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(54) Titre : DERIVES D'AMINO QUINAZOLINE SERVANT D'INHIBITEURS DE P2X₃
(54) Title: AMINO QUINAZOLINE DERIVATIVES AS P2X₃ INHIBITORS

(57) Abrégé/Abstract:

The present invention relates to compounds of formula I inhibiting P2X purinoceptor 3; particularly the invention relates to compounds that are amino quinazoline derivatives, methods of preparing such compounds, pharmaceutical compositions containing them and therapeutic use thereof. The compounds of the invention may be useful in the treatment of many disorders associated with P2X₃ receptors mechanisms, such as respiratory diseases including cough, asthma, idiopathic pulmonary fibrosis (IPF) and chronic obstructive pulmonary disease (COPD).

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(54) Title: AMINO QUINAZOLINE DERIVATIVES AS P2X3 INHIBITORS

(57) Abstract: The present invention relates to compounds of formula I inhibiting P2X purinoceptor 3; particularly the invention relates to compounds that are amino quinazoline derivatives, methods of preparing such compounds, pharmaceutical compositions containing them and therapeutic use thereof. The compounds of the invention may be useful in the treatment of many disorders associated with P2X₃ receptors mechanisms, such as respiratory diseases including cough, asthma, idiopathic pulmonary fibrosis (IPF) and chronic obstructive pulmonary disease (COPD).



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AMINO QUINAZOLINE DERIVATIVES AS P2X₃ INHIBITORS

FIELD OF THE INVENTION

The present invention relates to compounds inhibiting P2X purinoceptor 3 (hereinafter P2X₃ inhibitors); particularly the invention relates to compounds that are
5 amino quinazoline derivatives, methods of preparing such compounds, pharmaceutical compositions containing them and therapeutic use thereof.

The compounds of the invention may be useful in the treatment of many disorders associated with P2X₃ receptors mechanisms, such as respiratory diseases including cough, asthma, idiopathic pulmonary fibrosis (IPF) and chronic obstructive pulmonary
10 disease (COPD).

BACKGROUND OF THE INVENTION

P2X receptors are cell surface ion channels activated by extracellular Adenosine 5-TriPhosphate (ATP). P2X receptor family are trimeric assemblies composed of seven distinct subunit subtypes (P2X₁₋₇) that assemble as homomeric and heteromeric
15 channels. All subunits share a common topology containing intracellular termini, two transmembrane helices forming the ion channels and a large extracellular domain containing the ATP binding site. Homomeric P2X₁, P2X₂, P2X₃, P2X₄, P2X₅, and P2X₇ channels and heteromeric P2X_{2/3} and P2X_{1/5} channels have been fully characterized following heterologous expression. P2X receptors are abundantly distributed, and
20 functional responses are seen in neurons, glia, epithelia, endothelia, bone, muscle, and hemopoietic tissues. On smooth muscles, P2X receptors respond to ATP released from sympathetic motor nerves (e.g., in ejaculation). On sensory nerves, they are involved in the initiation of afferent signals in several viscera (e.g., bladder, intestine) and play a key role in sensing tissue-damaging and inflammatory stimuli. Paracrine roles for ATP
25 signaling through P2X receptors are likely in neurohypophysis, ducted glands, airway

epithelia, kidney, bone and hemopoietic tissues. (RA. North: Molecular Physiology of P2X Receptors; *Physiol Rev*, Vol 82, Oct 2002). All P2X receptors are non-selective cation channels permeable to Na⁺ and Ca⁺ ions and are activated by ATP; however, the pharmacology of the receptor subtypes varies with respect to sensitivity to ATP and to
5 small molecules antagonists. (K Kaczmarek-Hajek et al: Molecular and functional properties of P2X receptors – recent progress and persisting challenges; *Purinergic Signalling* 8:375-417, 2012)

In humans, the P2X₃ receptor has been reported in heart and spinal cord at the mRNA level and in DRG, intestine (myenteric plexus neurons), urinary bladder
10 (urothelium and suburothelium), and dental pulp at the protein level (Garcia-Guzman M et al: Molecular characterization and pharmacological properties of the human P2X₃ purinoceptor: *Brain Res Mol Brain Res*. 1997;47(1–2):59–66).

The neurophysiological role of P2X₃ receptors in sensory nerve function in the airways is similar to that mediating somatic nociception (Udem BJ and Nassenstein C:
15 Airway nerves and dyspnea associated with inflammatory airway disease, *Respir Physiol Neurobiol* 167: 36-44, 2009). This similarity has driven hypotheses concerning the involvement of P2X₃ receptors in the symptoms of airway dysfunction including cough and bronchial hyper-reactivity (Ford AP: In pursuit of P2X₃ antagonists: novel
20 therapeutics for chronic pain and afferent sensitization, *Purinergic signal* 8 (suppl 1):3-26, 2012; North RA, Jarvis MF P2X Receptors as Drug Targets; *Mol Pharmacol*, 83:759-769, 2013). P2X₃ subunits are also co-localized in many neurons, particularly within DRG, nodose ganglia, nucleus tractus solitarius, and taste buds (Cheung KK, Burnstock G: Localization of P2X₃ receptors and coexpression with P2X₂ receptors during rat embryonic neurogenesis. *J Comp Neurol* 443(4):368–382 2002)

25 P2X₃ antagonists have been proposed for the treatment of diabetic neuropathic pain (Guo J et al: Contributions of purinergic P2X₃ receptors within the midbrain

periaqueductal gray to diabetes-induced neuropathic pain, *J Physiol Sci Jan*;65(1):99-104 (2015).

P2X₃ and P2X_{2/3} channels play an important role in the development of articular hyperalgesia of arthritic joints (Teixeira JM et al: P2X₃ and P2X_{2/3} Receptors Play a
5 Crucial Role in Articular Hyperalgesia Development Through Inflammatory Mechanisms in the Knee Joint Experimental Synovitis, *Mol Neurobiol Oct*;54(8):6174-6186, 2017).

P2X₃ are also a potential target for therapeutic treatment of bladder pain. They were also proposed to be analgesic targets to treat ureteral colicky pain and to facilitate ureteral stone passage (Canda AE et al: Physiology and pharmacology of the human ureter: basis
10 for current and future treatments, *Urol Int.* 78(4):289-98, 2007).

P2X₃ over-expression is involved in poor recurrence-free survival in hepatocellular carcinoma patients and identifies the P2X₃ as a potential therapeutic target (Maynard JP et al: P2X₃ purinergic receptor overexpression is associated with poor recurrence-free survival in hepatocellular carcinoma patients *Oncotarget Dec* 1;6(38):41162-79, 2015).

15 It has been suggested that P2X₃ antagonists may improve recovery of erectile function (Li CL et al: Effects of intracavernous injection of P2X₃ and NK1 receptor antagonists on erectile dysfunction induced by spinal cord transection in rats, *Andrologia.* Feb;47(1):25-9, 2015).

ATP enhances citric acid-evoked and histamine-evoked cough in preclinical
20 models, effects that can be attenuated by P2X₃ selective antagonists (Kamei J and Takahashi Y: Involvement of ionotropic purinergic receptors in the histamine-induced enhancement of the cough reflex sensitivity in guinea pigs, *Oct* 10;547(1-3):160-4, 2006). In humans, local delivery of ATP initiates cough and bronchospasm (Basoglu OK et al: Effects of aerosolized adenosine 5'-triphosphate vs adenosine 5'-monophosphate on
25 dyspnea and airway caliber in healthy nonsmokers and patients with asthma, *Chest.* Oct;128(4):1905-9, 2005).

The therapeutic promise of P2X₃ antagonists for the treatment of chronic cough was first recognized by Ford and Udem (Ford AP, Udem BJ: The therapeutic promise of ATP antagonism at P2X₃ receptors in respiratory and urological disorders, *Front Cell Neurosci*, Dec 19;7:267, 2013). P2X₃ are expressed by airway afferent nerves and mediate hypersensitivity of the cough reflex, which is dramatically reduced by the oral P2X₃ antagonist, AF-219 (Abdulqawi et al: P2X₃ receptor antagonist (AF-219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study, *Lancet* 385, 1198-205, 2015).

ATP is a key neurotransmitter in the taste system, acting largely via P2X_{2/3} heteromultimer receptors. Consequently, disruption of taste function may be an unintentional consequence of therapeutic trials of pain, chronic cough and other conditions using purinergic P2X₃ antagonists (Vandenbeuch A et al: Role of the ectonucleotidase NTPDase2 in taste bud function, *Proc Natl Acad Sci U S A*, Sep 3;110(36):14789-94, 2013. Bo X et al: Localization of ATP-gated P2X₂ and P2X₃ receptor immunoreactive nerves in rat taste buds, *Neuroreport*, 10(5):1107-11, 1999).

Various compounds have been described in the literature as P2X₃ and/or P2X_{2/3} Inhibitors.

WO2017058645 (Afferent Pharmaceuticals INC) discloses the use of diaminopyrimidine P2X₃/P2X_{2/3} antagonists for the treatment of disorders including cough, chronic cough and urge to cough, including cough associated with a respiratory disease or disorder, administering an efficacious amount of the compound disclosed. However, amino quinazoline derivatives are not disclosed.

WO2017011729 (Patara Pharma LLC), discloses the use of cromolyn or a pharmaceutically acceptable salt thereof and P2X₃ and/or a P2X_{2/3} receptor antagonist as antitussive agent, for the treatment of lung diseases and conditions.

WO2016091776, (Evotec AG), discloses 1,3-thiazol-2-yl substituted benzamide compounds that inhibit P2X₃ receptor and to pharmaceutical compositions containing such compounds, and the use of compounds for the treatment of several disorders, including the respiratory diseases.

5 WO2016088838 (Shionogi), discloses purine derivatives compounds having a novel P2X₃ and/or P2X_{2/3} receptor antagonizing effect.

WO2016084922, (Shionogi), discloses triazine derivatives compounds having a novel P2X₃ and/or P2X_{2/3} receptor antagonizing effect

10 WO2008123963 (Renovis) relates to fused heterocyclic compounds of the class tetrahydropyrido[4,3-d]pyrimidines and pharmaceutical compositions comprising such compounds. Also provided are methods for preventing and/or treating several disorders, such as neurodegenerative disorders, pain, asthma, autoimmune disorders administering the disclosed compounds.

15 WO2008130481 (Renovis) discloses 2-cyanophenyl fused heterocyclic compounds of the class tetrahydropyrido[4,3-d]pyrimidines and pharmaceutical compositions comprising such compounds.

20 WO2010033168 (Renovis) discloses a series of benzamides substituted with phenyl or pyridyl which are stated to be useful for treatment of diseases associated with P2X purinergic receptors, and more particularly to P2X₃ receptor and/ or P2X_{2/3} receptor antagonists. However, amino quinazoline derivatives are not disclosed.

WO2009110985 (Renovis) relates to phenyl- and pyridyl-substituted benzamide compounds and pharmaceutical compositions comprising such compounds, but not thiazole-substituted benzamides, rendering said compounds different from the compounds of the present invention.

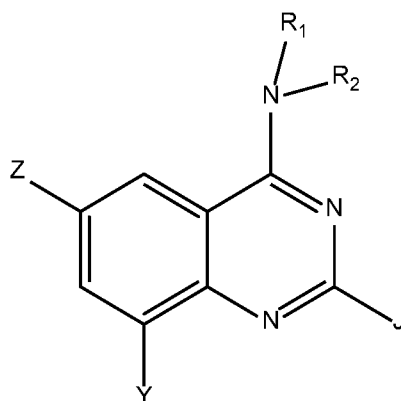
WO2008000645 (Roche) discloses tetrazole substituted arylamides compounds antagonists of P2X₃ and/or P2X_{2/3} receptors, useful for the treatment of genitourinary, pain, gastrointestinal and respiratory diseases, conditions and disorders.

Despite the above cited prior art, there is still the need of novel amino quinazoline compounds for treatment of diseases associated with P2X₃ receptors in many therapeutic areas such as in particular the respiratory diseases, preferably having a selective action on the P2X₃ receptor.

Of note, the state of the art does not describe or suggest amino quinazoline derivatives compounds of general formula (I) of the present invention which represent a solution to the aforementioned need.

