclyl substituted C₁-C₃-alkyl-cyano wherein the heterocyclyl substituent can be selected from a 4 to 6 membered heterocyclic ring having 1 to three hetero atoms selected from N, O and S;

and further optional additional substituents of R^{19} are selected from C_1 - C_6 -alkyl, C_1 - C_4 -alkoxy, C_1 - C_3 -alkyl- $N(C_1$ - C_3 -alkyl) $_2$, hydroxy- C_1 - C_6 -alkyl, amino- C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkinyl, thio- C_1 - C_6 -alkyl, C_1 - C_4 -alkyl-thio- C_1 - C_4 -alkyl, C_3 - C_8 -cycloalkyl, C_3 - C_8 -cycloalkenyl, five to six ring membered optionally benzo-fused heterocycloalkyl having 1 to 3 hetero atoms selected from N, O or S, C_6 or C_{10} -aryl, halogen, -COOH, -CONH $_2$, C_1 - C_6 -alkoxycarbonyl, halo- C_1 - C_6 -alkyl, halo- C_2 - C_6 -alkinyl, hydroxyl (OH), C_1 - C_6 -alkoxy, C_1 - C_4 -alkoxy- C_1 - C_4 -alkyl, thio- C_1 - C_6 -alkoxy, C_2 - C_6 -alkenyloxy, halo- C_1 - C_6 -alkoxy, halo- C_2 - C_6 -alkenyloxy, nitro, amino, nitro- C_1 - C_6 -alkyl, nitro- C_2 - C_6 -alkenyl, nitro- C_2 - C_6 -alkinyl, five to six ring membered optionally benzo-fused nitro-heterocyclyl having 1 to 3 hetero atoms selected from N, O or S, C_1 - C_4 -alkylamino- C_1 - C_4 -alkyl, C_1 - C_6 -alkylamino, di- C_1 - C_6 -alkylamino, C_2 - C_6 -alkenylamine, C_2 - C_6 -alkinylamine, C_1 - C_6 -acyl, C_2 - C_6 -alkenoyl, C_2 - C_6 -alkynoyl, C_1 - C_6 -acylamino, di- C_1 - C_6 -acylamino, C_1 - C_6 -acyloxy, C_1 - C_6 -alkylsulfonyloxy, five to six ring membered optionally benzo-fused heterocyclyl- C_1 - C_4 -alkyl having 1 to 3 hetero atoms selected from N, O or S, five to six ring membered optionally benzo-fused heterocycloxy having 1 to 3 hetero atoms selected from N, O or S, five to six ring membered optionally benzo-fused heterocyclylamino having 1 to 3 hetero atoms selected from N, O or S, five to six ring membered optionally benzo-fused halo-heterocycloalkyl having 1 to 3 hetero atoms selected from N, O or S, C_1 - C_6 -alkylsulfonyl, C_1 - C_6 -alkylcarbonyloxy, C_1 - C_6 -alkylthio, C_1 - C_6 -acylthio, phosphorus-containing groups such as phosphono and phosphinyl, aryl having 6 or 10 carbon atoms, five to six ring membered optionally benzo-fused heteroaryl having 1 to 3 hetero atoms selected from N, O or S, C_1 - C_4 -alkylaryl having 6 or 10 carbon atoms in the aryl, five to six ring membered optionally benzo-fused C_1 - C_6 -alkylheteroaryl having 1 to 3 hetero atoms selected from N, O or S, cyano, cyanate, isocyanate, -C(O)NH(C_1 - C_6 -alkyl), -NH-C(O)-(C_1 - C_6 -alkyl), -C(O)N(C_1 - C_6 -alkyl) $_2$ -CH $_2$ -N(C_1 - C_6 -alkyl) $_2$;

or two substituents of R^{19} may form a C_1 - C_4 -alkyl bridge; or two substituents of R^{19} together form a C_3 - C_6 -cycloalkyl-COOH group together with the ring to which they are bonded or form a pyrazol group which is optionally substituted by C_1 - C_3 -alkyl, -COOH, cyano or C_3 - C_6 -cycloalkyl;

R^{20} represents optionally halogen, hydroxyl, or cyano substituted C_1 - C_3 -alkyl;

R^2 represents a group -N(R^{18})-Q ^{2} -COOH, -N(R^{18})-Q ^{2} -CN or -N(R^{18})-Q ^{2} -tetrazolyl;

wherein R^{18} represents hydrogen, optionally C_3 - C_7 -cycloalkyl-substituted C_1 - C_4 -alkyl, C_3 - C_7 -cycloalkyl or a 4 to 6 membered heterocyclic ring having 1 to three hetero atoms selected from N, O and S;

Q ^{2} represents a direct bond, C_1 - C_4 -alkyl, C_3 - C_7 -cycloalkyl, C_1 - C_4 -alkyl- C_3 - C_7 -cycloalkyl or C_3 - C_7 -cycloalkyl- C_1 - C_4 -alkyl;

R^3 represents hydrogen, amino, methyl, ethyl, propyl, C_1 - C_3 -alkylthio, halo- C_1 - C_3 -alkyl, nitro, C_1 - C_3 -alkylamino, di- C_1 - C_3 -alkylamino, C_1 - C_3 -acyl or cyano;

R^{4a} and R^{4c} independently of each other represent hydrogen, amino, methyl, ethyl, propyl, C₁-C₃-alkoxy, C₁-C₃-alkylthio, halogen, halo- C₁-C₃-alkyl, nitro, C₁-C₃-alkylamino, di-C₁-C₃-alkylamino, C₁-C₃-acyl or cyano;

R^{4b} represents hydrogen, amino, methyl, ethyl, propyl, C₁-C₃-alkoxy, C₁-C₃-alkylthio, halogen, halo- C₁-C₃-alkyl, nitro, C₁-C₃-alkylamino, di-C₁-C₃-alkylamino or C₁-C₃-acyl;

Q¹ represents a single bond, -NH-, C₂-alkynyl, C₂-C₃-alkenyl, or C₁-C₃-alkyl; and

R⁶ represents a optionally substituted C₆ or C₁₀-aryl, optionally substituted C₃-C₈-cycloalkyl, optionally substituted C₃-C₈-cycloalkenyl or in each case optionally substituted and optionally heteroaryl- or benzo-fused, aromatic or non-aromatic heterocyclyl having in each case 5 to 7 ring members and 1 to 3 heteroatoms selected from N, O or S in the ring linked to Q¹;