SUMMARY OF THE INVENTION

The present invention refers to compounds of formula (I)



(I)

15 wherein

Z is selected from the group consisting of (C₃-C₈)heterocycloalkyl, (R^AR^B)N-, heteroaryl, aryl, wherein any of such alkyl, heteroaryl, heterocycloalkyl and aryl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl-, halo, CN, (R^AR^B)NC(O)-, (C₁-C₆)haloalkyl-, R^AO-, (R^AR^B)N(C₁-C₆)alkylene-, (C₃-C₇)cycloalkyl-, R^CSO₂-, (R^AR^B)N-;

R₁ is H or (C₁-C₄)alkyl;

R₂ is selected from the group consisting of (C₁-C₆)alkyl-, heteroaryl(C₁-C₄)alkyl-, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl-, heteroaryl-(C₁-C₆)hydroxyalkyl-, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl-(C₁-C₆)alkyl-, aryl-(C₁-C₄)alkyl-, (R^AR^B)N(C₁-C₆)alkylene-, (R^AR^B)N(O)C(C₁-C₄)alkylene-, R^AO(C₁-C₄)alkylene-
 5 wherein any of such alkyl, alkylene, aryl, heteroaryl and heterocycloalkyl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, R^AO(C₁-C₄)alkylene-, (C₁-C₆)haloalkyl, halo, oxo, R^AO-, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl-, heteroaryl, (R^AR^B)N-, -NHC(O)R^C, -C(O)N(R^AR^B), -SO₂N(R^AR^B), -O(C₁-C₄)alkylene-N(R^AR^B), aryl optionally substituted by halo, -OR^C, aryl-(C₁-
 10 C₄)alkyl-, -C(O)R^A;

R^A and R^B are at each occurrence independently H or selected from the group consisting of (C₁-C₄)alkyl-, (C₃-C₈)cycloalkyl, (C₁-C₆) haloalkyl, or

R^A and R^B may form together with the nitrogen atom to which they are attached a 5 or 6 membered saturated heterocyclic monocyclic ring system optionally containing a
 15 further heteroatom which is nitrogen or oxygen, which may be optionally substituted by one or more groups selected (C₁-C₄)alkyl and oxo;

R^C is at each occurrence H or selected from the group consisting of (C₁-C₆)alkyl, (R^AR^B)N-, aryl-(C₁-C₄)alkyl-;

Y is selected from the group consisting of H, -OR^D, R^CSO₂, halo, -NHSO₂R^C,
 20 heteroaryl, (C₃-C₈)heterocycloalkyl, wherein any of such heteroaryl and heterocycloalkyl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl and -C(O)N(R^AR^B);

R^D is selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl-, R^COC(O)(C₁-C₄)alkylene-,
 25 (R^AR^B)N(C₁-C₆)alkylene-, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl-(C₁-C₆)alkyl-, R^CO(C₁-C₄)alkylene-, (R^AR^B)N(O)C(C₁-C₄)alkylene-, wherein any of such

heterocycloalkyl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl;

J is H or selected from the group consisting of (C₁-C₆)alkyl, (R^AR^B)N-, (C₁-C₆) haloalkyl, -OR^C and halo.

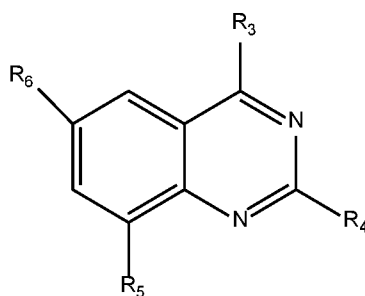
5 In a second aspect, the invention refers to a pharmaceutical composition comprising a compound of formula (I) or pharmaceutically acceptable salt thereof, either alone or in combination with another one or more active ingredient, in admixture with one or more pharmaceutically acceptable carrier or excipient.

10 In a third aspect, the invention provides a compound of formula (I) for the use as a medicament.

In a further aspect, the invention provides the use of a compound of formula (I) for use in treatment of any disease wherein the P2X₃ receptors are involved.

15 In a further aspect, the invention refers to a compound of formula (I) for use in the prevention and/or treatment of respiratory diseases including cough, sub-acute or chronic cough, treatment-resistant cough, idiopathic chronic cough, post-viral cough, iatrogenic cough, asthma, idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD) and cough associated with respiratory diseases such as COPD, asthma and bronchospasm.

In a further aspect, the invention refers to a compound of formula Ib



20

(Ib)

wherein

R₃ is OH or halo,

R₄ is H or OH,

R₅ is halo or -OMe,

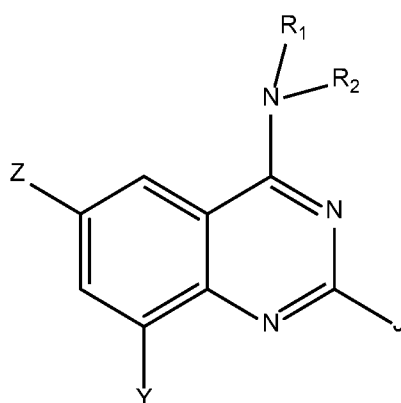
R₆ is halo or Z,

Z is as defined above.

- 5 In a further aspect, the invention refers to the use of compound of formula (Ib) as intermediate in the preparation of compounds of formula (I).

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to a compound of formula (I)



10

(I)

wherein

- Z** is selected from the group consisting of (C₃-C₈)heterocycloalkyl, (R^AR^B)N-, heteroaryl, aryl, wherein any of such alkyl, heteroaryl, heterocycloalkyl and aryl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl-, halo, CN, (R^AR^B)NC(O)-, (C₁-C₆)haloalkyl-, R^AO-, (R^AR^B)N(C₁-C₆)alkylene-, (C₃-C₇)cycloalkyl-, R^CSO₂-, (R^AR^B)N-;
- 15

R₁ is H or (C₁-C₄)alkyl;

- R₂** is selected from the group consisting of (C₁-C₆)alkyl-, heteroaryl(C₁-C₄)alkyl-, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl-, heteroaryl-(C₁-C₆)hydroxyalkyl-, (C₃-C₈)heterocycloalkyl-, (C₃-C₈)cycloalkyl-(C₁-C₆)alkyl-, aryl-(C₁-C₄)alkyl-, (R^AR^B)N(C₁-C₆)alkylene-, (R^AR^B)N(O)C(C₁-C₄)alkylene-, R^AO(C₁-C₄)alkylene-
- 20

wherein any of such alkyl, alkylene, aryl, heteroaryl and heterocycloalkyl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, R^AO(C₁-C₄)alkylene-, (C₁-C₆)haloalkyl, halo, oxo, R^AO-, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl-, heteroaryl, (R^AR^B)N-, -NHC(O)R^C, -C(O)N(R^AR^B), -SO₂N(R^AR^B), -O(C₁-C₄)alkylene-N(R^AR^B), aryl optionally substituted by halo, -OR^C, aryl-(C₁-C₄)alkyl-, -C(O)R^A;

R^A and R^B are at each occurrence independently H or selected from the group consisting of (C₁-C₄)alkyl-, (C₃-C₈)cycloalkyl, (C₁-C₆) haloalkyl, or

R^A and R^B may form together with the nitrogen atom to which they are attached a 5 or 6 membered saturated heterocyclic monocyclic ring system optionally containing a further heteroatom which is nitrogen or oxygen, which may be optionally substituted by one or more groups selected (C₁-C₄)alkyl and oxo;

R^C is at each occurrence H or selected from the group consisting of (C₁-C₆)alkyl, (R^AR^B)N-, aryl-(C₁-C₄)alkyl-;

Y is selected from the group consisting of H, -OR^D, R^CSO₂, halo, -NHSO₂R^C, heteroaryl, (C₃-C₈)heterocycloalkyl, wherein any of such heteroaryl and heterocycloalkyl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl and -C(O)N(R^AR^B);

R^D is selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl-, R^COC(O)(C₁-C₄)alkylene-, (R^AR^B)N(C₁-C₆)alkylene-, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl-(C₁-C₆)alkyl-, R^CO(C₁-C₄)alkylene-, (R^AR^B)N(O)C(C₁-C₄)alkylene-, wherein any of such heterocycloalkyl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl;

J is H or selected from the group consisting of (C₁-C₆)alkyl, (R^AR^B)N-, (C₁-C₆) haloalkyl, -OR^C and halo.

DEFINITIONS

The term “pharmaceutically acceptable salts”, as used herein, refers to derivatives of compounds of formula (I) wherein the parent compound is suitably modified by converting any of the free acid or basic group, if present, into the corresponding addition salt with any base or acid conventionally intended as being pharmaceutically acceptable.

5 Suitable examples of said salts may thus include mineral or organic acid addition salts of basic residues such as amino groups, as well as mineral or organic basic addition salts of acid residues such as carboxylic groups.

Cations of inorganic bases which can be suitably used to prepare salts comprise ions of alkali or alkaline earth metals such as potassium, sodium, calcium or magnesium.

10 Those obtained by reacting the main compound, functioning as a base, with an inorganic or organic acid to form a salt comprise, for example, salts of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methane sulfonic acid, camphor sulfonic acid, acetic acid, oxalic acid, maleic acid, fumaric acid, succinic acid and citric acid.

15 The term “halogen” or “halogen atoms” as used herein includes fluorine, chlorine, bromine, and iodine atom, preferably chlorine or fluorine.

The term “(C_x-C_y) alkyl” wherein x and y are integers, refers to a straight or branched chain alkyl radical having from x to y carbon atoms. Thus, when x is 1 and y is 6, for example, the term includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, 20 sec-butyl, t-butyl, n-pentyl and n-hexyl.

As used herein, the term “(C_x-C_y)alkylene” wherein x and y are integers, refers to a C_x-C_yalkyl radical having in total two unsatisfied valencies, such as a divalent methylene radical.

The expressions “(C_x-C_y) haloalkyl” wherein x and y are integers, refer to the 25 above defined “C_x-C_yalkyl” groups wherein one or more hydrogen atoms are replaced by one or more halogen atoms, which can be the same or different.

Examples of said “(C_x-C_y) haloalkyl” groups may thus include halogenated, poly-halogenated and fully halogenated alkyl groups wherein all of the hydrogen atoms are replaced by halogen atoms, e.g. trifluoromethyl or difluoro methyl, trifluoroethyl groups.

5 By way of analogy, the terms “(C₁-C₆) hydroxyalkyl” or “(C₁-C₆) aminoalkyl” refer to the above defined “(C₁-C₆) alkyl” groups wherein one or more hydrogen atoms are replaced by one or more hydroxy (OH) or amino group respectively. Examples include respectively hydroxymethyl, aminomethyl, dimethylaminopropyl and the like.

In the present description, unless otherwise provided, the aminoalkyl encompasses
10 alkyl groups (i.e. “(C₁-C₆) alkyl” groups) substituted by one or more amino group (-NR^AR^B). Thus, an example of aminoalkyl is a mono-aminoalkyl group such as R^AR^BN-(C₁-C₆) alkyl.

With reference to the substituent R^A and R^B as defined above and below, when R^A and R^B are taken together with the nitrogen atom they are linked to form 5 to 6 membered
15 heterocyclic radical, at least one further ring carbon atom in the said heterocyclic radical is optionally replaced by at least one heteroatom (e.g. N, S or O) and/or may bear -oxo (=O) substituent groups. It is understood that the said heterocyclic radical might be further optionally substituted on any available position in the ring, namely on a carbon atom, or on any heteroatom available for substitution. Substitution on a carbon atom includes spiro
20 disubstitution as well as substitution on two adjacent carbon atoms, in both cases thus form an additional 5 to 6 membered heterocyclic ring. Examples of said heterocycle radicals are 1-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl, 4-methylpiperazinyl, piperazin-4yl-2-one, 4-morpholinyl, morpholinyl-3-one, 1-(piperazin-1-yl)ethenone.

The term “(C_x-C_y) cycloalkyl” wherein x and y are integers, refers to saturated
25 cyclic hydrocarbon groups containing the indicated number of ring carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl.

The term "aryl" refers to mono cyclic carbon ring systems which have 6 ring atoms wherein the ring is aromatic. Examples of suitable aryl monocyclic ring systems include, for instance, phenyl.

The term "heteroaryl" refers to a mono- or bi-cyclic aromatic radical containing one or more heteroatoms selected from S, N and O, and includes radicals having two such monocyclic rings, or one such monocyclic ring and one monocyclic aryl ring, which are fused through a common bond. Examples of suitable 5,6-membered heteroaryl are: are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, isothiazolyl, pyrazolyl, oxazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, tetrazolyl and triazinyl.

The term "heterocyclyl" or "heterocyclic" relate to a saturated mono-, bi- or tri-cyclic non-aromatic radical containing one or more heteroatoms selected from S, N and O. In the case of bicyclic heterocyclic systems, included within the scope of the term are fused, spiro and bridged bicyclic systems.