and wherein one or more optional substituents of R⁶ are independently selected from C₁-C₆-alkyl, C₁-C₆-alkoxy, hydroxy-C₁-C₆-alkyl, amino-C₁-C₆-alkyl, amino-C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkinyl, thio-C₁-C₆-alkyl, C₁-C₄-alkyl-thio-C₁-C₄-alkyl, C₃-C₈-cycloalkyl, C₃-C₈-cycloalkenyl, optionally benzo- or heteroaryl-fused heterocycloalkyl having 5 to 7 ring members and 1 to 3 hetero atoms selected from N,O or S, C₆ or C₁₀-aryl, halogen, -COOH, -CONH₂, C₁-C₆-alkoxycarbonyl, halo-C₁-C₆-alkyl, halo-C₂-C₆-alkinyl, hydroxyl (OH), C₁-C₆-alkoxy, C₁-C₄-alkoxy-C₁-C₄-alkyl, thio-C₁-C₆-alkoxy, C₂-C₆-alkenyloxy, halo-C₁-C₆-alkoxy, halo-C₂-C₆-alkenyloxy, nitro, amino, nitro-C₁-C₆-alkyl, nitro-C₂-C₆-alkenyl, nitro-C₂-C₆-alkinyl, five to six ring membered optionally benzo-fused nitro-heterocycloalkyl having 5 to 7 ring members and 1 to 3 hetero atoms selected from N,O or S, C₁-C₄-alkylamino-C₁-C₄-alkyl, C₁-C₆-alkylamino, di-C₁-C₆-alkylamino, C₂-C₆-alkenylamino, C₂-C₆-alkinylamino, C₁-C₆-acyl, C₂-C₆-alkenoyl, C₂-C₆-alkinoyl, C₁-C₆-acylamino, di-C₁-C₆-acylamino, C₁-C₆-acyloxy, C₁-C₆-alkylsulfonyloxy, C₁-C₆-alkylsulfonyl, optionally benzo-fused heterocycloalkyl-C₁-C₄-alkyl having 5 to 7 ring members and 1 to 3 hetero atoms selected from N,O or S, optionally benzo-fused heterocycloalkyloxy having 5 to 7 ring members and 1 to 3 hetero atoms selected from N,O or S, optionally benzo-fused heterocycloalkylamino having 5 to 7 ring members and 1 to 3 hetero atoms selected from N,O or S, optionally benzo-fused halo-heterocycloalkyl having 5 to 7 ring members and 1 to 3 hetero atoms selected from N,O or S, C₁-C₆-alkylsulfonyl, C₁-C₆-alkylcarbonyloxy, C₁-C₆-alkylthio, C₁-C₆-acylthio, phosphorus-containing groups such as phosphono and phosphinyl, aryl having 6 to 10 carbon atoms, five to six ring membered optionally benzo-fused heteroaryl, C₁-C₄-alkylaryl having 6 or 10 carbon atoms in the aryl group, five to six ring membered optionally benzo-fused C₁-C₆-alkylheteroaryl having 5 to 7 ring members and 1 to 3 hetero atoms selected from N,O or S, cyano, cyanate, isocyanate, -C(O)NH(C₁-C₆-alkyl), -NH-C(O)-(C₁-C₆-alkyl), -C(O)N(C₁-C₆-alkyl)₂ or -CH₂N(C₁-C₆-alkyl)₂.

3. A compound of claim 1 or 2 and/or its solvates, hydrates and pharmaceutically acceptable salts wherein in formula (I)

R¹ represents -Q¹-R⁶;

R² represents -Q³-R¹⁹;

R¹⁹ represents optionally substituted cycloalkyl or optionally substituted piperidinyl, tetrahydropyranyl, thianyl, silianyl, azepanyl, oxepanyl, thiepanyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, tetrahydro-1,3,5-triazinyl, trioxanyl, trihianyl, diazepanyl, tetrahydropyridinyl, tetrahydropyrazolopyridine, oxotetrahydroquinolinyl, azabicycloheptanyl, azabicyclooctanyl, azaspirocyclooctanyl, dioxazaspirodecanyl;

and wherein R¹⁹ is unsubstituted or substituted by at least one substituent selected from cyano, C₃-C₈-cycloalkyl-cyano, C₁-C₃-alkyl-cyano, halo-C₁-C₃-alkyl, -COOH, C₁-C₃-alkyl-C(O)-NH₂, C₃-C₈-cycloalkyl-COOH, halo-C₃-C₈-cycloalkyl-COOH, piperidinyl-COOH, -SO₂H, -SO₃H, hydroxy-C₁-C₆-alkyl, hydroxyl (OH), -COCOOH, -CH(OH)-COOH, =CH-COOH, C₁-C₆-alkyl-COOH, halo-C₁-C₆-alkyl-COOH, cyano-C₁-C₆-alkyl-COOH, amino-C₁-C₆-alkyl-COOH, C₂-C₆-alkenyl-COOH, C₂-C₆-alkinyl-COOH, C₁-C₆-alkyl-OH, C₁-C₆-alkyl-O-C₁-C₆-alkyl, C₂-C₆-alkenyl-OH, C₁-C₆-alkyl-SH, C₂-C₆-alkenyl-SH, -C(O)-NH-OH, -C(O)-NH-NH₂, -C(O)-NH-S(O)₂-C₁-C₃-alkyl, tetrazolyl, triazolyl, imidazolyl, oxadiazolonyl, oxadiazolyl, C₁-C₃-alkyl-tetrazolyl, C₁-C₃-alkyl-triazolyl, C₁-C₃-alkyl-imidazolyl, C₁-C₃-alkyl-oxadiazolonyl, C₁-C₃-alkyl-oxadiazolyl, halo-C₁-C₃-alkyl-tetrazolyl, halo-C₁-C₃-alkyl-triazolyl, halo-C₁-C₃-alkyl-imidazolyl, halo-C₁-C₃-alkyl-oxadiazolonyl, halo-C₁-C₃-alkyl-oxadiazolyl, -N(C₁-C₃-alkyl)-C₁-C₃-alkyl-tetrazolyl, or =O (Oxo);

and further optional additional one to two substituents of R¹⁹ are selected from C₁-C₆-alkyl, hydroxy-C₁-C₆-alkyl, amino-C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkinyl, thio-C₁-C₆-alkyl, C₁-C₄-alkyl-thio-C₁-C₄-alkyl, C₃-C₈-cycloalkyl, C₃-C₈-cycloalkenyl, five to six membered optionally benzo-fused heterocycloalkyl having 1 to 3 hetero atoms selected from N, O or S, C₆ or C₁₀-aryl, halogen, -COOH, -CONH₂, C₁-C₆-alkoxycarbonyl, halo-C₁-C₆-alkyl, halo-C₂-C₆-alkinyl, hydroxyl (OH), C₁-C₆-alkoxy, C₁-C₄-alkoxy-C₁-C₄-alkyl, thio-C₁-C₆-alkoxy, C₂-C₆-alkenyloxy, halo-C₁-C₆-alkoxy, halo-C₂-C₆-alkenyloxy, nitro, amino, nitro-C₁-C₆-alkyl, nitro-C₂-C₆-alkenyl, nitro-C₂-C₆-alkinyl, five to six ring membered optionally benzo-fused nitro-heterocyclyl having 1 to 3 hetero atoms selected from N, O or S, C₁-C₄-alkylamino-C₁-C₄-alkyl, C₁-C₆-alkylamino, di-C₁-C₆-alkylamino, C₂-C₆-alkenylamine, C₂-C₆-alkinylamino, C₁-C₆-acyl, C₂-C₆-alkenoyl, C₂-C₆-alkinoyl, C₁-C₆-acylamino, di-C₁-C₆-acylamino, C₁-C₆-acyloxy, C₁-C₆-alkylsulfonyloxy, five to six ring membered optionally benzo-fused heterocyclyl-C₁-C₄-alkyl having 1 to 3 hetero atoms selected from N, O or S, five to six ring membered optionally benzo-fused heterocyclyloxy having 1 to 3 hetero atoms selected from N, O or S, five to six ring membered optionally benzo-fused heterocyclylamino having 1 to 3 hetero atoms selected from N, O or S, five to six ring membered optionally benzo-fused haloheterocycloalkyl having 1 to 3 hetero atoms selected from N, O or S, C₁-C₆-alkylsulfonyl, C₁-C₆-alkylcarbonyloxy, C₁-C₆-alkylthio, C₁-C₆-acylthio, phosphorus-containing groups such as phosphono and phosphinyl, aryl having 6 to 10 carbon atoms, five to six ring membered optionally benzo-fused heteroaryl having 1 to 3 hetero atoms selected from N, O or S, C₁-C₄-alkylaryl having 6 or 10 carbon atoms in the aryl, five to six ring membered optionally benzo-fused C₁-C₆-alkylheteroaryl having 1 to 3 hetero atoms selected from N, O or S, cyano, cyanate, isocyanate, -C(O)NH(C₁-C₆-alkyl), -NH-C(O)-(C₁-C₆-alkyl), -C(O)N(C₁-C₆-alkyl)₂ or -CH₂N(C₁-C₆-alkyl)₂; or

R² represents a group -N(R¹⁸)-Q²-COOH, -N(R¹⁸)-Q²-CN or -N(R¹⁸)-Q²-tetrazolyl;

wherein R¹⁸ represents hydrogen or methyl;

Q² represents a direct bond, C₁-C₄-alkyl, C₃-C₇-cycloalkyl-, C₁-C₄-alkyl-C₃-C₇-cycloalkyl- or C₃-C₇-cycloalkyl-C₁-C₄-alkyl-;

Q¹ represents a single bond or a -C≡C- group; and

R⁶ represents an optionally substituted phenyl or naphthyl, optionally substituted cyclohexyl, optionally substituted cyclohexenyl, or in each case optionally substituted pyrrolopyridinyl, pyridinyl, pyrimidinyl, pyrazinyl, thiophenyl, furanyl, indazolyl, benzoxazolyl, benzofuranyl, benzothiophenyl, indolyl, pyrrolyl, oxazolyl, pyrazolyl, thiazolyl, quinolinyl, imidazolyl, purinyl, dioxanyl, morpholinyl, piperazinyl or piperidinyl;

and wherein one or two optional substituents of R⁶ are selected from methyl, ethyl, propyl, butyl, C₁-C₃-alkoxy, hydroxy-C₁-C₆-alkyl, amino-C₁-C₃-alkyl, amino-carbonyl, C₂-C₄-alkenyl, C₂-C₃-alkinyl, thio-C₁-C₃-alkyl, cyclopropyl, cyclopentyl, cyclohexyl, C₃-C₆-cyclohexenyl, C₃-C₆-cyclopentenyl, morpholinyl, phenyl, fluorine, chlorine, bromine, -COOH, -CONH₂, C₁-C₃-alkoxycarbonyl, fluoro-C₁-C₆-alkyl, chloro-C₁-C₆-alkyl, hydroxyl (-OH), methoxy, C₁-C₃-alkoxy-C₁-C₄-alkyl, fluoro-C₁-C₃-alkoxy, chloro-C₁-C₃-alkoxy, nitro, amino, C₁-C₃-alkylamino, di-(C₁-C₃-alkyl)amino, C₁-C₃-acylamino, di-C₁-C₃-acylamino, C₁-C₃-acyloxy, C₁-C₃-alkylsulfonyloxy, C₁-C₃-alkylsulfonyl, optionally methyl substituted piperazinyl-C₁-C₄-alkyl, optionally methyl substituted morpholinyl-C₁-C₄-alkyl, optionally methyl substituted piperidinyl C₁-C₄-alkyl, C₁-C₃-alkylsulfonyl, C₁-C₃-alkylcarbonyloxy, C₁-C₃-alkylthio, C₁-C₆-acylthio, phenyl, five to six ring membered optionally benzo-fused heteroaryl, C₁-C₃-alkylphenyl, cyano, -C(O)NH(C₁-C₆-alkyl), -NH-C(O)-(C₁-C₃-alkyl), -C(O)N(C₁-C₆-alkyl)₂ or -CH₂N(C₁-C₆-alkyl)₂.

4. A compound of any of claims 1 to 3 and/or its solvates, hydrates and pharmaceutically acceptable salts wherein in formula (I)

R¹⁹ represents optionally substituted cycloalkyl or optionally substituted piperidinyl, azepanyl, piperazinyl, tetrahydropyrazolopyridine, oxotetrahydrochinolinyl;

and wherein R¹⁹ is unsubstituted or substituted by at least one substituent selected from cyano, cyano-C₁-C₃-alkyl, halo-C₁-C₃-alkyl, -COOH, -CH(OH)-COOH, =CH-COOH, -C₃-C₈-cycloalkyl-COOH, -SO₃H, C₁-C₆-alkyl-COOH, -C(O)-NH-OH, tetrazolyl, oxadiazolonyl, tetrazolyl-C₁-C₃-alkyl;

and further optional additional substituents of R¹⁹ are selected from methyl, ethyl, trifluoromethyl, hydroxyl (OH), amino or halogen.

5. A compound of any of claims 1 to 4 and/or its solvates, hydrates and pharmaceutically acceptable salts wherein in formula (I)

R¹⁹ represents optionally substituted piperidinyl which is bonded via the nitrogen ring atom and optionally carries at least one substituent in the 3-position of the ring selected from cyano,

cyano-C₁-C₃-alkyl, halo-C₁-C₃-alkyl, -COOH, -CH(OH)-COOH, =CH-COOH, -C₃-C₈-cycloalkyl-COOH, -SO₃H, C₁-C₆-alkyl-COOH, -C(O)-NH-OH, tetrazolyl, oxadiazolonyl, tetrazolyl-C₁-C₃-alkyl.

6. A compound of any of claims 1 to 5 and/or its solvates, hydrates and pharmaceutically acceptable salts wherein in formula (I)

wherein R¹ represents optionally substituted phenyl or optionally substituted piperidinyl which is bonded via the nitrogen ring atom.

7. A compound of any of claims 1 to 6 and/or its solvates, hydrates and pharmaceutically acceptable salts wherein in formula (I)

wherein R³ represents hydrogen, methyl or amino; and

R^{4a}, R^{4b} and R^{4c} independently of each other represent represent hydrogen, methyl, methoxy, or fluorine.

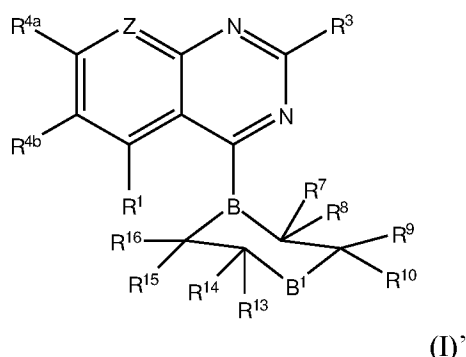
8. A compound of any of claims 1 to 7 and/or its solvates, hydrates and pharmaceutically acceptable salts wherein in formula (I)

wherein R¹⁹ represents piperidinyl bonded via its N-atom which is substituted in the 3-position with a -COOH, -(CH₂)_m-COOH or tetrazolyl and m represents 1, 2 or 3.