The term "(C_x-C_y) heterocycloalkyl" wherein x and y are integers, refers to saturated or partially unsaturated monocyclic (C_x-C_y) cycloalkyl groups in which at least one ring carbon atom is replaced by at least one heteroatom (e.g. N, S or O) or may bear an -oxo (=O) substituent group. Said heterocycloalkyl (i.e. heterocyclic radical or group) may be further optionally substituted on the available positions in the ring, namely on a carbon atom, or on an heteroatom available for substitution. Substitution on a carbon atom includes spiro disubstitution as well as substitution on two adjacent carbon atoms, in both cases thus form additional condensed 5 to 6 membered heterocyclic ring. Examples of (C_x-C_y) heterocycloalkyl are represented by: pyrrolidinyl, imidazolidinyl, thiazolidinyl, piperazinyl, piperidinyl, morpholinyl, thiomorpholinyl, dihydro- or tetrahydro-pyridinyl, tetrahydrothiophenyl, azetidiny, oxetanyl, tetrahydropyranyl, pyranyl, 2H- or 4H-pyranyl, dihydro- or tetrahydrofuranly, dihydroisoxazolyl, pyrrolidin-2-one-yl,

dihydropyrrolyl radicals and the like.

Specific examples of said heterocycle radicals are tetrahydrothiophene 1,1-dioxide, 3,3-difluoropyrrolidinyl, 1-pyrrolidinyl, 1-methyl-2-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl, 4-morpholinyl.

5 The expressions “Aryloxy” and “Aryl (C₁-C₆) alkoxy” likewise “heteroAryloxy” and “Heteroaryl (C₁-C₆) alkoxy” refer to Aryl or Heteroaryl groups attached through an oxygen bridge and chained Aryl-alkoxy or HeteroAryl-alkoxy groups. Examples of such groups are phenyloxy, benzyloxy and pyridinyloxy respectively.

The term “aryl (C₁-C₆) alkyl” refers to an aryl ring linked to a straight-chained or
10 branched alkyl groups wherein the number of carbon atoms is from 1 to 6, e.g. phenylmethyl (i.e. benzyl), phenylethyl or phenylpropyl.

The term (C_z-C_k)heterocycloalkyl-(C_x-C_y)alkyl wherein z and k are integers, refers to an heterocyclic ring linked to a straight-chained or branched alkyl groups having from x to y carbon atoms.

15 Likewise, the term “heteroaryl (C_x-C_y)alkyl” or “aryl (C_x-C_y)alkyl” refers to an heteroaryl or aryl ring linked to a straight-chained or branched alkyl groups having from x to y carbon atoms.

The expression “ring system” refers to mono- or bicyclic or polycyclic ring systems which may be saturated, partially unsaturated or unsaturated, such as aryl,
20 (C₃-C₁₀) cycloalkyl, (C₃-C₆) heterocycloalkyl or heteroaryl.

The terms “group”, “radical” or “fragment” or “substituent” are synonymous and are intended to indicate functional groups or fragments of molecules attachable to a bond or other fragments or molecules. Thus, as an example, a “heterocyclic radical” herein refers to a mono- or bi-cyclic saturated or partially saturated heterocyclic moiety (group,
25 radical), preferably a 4 to 11 membered monocyclic radical, at least one further ring carbon atom in the said heterocyclic radical is optionally replaced by at least one further

heteroatom independently selected from N, S or O and/or may bear an -oxo (=O) substituent group, said heterocyclic radical is further optionally including spiro disubstitution as well as substitution on two adjacent or vicinal atoms forming an additional 5 to 6 membered cyclic or heterocyclic, saturated, partially saturated or aromatic ring. Examples of said heterocycle radicals are 1-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl, 4-morpholinyl and the like.

A dash (“-”) that is not between two letters or symbols is meant to represent the point of attachment for a substituent. When graphically represented the point of attachment in a cyclic functional group is indicated with a dot (“•”) localized in one of the available ring atom where the functional group is attachable to a bond or other fragment of molecules.

An oxo moiety is represented by (O) as an alternative to the other common representation, e.g. (=O). Thus, in terms of general formula, the carbonyl group is herein represented as -C(O)-, in general, the bracketed group is a lateral group, not included into the chain, and brackets are used, when deemed useful, to help disambiguating linear chemical formulas; e.g. the sulfonyl group -SO₂- might be also represented as -S(O)₂- to disambiguate e.g. with respect to the sulfinic group -S(O)O-.

Whenever basic amino or quaternary ammonium groups are present in the compounds of formula I, physiologically acceptable anions may be present, selected among chloride, bromide, iodide, trifluoroacetate, formate, sulfate, phosphate, methanesulfonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate, p-toluenesulfonate, pamoate and naphthalene disulfonate. Likewise, in the presence of acidic groups such as COOH groups, corresponding physiological cation salts may be present as well, for instance including alkaline or alkaline earth metal ions.

It will be apparent that compounds of formula (I) when contain one or more

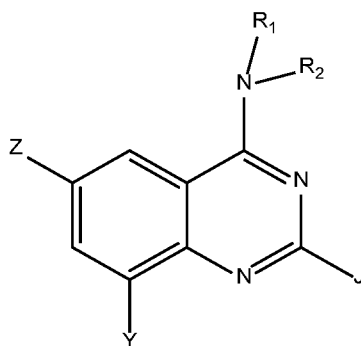
stereogenic center, may exist as optical stereoisomers.

Where the compounds according to the invention have at least one stereogenic center, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more stereogenic centers, they may additionally exist as diastereoisomers. All such single enantiomers, diastereoisomers and mixtures thereof in any proportion are encompassed within the scope of the present invention. The absolute configuration (R) or (S) for carbon bearing a stereogenic center is assigned on the basis of Cahn-Ingold-Prelog nomenclature rules based on groups' priorities.

The invention further concerns the corresponding deuterated derivatives of compounds of formula (I).

All preferred groups or embodiments described above and herebelow for compounds of formula I may be combined among each other and apply as well *mutatis mutandis*.

In a preferred embodiment, the invention is directed to compounds of formula (I) as defined above



(I)

wherein

Z is selected from the group consisting of heteroaryl, aryl, (R^AR^B)N-, (C₃-C₈)heterocycloalkyl, wherein any of such heteroaryl, aryl and heterocycloalkyl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, halo, CN, (R^AR^B)NC(O)-;

R₁ is H or (C₁-C₄)alkyl;

R₂ is selected from the group consisting of heteroaryl(C₁-C₄)alkyl-, (R^AR^B)N(O)C(C₁-C₄)alkylene-, wherein any of such heteroaryl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, halo, (C₁-C₆) haloalkyl;

5 **R^A** and **R^B** are at each occurrence independently H, (C₁-C₄)alkyl- and (C₃-C₈)cycloalkyl-, or R^A and R^B may form together with the nitrogen atom to which they are attached a 5 or 6 membered saturated heterocyclic monocyclic ring system optionally containing a further heteroatom which is oxygen or nitrogen, which may be optionally substituted by one or more groups selected from oxo, (C₁-C₄)alkyl;

10 **Y** is H;

J is H or selected from the group consisting of (C₁-C₄)alkyl, (R^AR^B)N-, halo, (C₁-C₆)haloalkyl.

In another preferred embodiment, the invention refers to compounds of formula (I) wherein

15 **Z** is selected from the group consisting of heteroaryl and aryl, wherein any of such heteroaryl and aryl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl and halo;

R₁ is H;

20 **R₂** is selected from the group consisting of (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl-, preferably (piperidinyl)methyl; heteroaryl(C₁-C₄)alkyl-, preferably (pyridinyl)methyl, (pyridinyl)ethyl, (pyridazinyl)methyl, (pyridazinyl)ethyl (pyrimidinyl)methyl, (pyrimidinyl)ethyl, (oxadiazolyl)ethyl, (thiadiazolyl)ethyl ([1,2,4]triazolo[4,3-a]pyrimidin-3-yl)methyl, and

25 Wherein any of such alkyl, heteroaryl and heterocycloalkyl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, (C₁-C₆)haloalkyl and -OH;

Y is selected from the group consisting of H and -OR^D,

R^D is at each occurrence selected from the group consisting of

(C₁-C₆)alkyl, preferably methyl,

(C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl-, preferably (oxetanyl)methyl,

(morpholinyl)methyl,

5 **R^C**OC(O)(C₁-C₄)alkylene-, preferably -CH₂C(O)OH;

(C₃-C₈)heterocycloalkyl, preferably tetrahydropyranyl, pyrrolidinyl, and

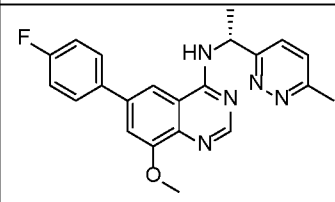
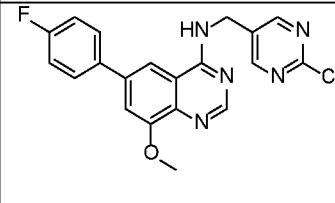
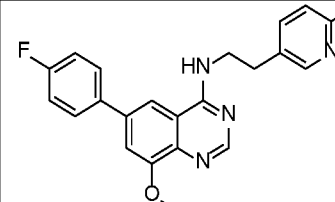
R^CO(C₁-C₄)alkylene-, preferably methoxyethyl;

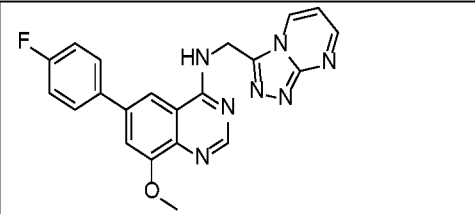
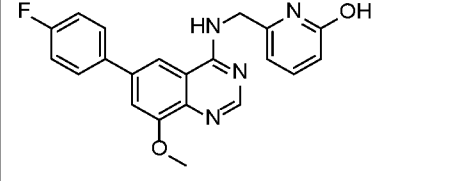
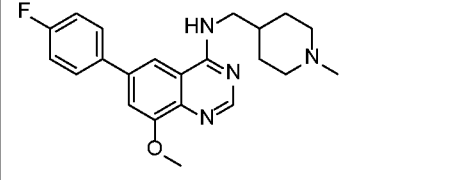
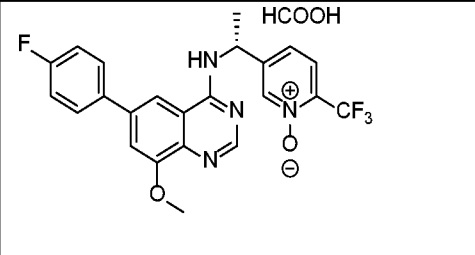
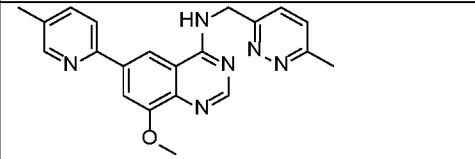
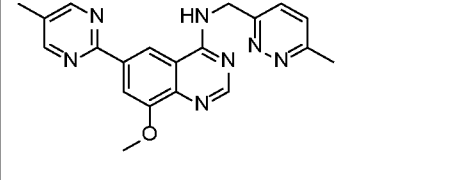
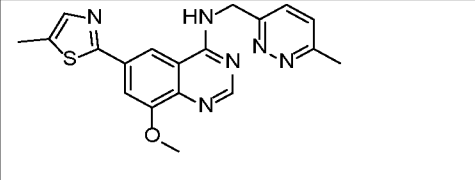
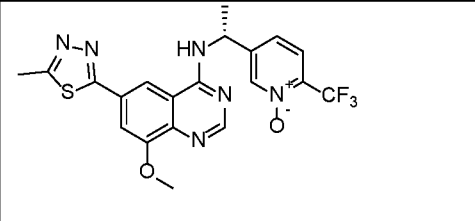
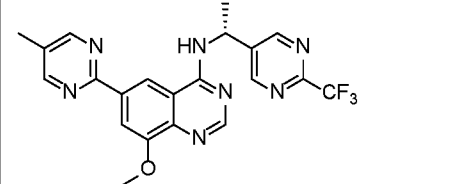
J is at each occurrence selected from the group consisting of H and -OR^C, preferably is H or -OH;

10 **R^C** is at each occurrence selected from the group consisting of H and (C₁-C₆)alkyl.

According to a preferred embodiment, the invention refers to at least one of the compounds listed in the Table 1 below and pharmaceutical acceptable salts thereof.