9. A compound of any of claims 1 to 8 and/or its solvates, hydrates and pharmaceutically acceptable salts wherein in formula (I)

wherein R¹ represents phenyl which is 3,4-substituted with halogen and/or C₁-C₃-alkyl.

10. A compound of any the claims 1 to 3 and/or its solvates, hydrates and pharmaceutically acceptable salts wherein formula (I) is represented by formula (I)'



wherein R¹, R³, R^{4a}, R^{4b} and Z are defined as in any of the claims 1 to 3 and

B¹ represents O, S, NR²¹, CH₂, CHR¹¹, C=O or CR¹¹R¹²;

B represents N, CH or CR¹⁷, preferably N;

R^7 , R^8 , R^9 , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} and R^{17} independently from another represent hydrogen, -COOH, C_1 - C_3 -alkyl-COOH, fluorine, chlorine, hydroxyl (-OH), C_1 - C_3 -alkyl-O- C_1 - C_3 -alkyl-, C_1 - C_3 -alkyl-N(C_1 - C_3 -alkyl)₂, C_1 - C_3 -alkyl-OH, or C_1 - C_4 -alkyl; and

R^{10} represents hydrogen, cyano, C_1 - C_3 -alkyl-cyano, halo- C_1 - C_3 -alkyl-cyano, halo- C_1 - C_3 -alkyl-, -NHCOO- C_1 - C_3 -alkyl, -COOH, -COCOOH, -CH(OH)-COOH, =CH-COOH, C_3 - C_8 -cycloalkyl-COOH, -NHSO₂- C_1 - C_3 -alkyl, -SO₂H, -SO₃H, C_1 - C_6 -alkyl-COOH, halo- C_1 - C_6 -alkyl-COOH, halo- C_1 - C_6 -alkyl-COOH, C_2 - C_6 -alkenyl-COOH, C_2 - C_6 -alkinyl-COOH, C_1 - C_6 -alkyl-OH, C_2 - C_6 -alkenyl-OH -, C_1 - C_6 -alkyl-SH, C_2 - C_6 -alkenyl-SH, -C(O)-NH-OH, C_1 - C_6 -alkinyl-COOH, tetrazolyl, triazolyl, imidazolyl, oxadiazolonyl, oxadiazolyl, C_1 - C_3 -alkyl-tetrazolyl, C_1 - C_3 -alkyl-triazolyl, C_1 - C_3 -alkyl-imidazolyl, C_1 - C_3 -alkyl-oxadiazolonyl, C_1 - C_3 -alkyl-oxadiazolyl, halo- C_1 - C_3 -alkyl-tetrazolyl, halo- C_1 - C_3 -alkyl-triazolyl, halo- C_1 - C_3 -alkyl-imidazolyl, halo- C_1 - C_3 -alkyl-oxadiazolonyl, halo- C_1 - C_3 -alkyl-oxadiazolyl, C_1 - C_6 -alkyl-CN, halo- C_1 - C_6 -alkyl-CN, C_3 - C_8 -cycloalkyl-CN, halo- C_1 - C_6 -alkyl-CN, C_2 - C_6 -alkenyl-CN, C_2 - C_6 -alkinyl-CN, C_3 - C_6 -cycloalkyl-tetrazolyl, C_3 - C_6 -cycloalkyl-triazolyl, C_3 - C_6 -cycloalkyl-imidazolyl, C_3 - C_6 -cycloalkylalkyl-oxadiazolonyl, C_3 - C_6 -cycloalkyl-oxadiazolyl, -CO-NH-tetrazolyl, -CO-NH-triazolyl, -CO-NH-imidazolyl, -CO-NH-oxadiazolonyl, -CO-NH-oxadiazolyl, cyano- C_1 - C_3 -alkyl-tetrazolyl, cyano- C_1 - C_3 -alkyl-triazolyl, cyano- C_1 - C_3 -alkyl-imidazolyl, cyano- C_1 - C_3 -alkyl-oxadiazolonyl, cyano- C_1 - C_3 -alkyl-oxadiazolyl, heterocyclyl substituted C_1 - C_3 -alkyl-tetrazolyl, heterocyclyl substituted C_1 - C_3 -alkyl-triazolyl, heterocyclyl substituted C_1 - C_3 -alkyl-imidazolyl, heterocyclyl substituted C_1 - C_3 -alkyl-oxadiazolonyl, heterocyclyl substituted C_1 - C_3 -alkyl-oxadiazolyl, heterocyclyl substituted C_1 - C_3 -alkyl-cyano wherein the heterocyclyl substituent can be selected from a 4 to 6 membered heterocyclic ring having 1 to three hetero atoms selected from N, O and S;

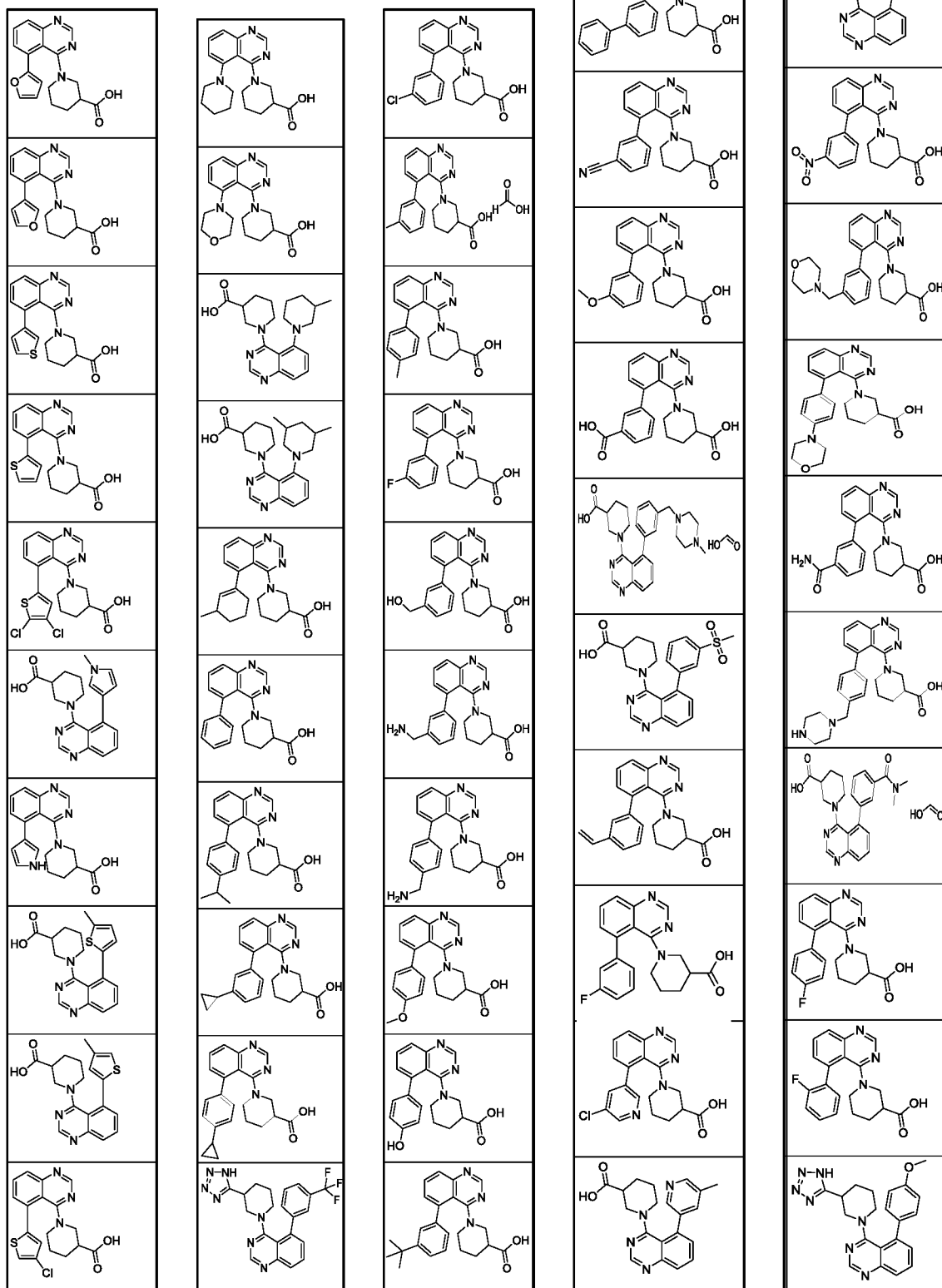
or R^9 and R^{10} together form a C_3 - C_6 -cycloalkyl-COOH group together with the ring to which they are bonded or form a pyrazol group which is optionally substituted by C_1 - C_3 -alkyl, COOH, cyano or C_3 - C_6 -cycloalkyl;

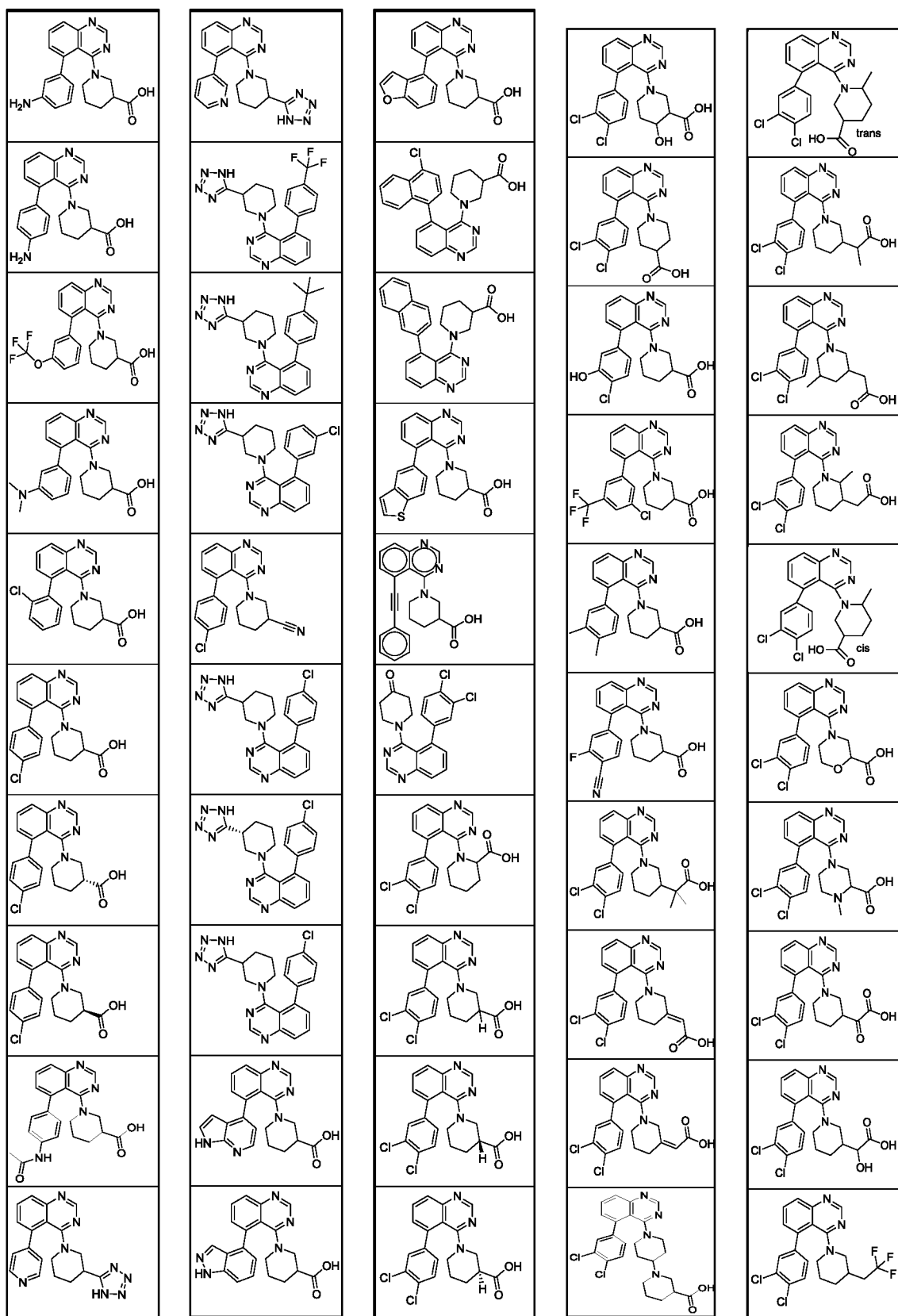
or R^{11} and R^{12} together represent a -O-CH₂-CH₂-O- spirocyclic moiety;