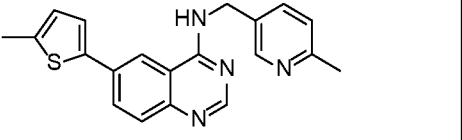
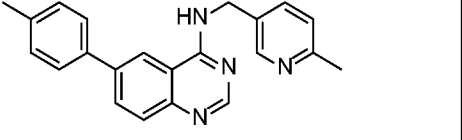
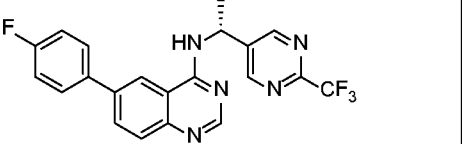
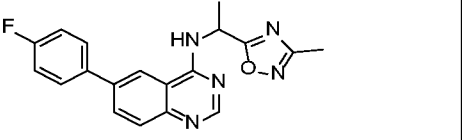
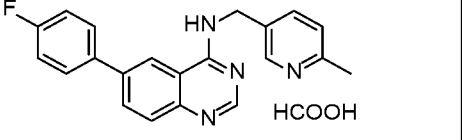
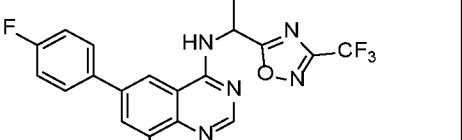
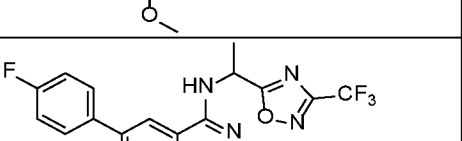
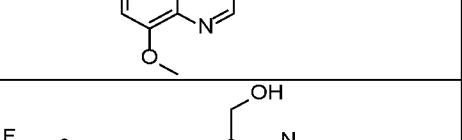
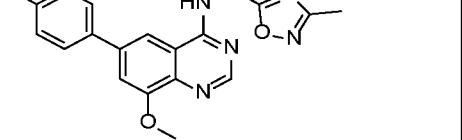
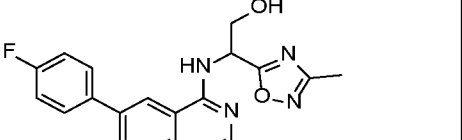
Table 1: List of preferred compounds having Formula (I)

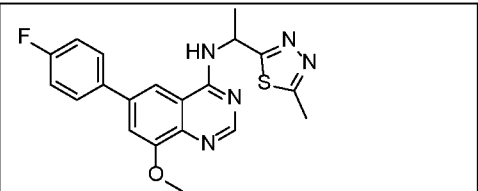
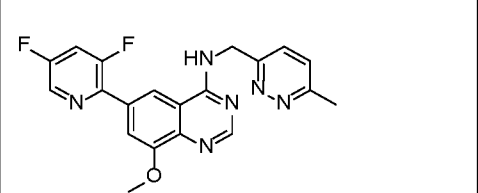
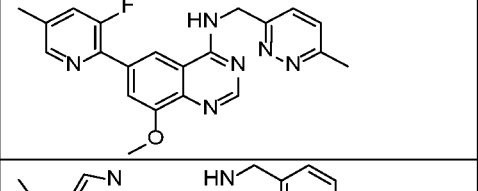
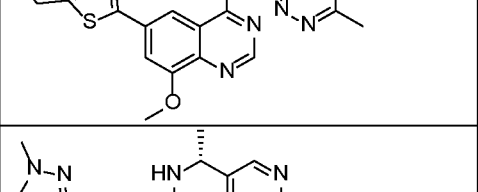
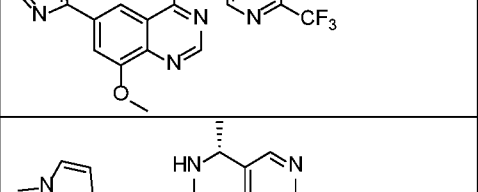
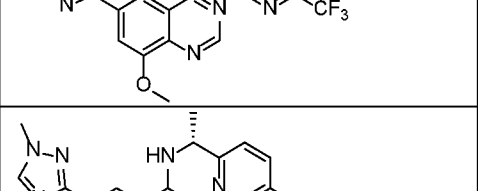
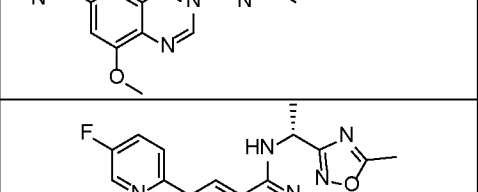
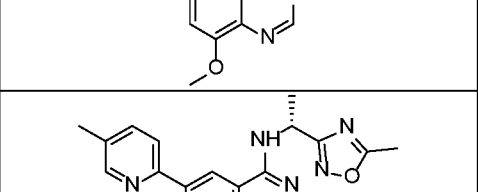
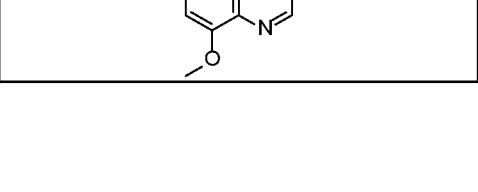
Ex. N.	Structure	Chemical Name
Example 4		(R)-6-(4-Fluorophenyl)-8-methoxy-N-(1-(6-methylpyridazin-3-yl)ethyl)quinazolin-4-amine
Example 19		6-(4-Fluorophenyl)-8-methoxy-N-((2-(trifluoromethyl)pyrimidin-5-yl)methyl)quinazolin-4-amine
Example 28		6-(4-Fluorophenyl)-8-methoxy-N-(2-(6-methylpyridin-3-yl)ethyl)quinazolin-4-amine

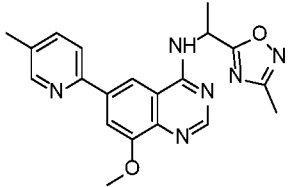
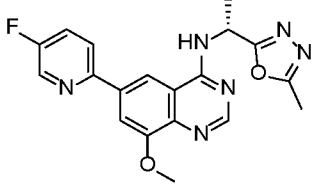
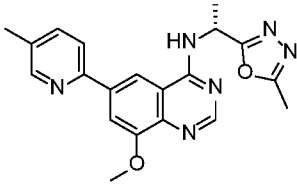
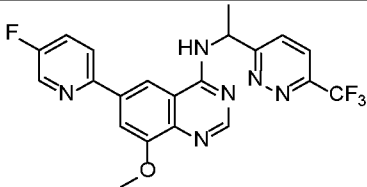
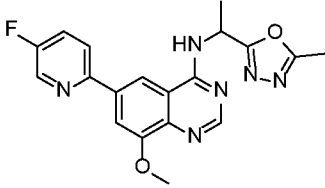
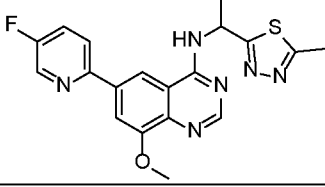
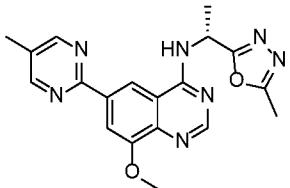
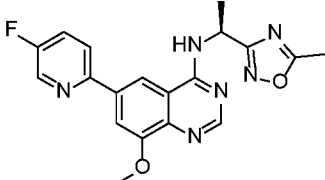
Example 48		N-([1,2,4]Triazolo[4,3-a]pyrimidin-3-ylmethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 65		6-[[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]methyl]-1H-pyridin-2-one
Example 110		6-(4-Fluorophenyl)-8-methoxy-N-[(1-methyl-4-piperidyl)methyl]quinazolin-4-amine
Example 112		(R)-5-(1-((6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)amino)ethyl)-2-(trifluoromethyl)pyridine 1-oxide formate
Example 116		8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(5-methylpyridin-2-yl)quinazolin-4-amine
Example 134		8-Methoxy-N-[(6-methylpyridazin-3-yl)methyl]-6-(5-methylpyrimidin-2-yl)quinazolin-4-amine
Example 140		8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(5-methylthiazol-2-yl)quinazolin-4-amine
Example 145		(R)-5-(1-((8-Methoxy-6-(5-methyl-1,3,4-thiadiazol-2-yl)quinazolin-4-yl)amino)ethyl)-2-(trifluoromethyl)pyridine 1-oxide
Example 148		8-Methoxy-6-(5-methylpyrimidin-2-yl)-N-[(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl]quinazolin-4-amine

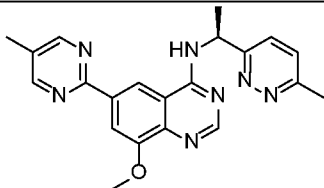
Example 149		6-(5-Fluoropyrimidin-2-yl)-8-methoxy-N-[(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl]quinazolin-4-amine
Example 150		6-(5-Fluoro-2-pyridyl)-8-methoxy-N-[(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl]quinazolin-4-amine
Example 151		8-Methoxy-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-6-(5-methylpyrimidin-2-yl)quinazolin-4-amine
Example 152		8-Methoxy-6-(1-methylpyrazol-3-yl)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]quinazolin-4-amine
Example 155		6-(5-Fluoro-2-pyridyl)-8-methoxy-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]quinazolin-4-amine
Example 175		6-(4-chlorophenyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 181		(R)-6-(4-fluorophenyl)-8-methoxy-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 182		6-(4-fluorophenyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 184		(R)-6-(4-Fluorophenyl)-8-methoxy-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)-amino)-quinazolin-2-ol

Example 206		6-(4-fluorophenyl)-8-(2-methoxyethoxy)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine
Example 207		6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-(oxetan-3-ylmethoxy)quinazolin-4-amine
Example 208		6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-tetrahydropyran-4-yloxyquinazolin-4-amine
Example 214		2-[6-(4-fluorophenyl)-4-[(6-methylpyridazin-3-yl)methylamino]quinazolin-8-yl]oxyacetic acid, sodium salt
Example 216		6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-pyrrolidin-3-yloxyquinazolin-4-amine
Example 217		6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-(morpholin-2-ylmethoxy)quinazolin-4-amine
Example 228		6-(5-methylpyridin-2-yl)-N-[(6-methylpyridin-3-yl)methyl]quinazolin-4-amine
Example 231		N-[(6-methylpyridazin-3-yl)methyl]-6-(5-methylpyridin-2-yl)quinazolin-4-amine

Example 240		N-((6-methylpyridin-3-yl)methyl)-6-(5-methylthiophen-2-yl)quinazolin-4-amine
Example 241		N-((6-methylpyridin-3-yl)methyl)-6-(p-tolyl)quinazolin-4-amine
Example 243		(R)-6-(4-fluorophenyl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 244		6-(4-fluorophenyl)-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine
Example 247		6-(4-fluorophenyl)-N-((6-methylpyridin-3-yl)methyl)quinazolin-4-amine formate
Example 257		Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine
Example 258		Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine
Example 267		Single enantiomer 1 of 2-((6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)amino)-2-(3-methyl-1,2,4-oxadiazol-5-yl)ethan-1-ol
Example 268		Single enantiomer 2 of 2-((6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)amino)-2-(3-methyl-1,2,4-oxadiazol-5-yl)ethan-1-ol
Example 281		Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,3,4-thiadiazol-2-yl)ethyl)quinazolin-4-amine

Example 282		Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,3,4-thiadiazol-2-yl)ethyl)quinazolin-4-amine
Example 296		6-(3,5-Difluoropyridin-2-yl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 297		6-(3-Fluoro-5-methyl-2-pyridyl)-8-methoxy-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine
Example 298		6-(5-Ethylthiazol-2-yl)-8-methoxy-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine
Example 299		(R)-8-methoxy-6-(1-methyl-1H-1,2,4-triazol-3-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 300		(R)-8-methoxy-6-(1-methyl-1H-pyrazol-3-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 301		(R)-8-methoxy-6-(1-methyl-1H-1,2,4-triazol-3-yl)-N-(1-(6-methylpyridazin-3-yl)ethyl)quinazolin-4-amine
Example 315		(R)-6-(5-fluoropyridin-2-yl)-8-methoxy-N-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine
Example 316		(R)-8-methoxy-N-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)-6-(5-methylpyridin-2-yl)quinazolin-4-amine

Example 317		8-Methoxy-N-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]-6-(5-methyl-2-pyridyl)quinazolin-4-amine
Example 318		6-(5-fluoro-2-pyridyl)-8-methoxy-N-[(1R)-1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl]quinazolin-4-amine
Example 319		8-methoxy-N-[(1R)-1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl]-6-(5-methyl-2-pyridyl)quinazolin-4-amine
Example 321		6-(5-fluoro-2-pyridyl)-8-methoxy-N-[1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl]quinazolin-4-amine
Example 322		6-(5-fluoropyridin-2-yl)-8-methoxy-N-(1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)quinazolin-4-amine
Example 323		6-(5-fluoropyridin-2-yl)-8-methoxy-N-(1-(5-methyl-1,3,4-thiadiazol-2-yl)ethyl)quinazolin-4-amine
Example 324		8-methoxy-N-[(1R)-1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl]-6-(5-methylpyrimidin-2-yl)quinazolin-4-amine
Example 325		(S)-6-(5-fluoropyridin-2-yl)-8-methoxy-N-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine

Example 326		8-Methoxy-N-[(1S)-1-(6-methylpyridazin-3-yl)ethyl]-6-(5-methylpyrimidin-2-yl)quinazolin-4-amine
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In a further preferred embodiment, the invention refers to compound of formula (I) wherein

Z is selected from the group consisting of

heteroaryl, preferably pyrimidinyl, thiazolyl, pyridinyl, thiophenyl,

5 aryl, preferably phenyl,

($R^A R^B$)N-, wherein R^A and R^B form together with the nitrogen atom to which they are attached a 5 or 6 membered saturated heterocyclic monocyclic ring system containing a further heteroatom which is oxygen or nitrogen, said heterocyclic radical being optionally in its turn further substituted with one or more oxo, methyl and fluorine;

10 any of such heteroaryl and aryl is further optionally substituted by one or more groups selected from

methyl,

fluorine,

$R^C SO_2$ - wherein R^C is selected from the group consisting of fluorine, -OH and

15 ($R^A R^B$)N- wherein R^A and R^B are H,

CN,

($R^A R^B$)NC(O)- wherein R^A and R^B are H,

R₁ is H or methyl;

R₂ is selected from the group consisting of

20 heteroaryl(C1-C4)alkyl-, preferably (pyridinyl)methyl, (pyridazyl)methyl, (pyrimidinyl)ethyl, (oxadiazolyl)ethyl

($R^A R^B$)N(O)C(C1-C4)alkylene-, preferably $R^A R^B$ are H, cyclopropyl;

any of said heteroaryl may be optionally substituted by one or more groups selected from

methyl, fluorine, and trifluoromethyl.

Y is H;

J is H or selected from the group consisting of

halo, preferably chlorine,

5 (C₁-C₄)alkyl, preferably methyl,

(C₁-C₆)haloalkyl preferably trifluoromethyl,

(R^AR^B)N- wherein R^A and R^B are at each occurrence independently H, cyclopropyl and methyl or, in alternative,

10 R^A and R^B form together with the nitrogen atom to which they are attached a 6 membered saturated heterocyclic monocyclic ring system containing a further heteroatom which is oxygen.

According to a preferred embodiment, the invention refers to at least one of the compounds listed in the Table 2 below and pharmaceutical acceptable salts thereof.

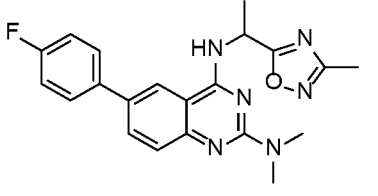
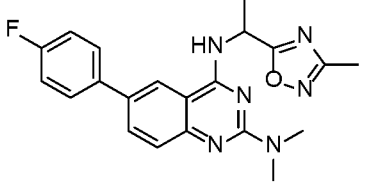
Table 2: List of preferred compounds having Formula (I)

Ex. N.	Structure	Chemical Name
Example 228		6-(5-methylpyridin-2-yl)-N-((6-methylpyridin-3-yl)methyl)quinazolin-4-amine
Example 229		N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)-6-(5-methylpyridin-2-yl)quinazolin-4-amine
Example 230		N-((6-methylpyridazin-3-yl)methyl)-6-(5-methylpyridin-2-yl)-2-(trifluoromethyl)quinazolin-4-amine
Example 231		N-((6-methylpyridazin-3-yl)methyl)-6-(5-methylpyridin-2-yl)quinazolin-4-amine

Example 232		N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)-6-(5-methylthiazol-2-yl)quinazolin-4-amine
Example 233		2-chloro-6-(4-fluorophenyl)-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine
Example 234		6-(4-fluorophenyl)-N2,N2-dimethyl-N4-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazoline-2,4-diamine
Example 235		N2-cyclopropyl-6-(4-fluorophenyl)-N4-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazoline-2,4-diamine
Example 236		6-(4-fluorophenyl)-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)-2-morpholinoquinazolin-4-amine
Example 237		2-((2-(cyclopropylamino)-6-(4-fluorophenyl)quinazolin-4-yl)amino)propanamide
Example 238		N-cyclopropyl-2-((2-(cyclopropylamino)-6-(4-fluorophenyl)quinazolin-4-yl)amino)propanamide
Example 239		6-(4-fluorophenyl)-2-methyl-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 240		N-((6-methylpyridin-3-yl)methyl)-6-(5-methylthiophen-2-yl)quinazolin-4-amine

Example 241		N-((6-methylpyridin-3-yl)methyl)-6-(p-tolyl)quinazolin-4-amine
Example 242		N-((6-methylpyridazin-3-yl)methyl)-6-(2-methylpyrimidin-5-yl)quinazolin-4-amine
Example 243		(R)-6-(4-fluorophenyl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 244		6-(4-fluorophenyl)-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine
Example 245		2-(4-(((6-methylpyridin-3-yl)methyl)amino)quinazolin-6-yl)benzonitrile
Example 246		2-(4-(((6-methylpyridin-3-yl)methyl)amino)quinazolin-6-yl)benzamide
Example 247		6-(4-fluorophenyl)-N-(((6-methylpyridin-3-yl)methyl)quinazolin-4-amine formate
Example 248		6-(4-fluorophenyl)-N-(((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 249		N-((3,5-difluoropyridin-2-yl)methyl)-6-(4-fluorophenyl)quinazolin-4-amine hydrochloride
Example 250		6-(4-fluorophenyl)-N-methyl-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine
Example 251		(R)-6-(3,3 difluoropyrrolidin-1-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine

Example 252		(R)-6-morpholino-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 253		(R)-1-methyl-4-(4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino) quinazolin-6-yl)piperazin-2-one
Example 254		N-((6-methylpyridazin-3-yl)methyl)-6-morpholinoquinazolin-4-amine
Example 283		Single enantiomer 1 of 6-(4-fluorophenyl)-N-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]quinazolin-4-amine
Example 284		Single enantiomer 2 of 6-(4-fluorophenyl)-N-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]quinazolin-4-amine
Example 285		Single enantiomer 1 of N2-cyclopropyl-6-(4-fluorophenyl)-N4-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]quinazoline-2,4-diamine
Example 286		Single enantiomer 2 of N2-cyclopropyl-6-(4-fluorophenyl)-N4-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]quinazoline-2,4-diamine
Example 287		Single enantiomer 1 of 6-(4-fluorophenyl)-N-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]-2-morpholino-quinazolin-4-amine
Example 288		Single enantiomer 2 of 6-(4-fluorophenyl)-N-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]-2-morpholino-quinazolin-4-amine

Example 289		Single enantiomer of 6-(4-fluorophenyl)-N2,N2-dimethyl-N4-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]quinazoline-2,4-diamine
Example 290		Single enantiomer of 6-(4-fluorophenyl)-N2,N2-dimethyl-N4-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]quinazoline-2,4-diamine

In a further preferred embodiment, the invention is addressed to compound of formula (I) wherein

Z is H or selected from the group consisting of heteroaryl and aryl, wherein any of such heteroaryl and aryl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl and halo;

R1 is H;

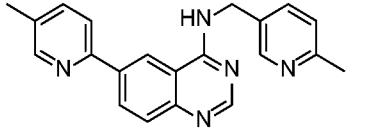
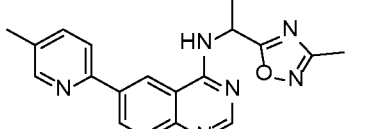
R2 is selected from the group consisting of heteroaryl(C₁-C₄)alkyl-, wherein any of such heteroaryl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl and (C₁-C₆) haloalkyl;

Y is H;

J is H or halo.

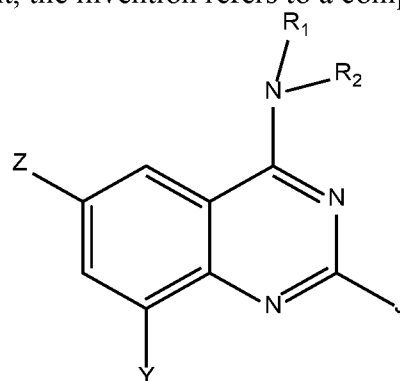
According to a preferred embodiment, the invention refers to at least one compound of Table 3, selected from:

Table 3: List of preferred compounds having Formula (I)

Ex. N.	Structure	Chemical Name
Example 228		6-(5-methylpyridin-2-yl)-N-((6-methylpyridin-3-yl)methyl)quinazolin-4-amine
Example 229		N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)-6-(5-methylpyridin-2-yl)quinazolin-4-amine

Example 231		N-((6-methylpyridazin-3-yl)methyl)-6-(5-methylpyridin-2-yl)quinazolin-4-amine
Example 232		N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)-6-(5-methylthiazol-2-yl)quinazolin-4-amine
Example 233		2-chloro-6-(4-fluorophenyl)-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine
Example 240		N-((6-methylpyridin-3-yl)methyl)-6-(5-methylthiophen-2-yl)quinazolin-4-amine
Example 241		N-((6-methylpyridin-3-yl)methyl)-6-(p-tolyl)quinazolin-4-amine
Example 243		(R)-6-(4-fluorophenyl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 244		6-(4-fluorophenyl)-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine
Example 247		6-(4-fluorophenyl)-N-((6-methylpyridin-3-yl)methyl)quinazolin-4-amine formate
Example 248		6-(4-fluorophenyl)-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 283		Single enantiomer 1 of 6-(4-fluorophenyl)-N-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]quinazolin-4-amine
Example 284		Single enantiomer 2 of 6-(4-fluorophenyl)-N-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]quinazolin-4-amine

In a preferred embodiment, the invention refers to a compound of formula (I)



(I)

wherein

- 5 **Z** is selected from the group consisting of heteroaryl and aryl, wherein any of such heteroaryl and aryl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, halo, CN, (R^AR^B)NC(O)-, (C₁-C₆)haloalkyl, R^AO-, (R^AR^B)N(C₁-C₆)alkylene-, (C₃-C₇)cycloalkyl-, R^CSO₂-, (R^AR^B)N-;
- R₁** is H or (C₁-C₄)alkyl,
- 10 **R₂** is selected from the group consisting of (C₁-C₆)alkyl, heteroaryl(C₁-C₄)alkyl-, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl, heteroaryl-(C₁-C₆)hydroxyalkyl, aryl-(C₁-C₄)alkyl-, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl-(C₁-C₆)alkyl-, (R^AR^B)N(C₁-C₆)alkylene-; R^AO(C₁-C₄)alkylene,
- wherein any of such alkyl, alkylene, aryl, heteroaryl, cycloalkyl and heterocycloalkyl may
- 15 be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, R^AO(C₁-C₄)alkylene, (C₁-C₆)haloalkyl, oxo, R^AO-, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl, heteroaryl, aryl optionally substituted by halo, R^CO-, (R^AR^B)N-, -NHC(O)R^C, -C(O)N(R^AR^B), halo, -SO₂N(R^AR^B), -O(R^AO(C₁-C₄)alkylene-N(R^AR^B), aryl-(C₁-C₄)alkyl-, -C(O)R^A,
- 20 **R^A and R^B** are at each occurrence independently H or selected from the group consisting of (C₁-C₄)alkyl-, aryl, (C₁-C₆) haloalkyl, or
- R^A and R^B may form together with the nitrogen atom to which they are attached a

6 membered saturated heterocyclic monocyclic ring system optionally containing a further heteroatom which is nitrogen or oxygen, which may be optionally substituted by (C₁-C₄)alkyl- and oxo;

R^C is H or selected from the group consisting of (C₁-C₆)alkyl, (R^AR^B)N-, aryl-(C₁-C₄)alkyl-,

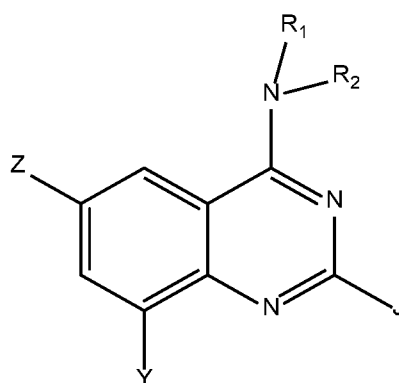
Y is selected from the group consisting of -OR^D, R^CSO₂-, halo, -NHSO₂R^C, heteroaryl, (C₃-C₈)heterocycloalkyl,

wherein any of such heteroaryl and heterocycloalkyl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, -C(O)N(R^AR^B);

J is H or selected from the group consisting of (C₁-C₆)alkyl, -OR^C,

R^D is H or (C₁-C₆)alkyl.