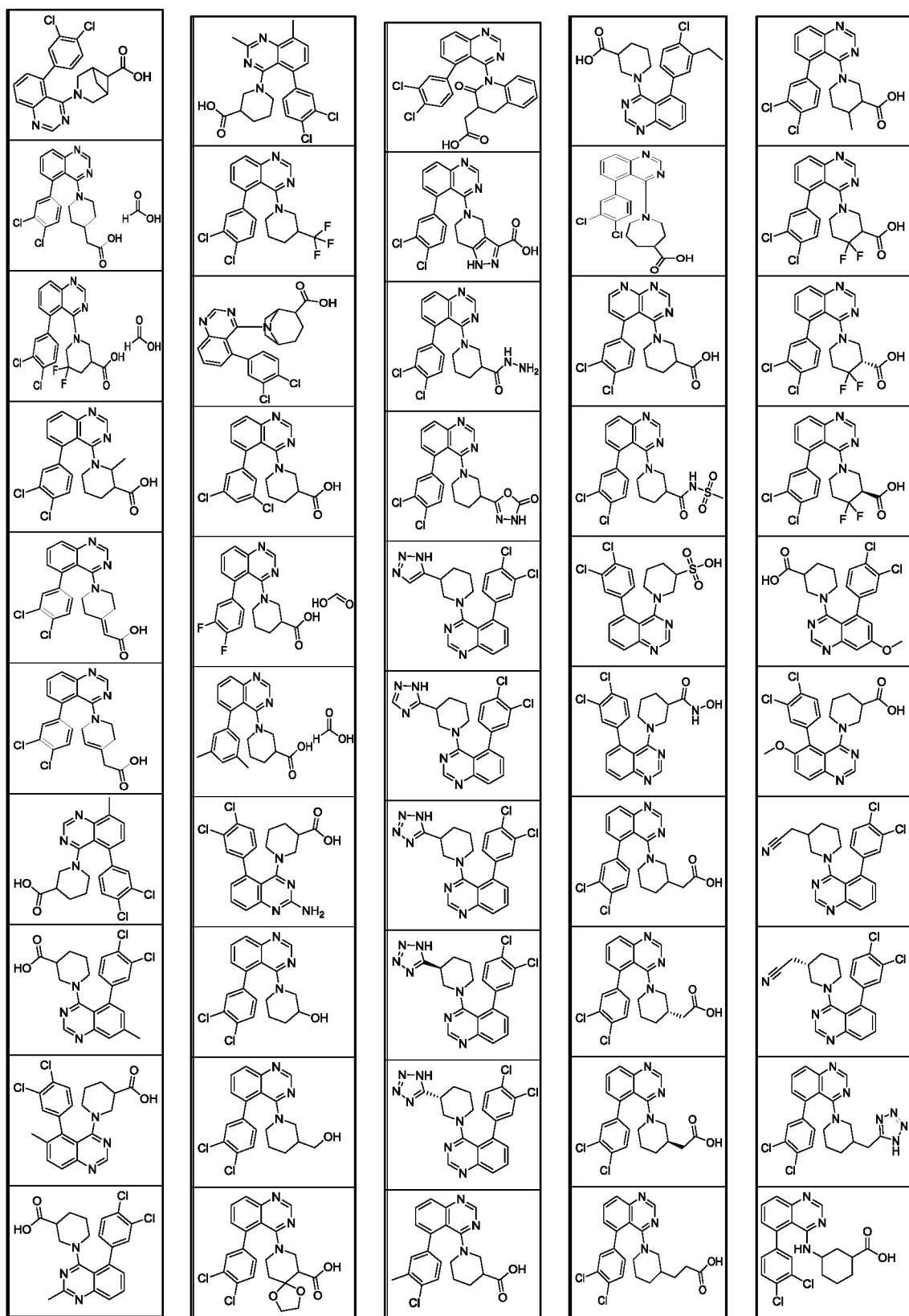
or two substituents of R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} and R^{17} form a C_1 - C_3 -alkyl bridge which may be substituted with -COOH,

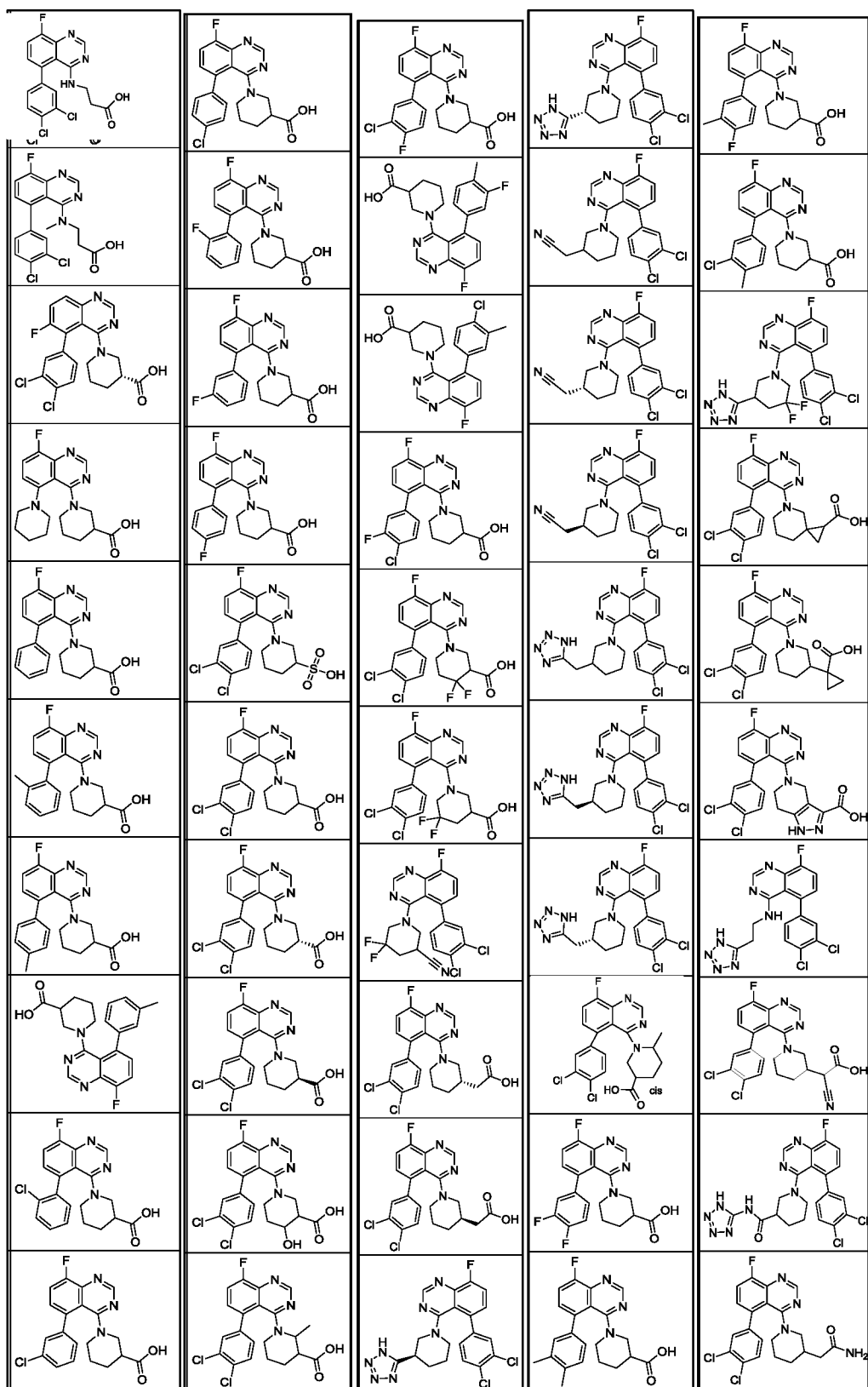
and R^{21} is hydrogen or C_{1-6} alkyl.

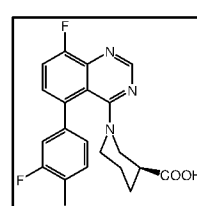
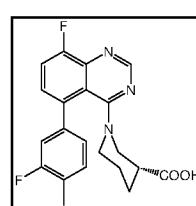
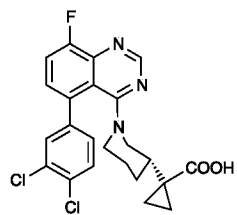
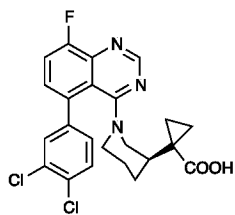
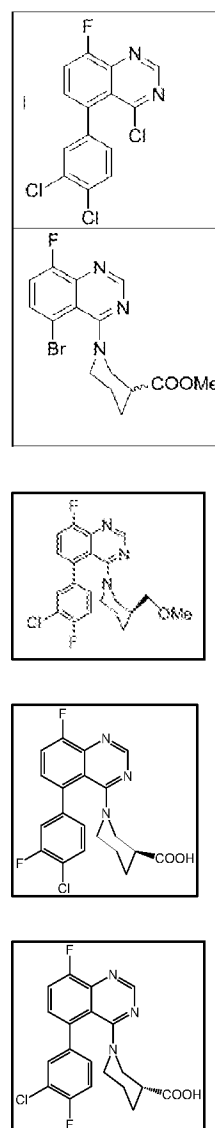
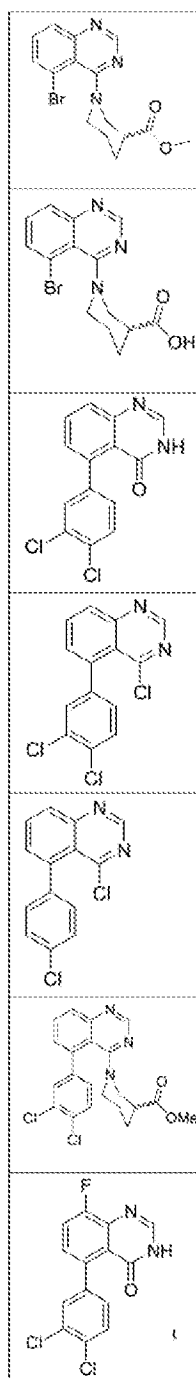
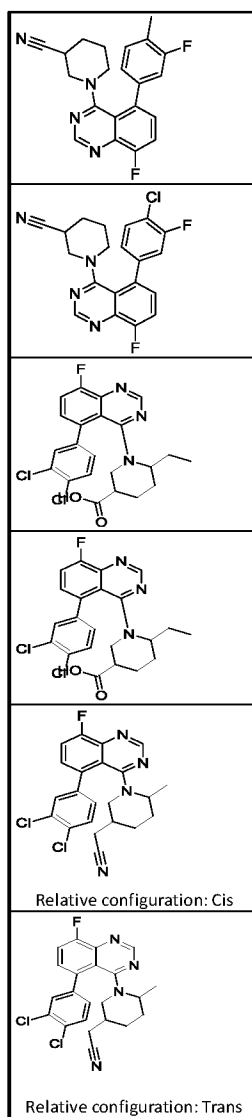
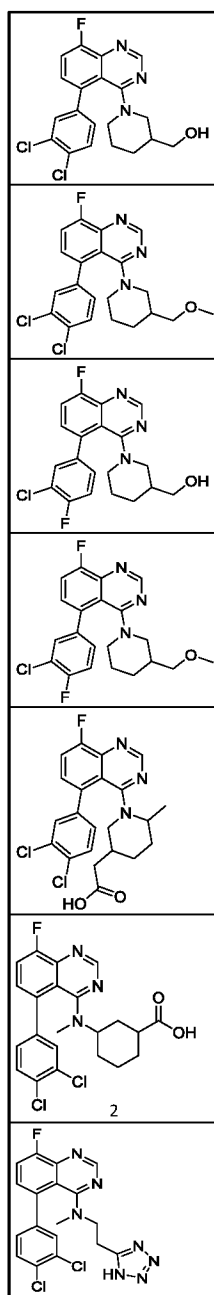
11. A compound according to any one of the preceding claims, selected from the group comprising:

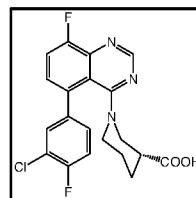
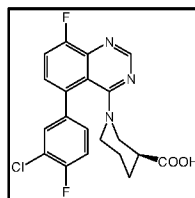
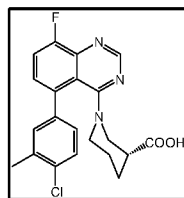
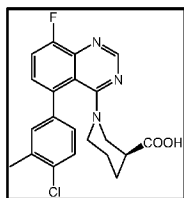






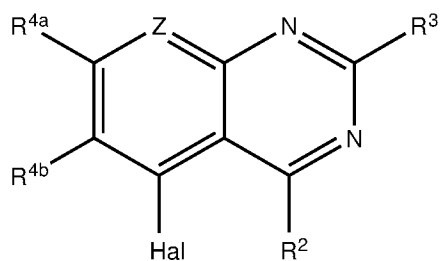






12. A process for making a compound of formula (I) according to claim 1 comprising the step of

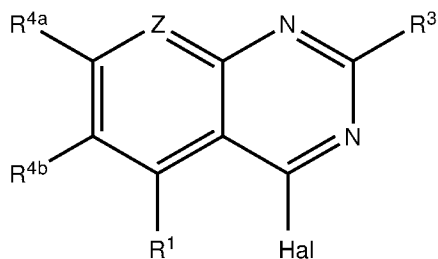
(a) reacting a compound of formula (II),



(II)

wherein R^2 , R^3 , R^{4a} , R^{4b} and Z are defined as mentioned in claim 1 and Hal represents halogen, preferably chlorine,

or reacting a compound of formula (III),



(III)

wherein R^1 , R^3 , R^{4a} , R^{4b} and Z are defined as mentioned in claim 1 and Hal represents halogen, preferably chlorine,

in an organic solvent in the presence of a base and optionally L-proline with an amine of formula (IV)

R^1 -H (IV)

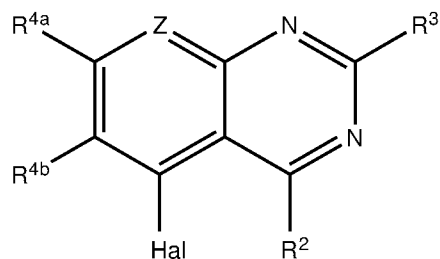
or (IV)' respectively,

R^2 -H (IV)'

wherein R^1 and R^2 are defined as in claim 1;

or

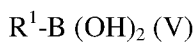
(b) reacting a compound of formula (II),



(II)