In a still preferred embodiment, the invention refers to a compound of formula (I) as defined above



(I)

wherein

Z is selected from the group consisting of heteroaryl and aryl, wherein any of such heteroaryl and aryl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, halo, CN, (R^AR^B)NC(O)-, (C₁-C₆)haloalkyl, R^AO-, (R^AR^B)N(C₁-C₆)alkylene-, (C₃-C₇)cycloalkyl-, R^CSO₂-, (R^AR^B)N-;

R₁ is H;

R₂ is selected from the group consisting of (C₁-C₆)alkyl, heteroaryl(C₁-C₄)alkyl-,

(C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl, heteroaryl-(C₁-C₆)hydroxyalkyl, aryl-(C₁-C₄)alkyl-, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl-(C₁-C₆)alkyl-, (R^AR^B)N(C₁-C₆)alkylene-; R^AO(C₁-C₄)alkylene,

wherein any of such alkyl, alkylene, aryl, heteroaryl, cycloalkyl and
 5 heterocycloalkyl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, R^AO(C₁-C₄)alkylene-, (C₁-C₆)haloalkyl, oxo, R^AO-, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl, heteroaryl, aryl optionally substituted by halo, R^CO-, (R^AR^B)N-, -NHC(O)R^C, -C(O)N(R^AR^B), halo, -SO₂N(R^AR^B), -O(R^AO(C₁-C₄)alkylene-N(R^AR^B), aryl-(C₁-C₄)alkyl-, -C(O)R^A;

10 **R^A and R^B** are at each occurrence independently H or selected from the group consisting of (C₁-C₄)alkyl-, aryl, (C₁-C₆) haloalkyl, or

R^A and R^B may form together with the nitrogen atom to which they are attached a
 6 membered saturated heterocyclic monocyclic ring system optionally containing a further heteroatom which is nitrogen or oxygen, which may be optionally substituted by
 15 (C₁-C₄)alkyl- and oxo;

R^C is H or selected from the group consisting of (C₁-C₆)alkyl, (R^AR^B)N-, aryl-(C₁-C₄)alkyl-,

Y is selected from the group consisting of -OR^D, R^CSO₂, halo, -NHSO₂R^C, heteroaryl, (C₃-C₈)heterocycloalkyl, wherein any of such heteroaryl and heterocycloalkyl
 20 may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, -C(O)N(R^AR^B);

J is H or selected from the group consisting of (C₁-C₆)alkyl, OR^C;

R^D is H or (C₁-C₆)alkyl.

In a further preferred embodiment, the invention is addressed to compound of
 25 formula (I) wherein

Z is H or selected from the group consisting of

(R^AR^B)N-,

heteroaryl, preferably thiadiazolyl, thiazolyl, pyrazolyl, pyridazyl, oxadiazolyl, pyridinyl, pyrimidinyl,

aryl, preferably phenyl,

5 R^AO-, wherein R^A is H,

each of said heteroaryl and aryl may be optionally substituted by one or more groups selected from

methyl,

halo, preferably fluorine and chlorine,

10 CN,

(R^AR^B)NC(O)-, wherein R^A and R^B are at each occurrence independently H or methyl,

C₁-C₆haloalkyl, preferably trifluoromethyl and difluoromethyl,

15 R^AO-, wherein R^A is H or selected from methyl, trifluoromethyl and difluoromethyl,

(R^AR^B)N(C₁-C₆)alkylene-, wherein R^A and R^B are methyl,

cyclopropyl,

R^CSO₂-, wherein R^C is methyl,

(R^AR^B)N- wherein R^A and R^B are independently H and methyl;

20 **R₁** is H;

R₂ is selected from the group consisting of

heteroaryl(C₁-C₄)alkyl-, preferably ([1,2,4]triazolo[4,3-a]pyrimidin-3-yl)methyl, (triazolyl)methyl, (triazolyl)ethyl, (imidazo[1,2-a]pyrimidinyl)methyl,

(pyrimidinyl)ethyl, (pyrimidinyl)methyl, (pyrazolyl)methyl, (pyridazinyl)methyl,

25 (pyridazinyl)ethyl (oxadiazolyl)methyl, (oxadiazolyl)propyl, (pyridinyl)methyl,

(pyridinyl)ethyl, (oxadiazolyl)ethyl,

(C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl, preferably (piperidinyl)methyl,
(tetrazolyl)methyl, (morpholinyl)ethyl,

heteroaryl(C₁-C₆)hydroxyalkyl-, preferably (oxadiazolyl)methanol,

(C₃-C₈)cycloalkyl(C₁-C₆)alkyl-, preferably (cyclopropyl)methyl,

5 aryl-(C₁-C₄)alkyl-, preferably (phenyl)methyl,

(R^AR^B)N(C₁-C₆)alkylene-, preferably dimethylaminobutyl,
dimethylaminopropyl,

each of said aryl, heteroaryl, cycloalkyl and heterocycloalkyl is optionally further
substituted by one or more groups selected from

10 (C₁-C₃)alkyl, preferably methyl and ethyl,

trifluoromethyl,

oxo,

chlorine,

R^AO-, wherein R^A is selected from the group of trifluoroethyl, difluoroethyl,

15 methyl and ethyl,

(C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl-, preferably (piperidinyl)methyl,

(C₃-C₈)heterocycloalkyl, preferably piperazinyl optionally further substituted by
methyl,

heteroaryl, preferably pyridinyl,

20 -NHC(O)R^C, wherein R^C is methyl,

(R^AR^B)N-, wherein R^A and R^B are methyl,

R^CO-, wherein R^C is methyl,

-C(O)N(R^AR^B); wherein R^A is H and R^B is methyl;

Y is selected from the group consisting of -OR^D, R^CSO₂, halo, -NHSO₂R^C,
25 heteroaryl wherein any of such heteroaryl may be optionally substituted by one or more
groups selected from (C₁-C₃)alkyl, -C(O)N(R^AR^B);

R^D is (C₁-C₆)alkyl, preferably methyl;

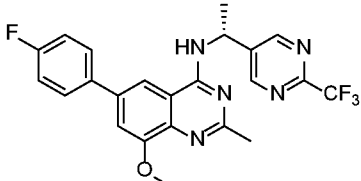
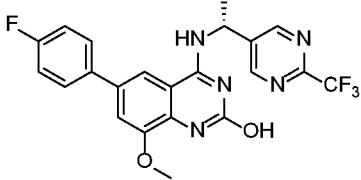
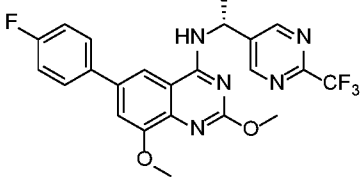
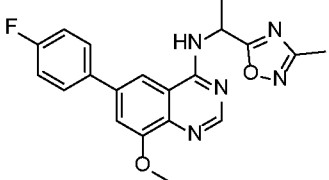
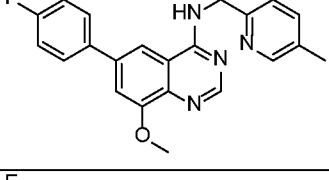
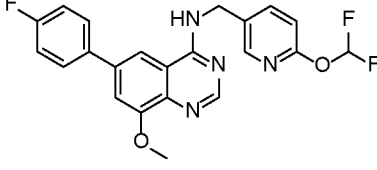
J is selected from the group consisting of

(C₁-C₆)alkyl, preferably methyl,

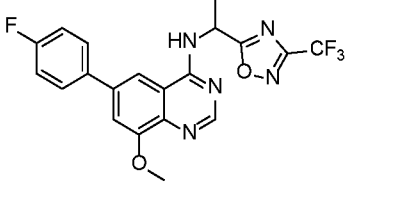
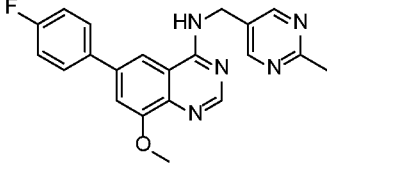
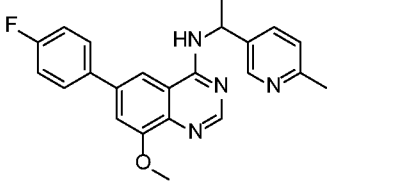
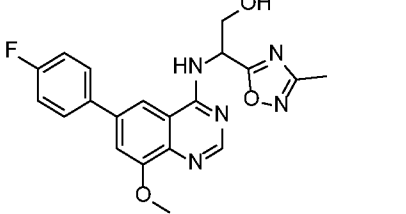
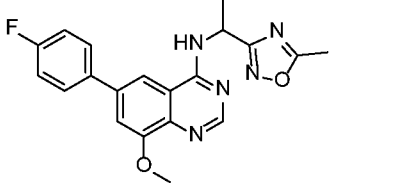
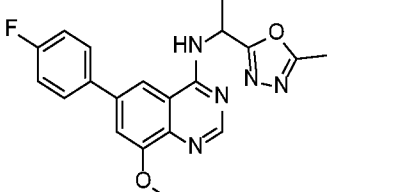
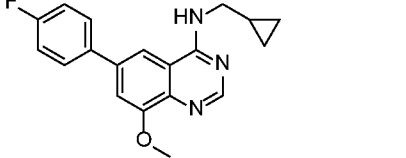
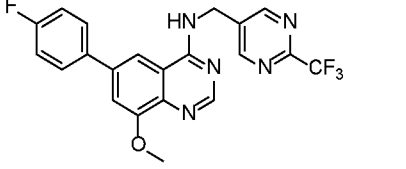
-OR^C wherein R^C is H or (C₁-C₆)alkyl, preferably methyl.

5 According to specific embodiments, the invention refers to at least one compound as listed in the Table 4 below and pharmaceutical acceptable salts thereof.

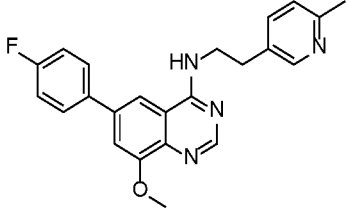
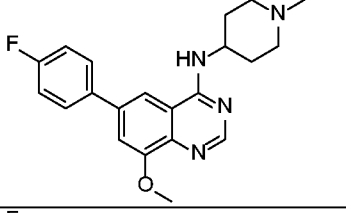
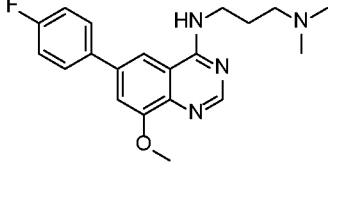
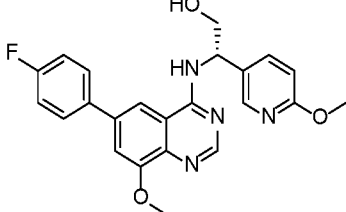
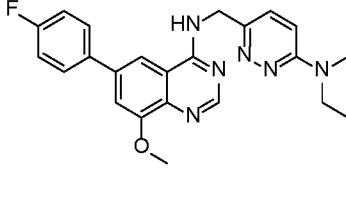
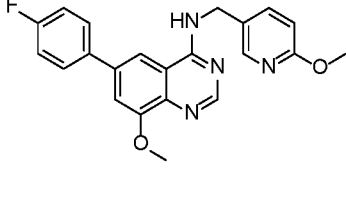
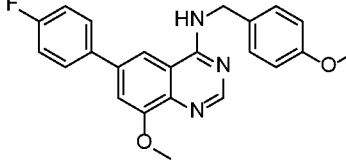
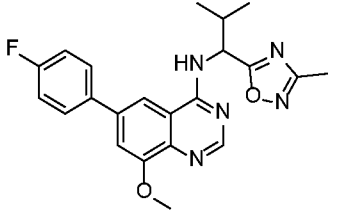
Table 4: List of preferred compounds having Formula (I)

Ex. N.	Structure	Chemical Name
Example 183		(R)-6-(4-Fluorophenyl)-8-methoxy-2-methyl-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 184		(R)-6-(4-Fluorophenyl)-8-methoxy-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)-amino)-quinazolin-2-ol
Example 185		(R)-6-(4-Fluorophenyl)-2,8-dimethoxy-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 1		6-(4-Fluorophenyl)-8-methoxy-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine
Example 2		6-(4-Fluorophenyl)-8-methoxy-N-((5-methylpyridin-2-yl)methyl)quinazolin-4-amine
Example 3		N-((6-(Difluoromethoxy)pyridin-3-yl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine

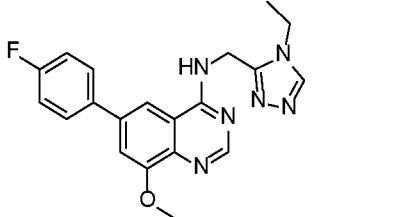
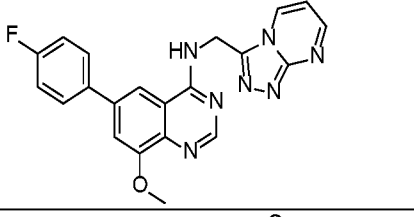
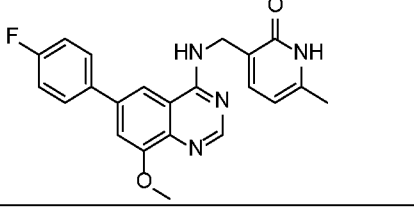
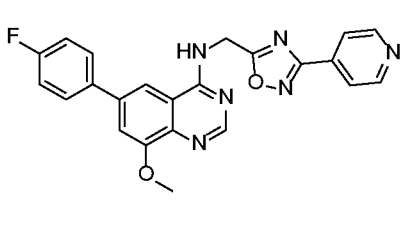
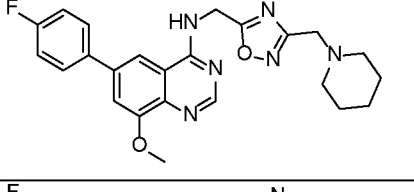
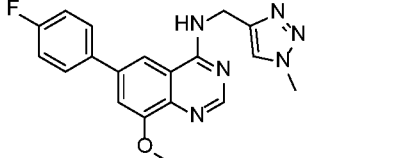
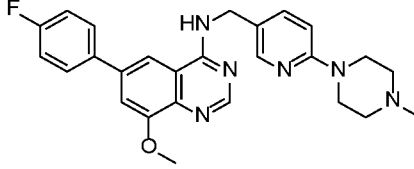
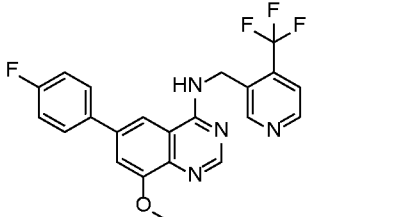
Example 4		(R)-6-(4-Fluorophenyl)-8-methoxy-N-(1-(6-methylpyridazin-3-yl)ethyl)quinazolin-4-amine
Example 5		6-(4-Fluorophenyl)-8-methoxy-N-((6-methylpyridin-3-yl)methyl)quinazolin-4-amine
Example 6		4-(((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)methyl)-1-methylpyridin-2(1H)-one
Example 7		N-((2-(Dimethylamino)pyrimidin-5-yl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 8		N-((5-Chloropyrimidin-2-yl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 9		5-(((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)methyl)-N-methylpicolinamide
Example 10		N-(1-(3-Ethyl-1,2,4-oxadiazol-5-yl)ethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 11		6-(4-Fluorophenyl)-8-methoxy-N-(1-(6-methoxypyridin-3-yl)ethyl)quinazolin-4-amine

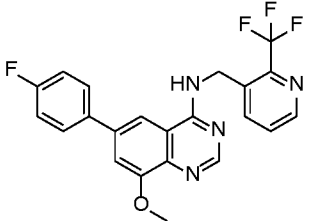
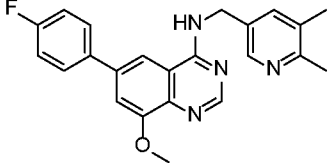
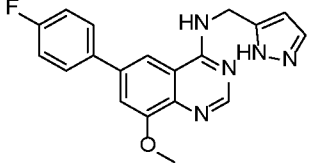
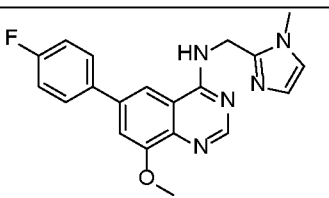
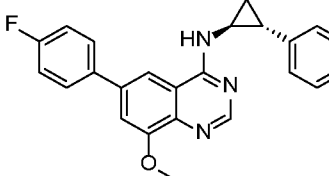
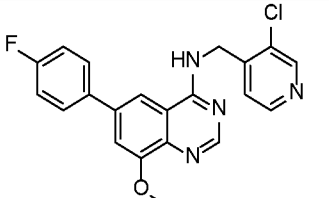
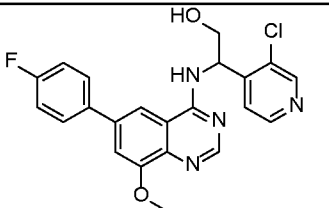
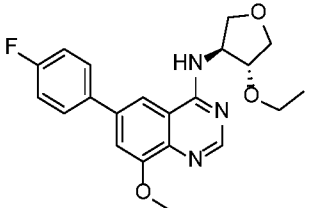
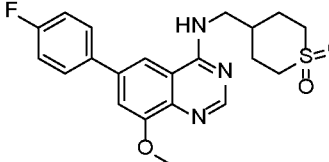
Example 12		6-(4-Fluorophenyl)-8-methoxy-N-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine
Example 13		6-(4-Fluorophenyl)-8-methoxy-N-((2-methylpyrimidin-5-yl)methyl)quinazolin-4-amine
Example 14		6-(4-Fluorophenyl)-8-methoxy-N-(1-(6-methylpyridin-3-yl)ethyl)quinazolin-4-amine
Example 15		2-((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)-2-(3-methyl-1,2,4-oxadiazol-5-yl)ethan-1-ol
Example 16		6-(4-Fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine
Example 18		6-(4-Fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)quinazolin-4-amine
Example 17		N-(Cyclopropylmethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 19		6-(4-Fluorophenyl)-8-methoxy-N-((2-(trifluoromethyl)pyrimidin-5-yl)methyl)quinazolin-4-amine

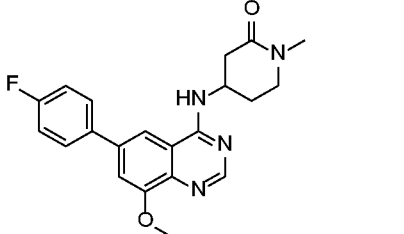
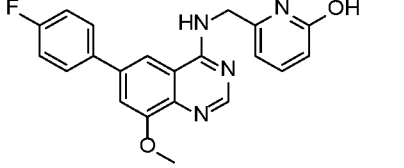
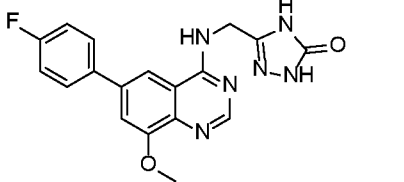
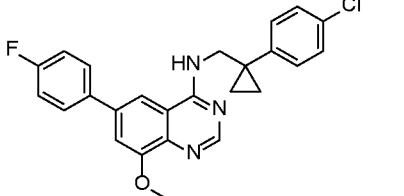
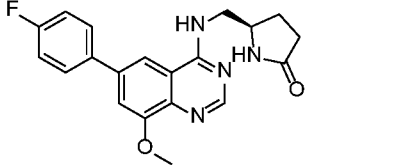
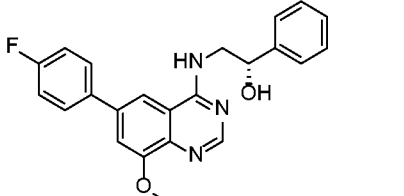
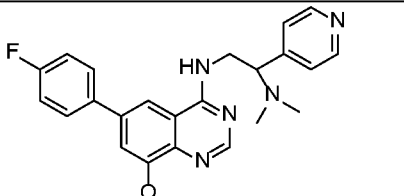
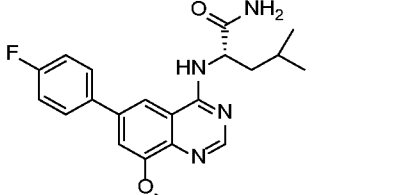
Example 20		6-(4-Fluorophenyl)-8-methoxy-N-((6-(trifluoromethyl)pyridin-3-yl)methyl)quinazolin-4-amine
Example 21		6-(4-Fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,3,4-thiadiazol-2-yl)ethyl)quinazolin-4-amine
Example 22		6-(4-Fluorophenyl)-N-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)ethyl)-8-methoxyquinazolin-4-amine
Example 23		N-((6-(Dimethylamino)pyridin-3-yl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 24		6-(4-Fluorophenyl)-8-methoxy-N-[[5-(trifluoromethyl)-3-pyridyl]methyl]quinazolin-4-amine
Example 25		6-(4-Fluorophenyl)-8-methoxy-N-((tetrahydro-2H-pyran-4-yl)methyl)quinazolin-4-amine
Example 26		3-(((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)tetrahydrothiophene 1,1-dioxide
Example 27		N-(5-(((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)methyl)pyridin-2-yl)acetamide

Example 28		6-(4-Fluorophenyl)-8-methoxy-N-(2-(6-methylpyridin-3-yl)ethyl)quinazolin-4-amine
Example 29		6-(4-Fluorophenyl)-8-methoxy-N-(1-methylpiperidin-4-yl)quinazolin-4-amine
Example 30		N1-(6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)-N3,N3-dimethylpropane-1,3-diamine
Example 31		(S)-2-((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)-2-(6-methoxypyridin-3-yl)ethan-1-ol
Example 32		6-(4-Fluorophenyl)-8-methoxy-N-((6-morpholinopyridazin-3-yl)methyl)quinazolin-4-amine
Example 33		6-(4-Fluorophenyl)-8-methoxy-N-((6-methoxypyridin-3-yl)methyl)quinazolin-4-amine
Example 34		N-(4-ethoxybenzyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 35		6-(4-Fluorophenyl)-8-methoxy-N-(2-methyl-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl)quinazolin-4-amine

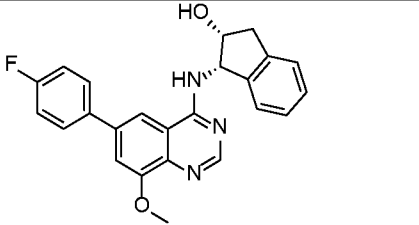
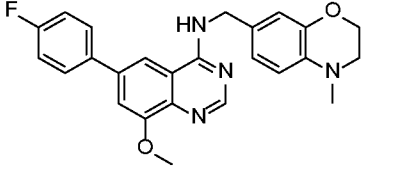
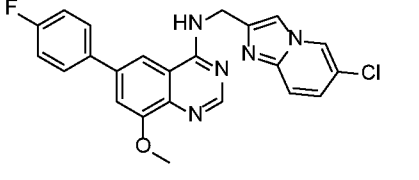
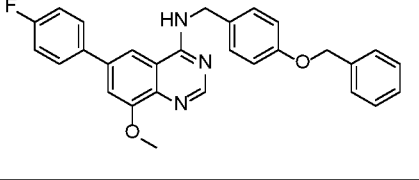
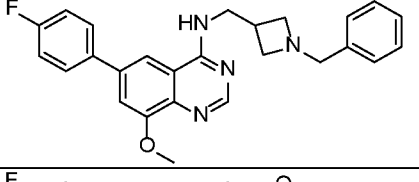
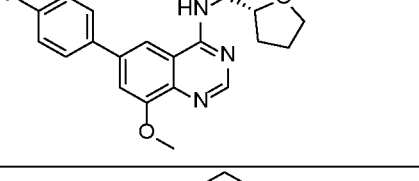
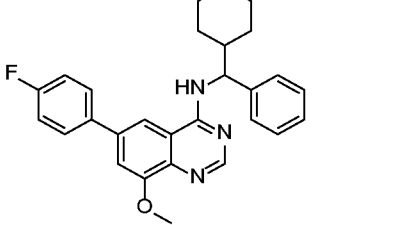
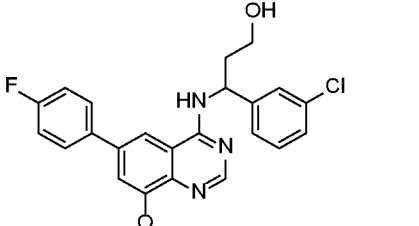
Example 36		6-(4-Fluorophenyl)-8-methoxy-N-[[2-(trifluoromethyl)-4-pyridyl]methyl]quinazolin-4-amine
Example 38		6-(4-Fluorophenyl)-8-methoxy-N-((1-methyl-1H-tetrazol-5-yl)methyl)quinazolin-4-amine
Example 39		6-(4-Fluorophenyl)-8-methoxy-N-((1-methyl-1H-pyrazol-4-yl)methyl)quinazolin-4-amine
Example 41		4-(2-((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)ethyl)morpholin-3-one
Example 42		6-(4-Fluorophenyl)-8-methoxy-N-((1-methyl-1H-1,2,4-triazol-5-yl)methyl)quinazolin-4-amine
Example 43		6-(4-Fluorophenyl)-8-methoxy-N-((2-methyl-2H-tetrazol-5-yl)methyl)quinazolin-4-amine
Example 44		6-(4-Fluorophenyl)-8-methoxy-N-((1-methyl-1H-1,2,4-triazol-3-yl)methyl)quinazolin-4-amine
Example 45		6-(4-Fluorophenyl)-N-(imidazo[1,2-a]pyrimidin-6-ylmethyl)-8-methoxyquinazolin-4-amine
Example 46		6-(4-Fluorophenyl)-8-methoxy-N-((6-(2,2,2-trifluoroethoxy)pyridazin-3-yl)methyl)quinazolin-4-amine