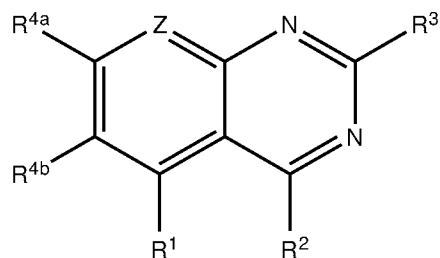
wherein R^2 , R^3 , R^{4a} , R^{4b} and Z are defined as mentioned in claim 1 and Hal represents halogen, preferably bromine,

in an organic solvent or organic solvent/water mixture in the presence of a base and a palladium catalyst with a boronic acid of formula (V),



wherein R^1 is defined as in claim 1;

or (c) converting a compound of formula (I)'',

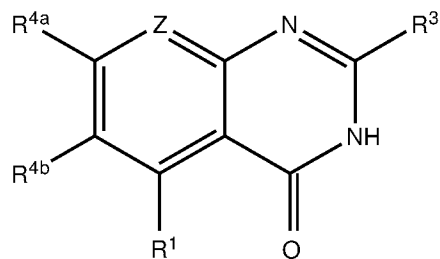


(I)''

R^1 , R^2 , R^3 , R^{4a} , R^{4b} and Z are defined as mentioned in claim 1 and wherein R^2 carries a $-COO-C_1-C_3$ -alkyl or $-SO_2-O-C_1-C_3$ -alkyl ester group,

in an organic solvent or organic solvent/water mixture in the presence of a base into a an acid group carrying compound,

or (d) reacting a compound of formula (VI),



(VI)

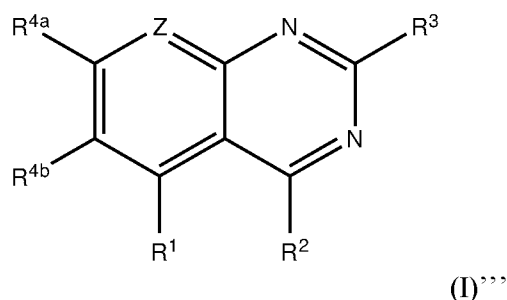
R^1 , R^3 , R^{4a} , R^{4b} and Z are defined as mentioned in claim 1,

in the presence of a dehydrating agent, preferably phosphoryl chloride, with an amine of formula (IV)'

R^2 -H (IV)'

herein R^2 is defined as in claim 1,

or (e) reacting a compound of the formula (I)'''



wherein R^1 , R^2 , R^3 , R^{4a} , R^{4b} and Z are defined as mentioned in claim 1 and wherein R^2 is carrying a cyano group,

in an organic solvent optionally in the presence of an amine with a triazide, preferably an alkali metal triazide,

and in all alternatives (a) to (e) the reaction product is isolated.

13. A compound of formula (I) according to any of claims 1 to 11 or pharmaceutically acceptable salts, hydrates or solvates thereof for use as a medicament.

14. A compound of formula (I) according to any of claims 1 to 11 or pharmaceutically acceptable salts, hydrates or solvates thereof for use in the treatment of diseases, disorders and conditions associated with glycine metabolism.

15. A compound of formula (I) according to any of claims 1 to 11 or pharmaceutically acceptable salts, hydrates or solvates thereof for use in the treatment of diseases, disorders and conditions which are selected from cancer, inflammation, Alzheimer's disease, metabolic disorders, neurological disorders and central nervous system disorders.

16. Use of a compound of formula (I) according to any of claims 1 to 11 or pharmaceutically acceptable salts, hydrates or solvates thereof in the manufacture of a medicament for the treatment of a disease, disorder or condition associated with glycine metabolism.

17. A method of treating a disease, disorder or condition associated with glycine metabolism in a subject in need of such treatment, comprising administering to said subject a

compound of formula (I) according to any of claims 1 to 11 or pharmaceutically acceptable salts, hydrates or solvates thereof.

18. A pharmaceutical composition comprising a compound of formula (I) according to any of claims 1 to 11 or pharmaceutically acceptable salts, hydrates and solvates thereof and a pharmaceutically acceptable excipient.

19. A pharmaceutical composition comprising a compound of formula (I) according to any of claims 1 to 11 or pharmaceutically acceptable salts, hydrates or solvates thereof and a pharmaceutically acceptable excipient for treatment of a disease, disorder or condition associated with glycine metabolism.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SG2017/050389

A. CLASSIFICATION OF SUBJECT MATTER

See Supplemental Box

According to International Patent Classification (IPC)

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Registry and CAPlus: structural search based on Formula (I)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/041655 A1 (THE UNITED STATES OF AMERICA, AS REPRESENTED BY THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES) 07 April 2011 compound 44, example 7, paragraph [0082]	1-19
X	QUINTELA J. M. ET AL., Pyridopyrimidines, pyrazolopyrimidines, pyridothienopyrimidines and pyridothienotriazines. Synthesis and biological activity. <i>Trends Heterocycl. Chem.</i> , 31 December 2005, Vol. 10, pages 97-114 [Retrieved on 2017-09-20] <DOI: NOT AVAILABLE> Abstract from STN, CAS registry number: 197645-82-2, 197645-86-6, 197645-88-8, 197645-89-9, and 197645-97-9	1-19
X	SAID S. A., Synthesis and Antianxiety Activity of Some New Pentaazacyclopenta[a]-naphthalenepyrido[2,3-d]pyrimidine Derivatives. <i>World J. Chem.</i> , 31 December 2009, Vol. 4, No. 2, pages 92-99 [Retrieved on 2017-09-20] <DOI: NOT AVAILABLE> compound 7, Scheme 1, Table 1	1-19

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

*Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search

20/09/2017 (day/month/year)

Date of mailing of the international search report

09/10/2017 (day/month/year)

Name and mailing address of the ISA/SG

Intellectual Property Office of Singapore

 51 Bras Basah Road
 #01-01 Manulife Centre
 Singapore 189554

Email: pct@ipos.gov.sg

Authorized officer

Gao Ye (Dr)

IPOS Customer Service Tel. No.: (+65) 6339 8616

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SG2017/050389

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	QUINTELA J. M. ET AL., Synthesis and antihistaminic activity of 2-guanadino-3-cyanopyridines and pyrido[2,3-d]-pyrimidines. <i>Bioorg. Med. Chem.</i> , 31 August 1997, Vol. 5, No. 8, pages 1543-1553 [Retrieved on 2017-09-20] <DOI: 10.1016/S0968-0896(97)00108-9> compounds 35-52, Figs. 3-4, Table 2, Scheme 1	1-19
X	SAID S. A. ET AL., Synthesis and Anti-Inflammatory Activities of Some New Pyridopyridine, Pyridopyrimidine and Pyridopyrimidotriazine Derivatives. <i>World Appl. Sci. J.</i> , 31 December 2010, Vol. 9, No. 6, pages 589-599 [Retrieved on 2017-09-20] <DOI: NOT AVAILABLE> compounds 19-20, scheme 3, table 2	1-19

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SG2017/050389

Supplemental Box

(Classification of Subject Matter)

Int. Cl.

C07D 239/94 (2006.01)

C07D 401/14 (2006.01)

C07D 403/12 (2006.01)

C07D 413/12 (2006.01)

C07D 471/04 (2006.01)

C07D 471/06 (2006.01)

A61K 31/517 (2006.01)

A61P 3/00 (2006.01)

A61P 25/00 (2006.01)

A61P 25/28 (2006.01)

A61P 29/00 (2006.01)

A61P 35/00 (2006.01)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050389

Note: This Annex lists known patent family members relating to the patent documents cited in this International Search Report. This Authority is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011/041655 A1	4/07/2011	NONE	