Example 47		N-((4-Ethyl-4H-1,2,4-triazol-3-yl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 48		N-([1,2,4]Triazolo[4,3-a]pyrimidin-3-ylmethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 49		3-(((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)methyl)-6-methylpyridin-2(1H)-one
Example 50		6-(4-Fluorophenyl)-8-methoxy-N-(((3-(pyridin-4-yl)-1,2,4-oxadiazol-5-yl)methyl)quinazolin-4-amine
Example 51		6-(4-Fluorophenyl)-8-methoxy-N-(((3-(piperidin-1-yl)methyl)-1,2,4-oxadiazol-5-yl)methyl)quinazolin-4-amine
Example 52		6-(4-Fluorophenyl)-8-methoxy-N-(((1-methyl-1H-1,2,3-triazol-4-yl)methyl)quinazolin-4-amine
Example 53		6-(4-Fluorophenyl)-8-methoxy-N-(((6-(4-methylpiperazin-1-yl)pyridin-3-yl)methyl)quinazolin-4-amine
Example 54		6-(4-Fluorophenyl)-8-methoxy-N-(((4-(trifluoromethyl)pyridin-3-yl)methyl)quinazolin-4-amine

Example 55		6-(4-Fluorophenyl)-8-methoxy-N-((2-(trifluoromethyl)pyridin-3-yl)methyl)quinazolin-4-amine
Example 56		N-((5,6-Dimethylpyridin-3-yl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 57		6-(4-Fluorophenyl)-8-methoxy-N-(2-methyl-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl)quinazolin-4-amine
Example 58		6-(4-Fluorophenyl)-8-methoxy-N-[(1-methylimidazol-2-yl)methyl]quinazolin-4-amine
Example 59		6-(4-Fluorophenyl)-8-methoxy-N-(2-phenylcyclopropyl)quinazolin-4-amine
Example 60		N-[(3-Chloro-4-pyridyl)methyl]-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 61		2-(3-Chloro-4-pyridyl)-2-[[6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl]amino]ethanol
Example 62		N-[(3S,4R)-4-Ethoxytetrahydrofuran-3-yl]-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 63		N-[(1,1-Dioxothian-4-yl)methyl]-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine

Example 64		4-[[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]-1-methyl-piperidin-2-one
Example 65		6-[[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]methyl]-1H-pyridin-2-one
Example 66		3-[[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]methyl]-1,4-dihydro-1,2,4-triazol-5-one
Example 67		N-[[1-(4-Chlorophenyl)cyclopropyl]methyl]-6-(4-fluorophenyl)-8-methoxy-quinazolin-4-amine
Example 68		(5R)-5-[[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]methyl]pyrrolidin-2-one
Example 69		(1S)-2-[[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]-1-phenyl-ethanol
Example 70		N'-[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]-N,N-dimethyl-1-(4-pyridyl)ethane-1,2-diamine
Example 71		(2S)-2-[[[6-(4-fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]-4-methyl-pentanamide

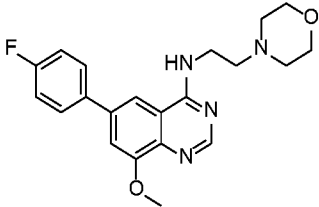
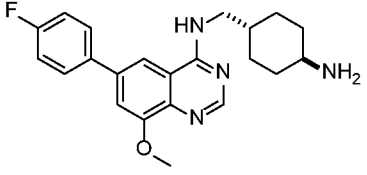
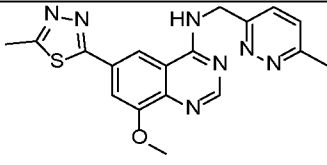
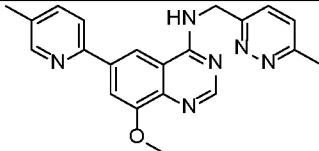
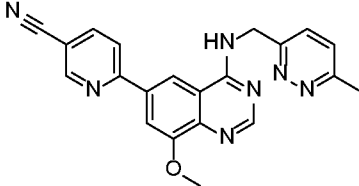
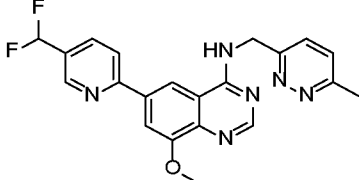
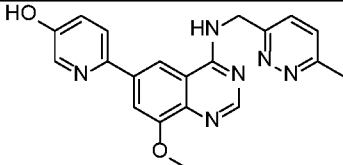
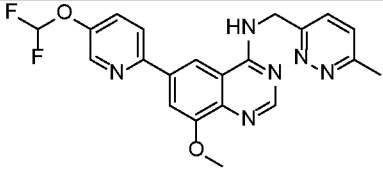
Example 72		6-(4-Fluorophenyl)-8-methoxy-N-(2H-tetrazol-5-ylmethyl)quinazolin-4-amine
Example 73		6-(4-Fluorophenyl)-8-methoxy-N-[(2-methylindazol-6-yl)methyl]methyl]quinazolin-4-amine
Example 74		N-[2-[4-(Dimethylamino)phenyl]ethyl]-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 75		4-[[[6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl]amino]methyl]-N,N-dimethylbenzenesulfonamide
Example 76		6-(4-Fluorophenyl)-8-methoxy-N-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-yl)quinazolin-4-amine
Example 77		N-[(1R,5S)-8-Benzyl-8-azabicyclo[3.2.1]octan-3-yl]-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 78		N-[[4-[2-(dimethylamino)ethoxy]phenyl]methyl]-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 79		6-(4-Fluorophenyl)-8-methoxy-N-(3-pyrrolidin-1-ylpropyl)quinazolin-4-amine

Example 80		(1S,2R)-1-[[6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl]amino]indan-2-ol
Example 81		6-(4-Fluorophenyl)-8-methoxy-N-[(4-methyl-2,3-dihydro-1,4-benzoxazin-7-yl)methyl]quinazolin-4-amine
Example 82		N-[(6-Chloroimidazo[1,2-a]pyridin-2-yl)methyl]-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 83		N-[(4-Benzyloxyphenyl)methyl]-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 84		N-[(1-Benzylazetidin-3-yl)methyl]-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 85		6-(4-Fluorophenyl)-8-methoxy-N-[(2R)-tetrahydrofuran-2-yl]methyl]quinazolin-4-amine
Example 86		N-[Cyclohexyl(phenyl)methyl]-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 87		3-(3-Chlorophenyl)-3-[[6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl]amino]propan-1-ol

Example 88		6-(4-Fluorophenyl)-8-methoxy-N-[(1-methylbenzimidazol-5-yl)methyl]quinazolin-4-amine
Example 89		6-(4-Fluorophenyl)-8-methoxy-N-[2-(4-methylpiperazin-1-yl)-1-phenyl-ethyl]quinazolin-4-amine
Example 90		6-(4-Fluorophenyl)-8-methoxy-N-[(1S)-1-methyl-2-pyrrolidin-1-yl-ethyl]quinazolin-4-amine
Example 91		6-(4-Fluorophenyl)-8-methoxy-N-[(1-methylindazol-7-yl)methyl]quinazolin-4-amine
Example 92		6-(4-Fluorophenyl)-8-methoxy-N-[(1-methylazetidin-3-yl)methyl]quinazolin-4-amine
Example 93		(1R,2S)-1-[[6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl]amino]indan-2-ol
Example 94		3-[[6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl]amino]-1-methylpyrrolidin-2-one
Example 95		6-(4-Fluorophenyl)-8-methoxy-N-(1-tetrahydropyran-4-ylethyl)quinazolin-4-amine

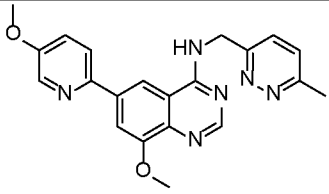
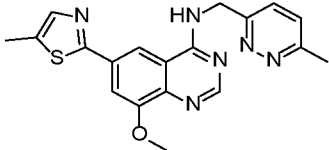
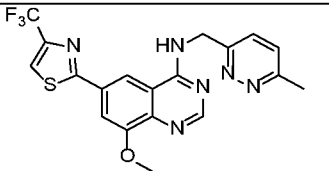
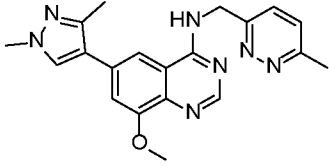
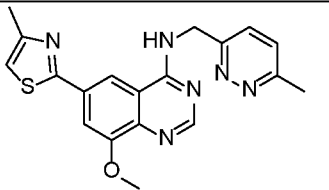
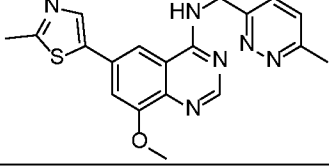
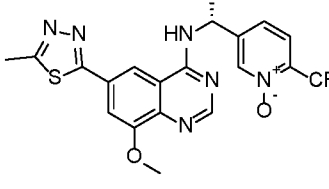
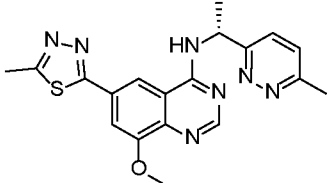
Example 96		N-[[3-Chloro-5-(trifluoromethyl)-2-pyridyl]methyl]-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 97		1-[4-[[[6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl]amino]methyl]-1-piperidyl]ethanone
Example 98		2,2-Difluoro-3-[[6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl]amino]propan-1-ol
Example 99		6-(4-Fluorophenyl)-8-methoxy-N-(2-piperazin-1-ylethyl)quinazolin-4-amine
Example 100		6-(4-Fluorophenyl)-8-methoxy-N-(pyrrolidin-3-ylmethyl)quinazolin-4-amine
Example 101		6-(4-Fluorophenyl)-8-methoxy-N-(pyrrolidin-2-ylmethyl)quinazolin-4-amine
Example 102		6-(4-Fluorophenyl)-8-methoxy-N-(1-methyl-2-morpholino-ethyl)quinazolin-4-amine
Example 103		(S)-6-(4-Fluorophenyl)-8-methoxy-N-((tetrahydrofuran-2-yl)methyl)quinazolin-4-amine
Example 104		6-(4-Fluorophenyl)-8-methoxy-N-((1-methylpyrrolidin-3-yl)methyl)quinazolin-4-amine

Example 105		N1,N1-Diethyl-N3-(6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)propane-1,3-diamine
Example 106		(R)-6-(4-Fluorophenyl)-8-methoxy-N-(1-methylpiperidin-3-yl)quinazolin-4-amine
Example 107		6-(4-Fluorophenyl)-8-methoxy-N-((1-methylpiperidin-2-yl)methyl)quinazolin-4-amine
Example 108		6-(4-Fluorophenyl)-8-methoxy-N-(2-(1-methylazetidin-3-yl)ethyl)quinazolin-4-amine
Example 109		2-[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]-2-tetrahydropyran-4-yl-ethanol formate
Example 110		6-(4-Fluorophenyl)-8-methoxy-N-[(1-methyl-4-piperidyl)methyl]quinazolin-4-amine
Example 111		6-(4-Fluorophenyl)-8-methoxy-N-[(1-methylindazol-4-yl)methyl]quinazolin-4-amine
Example 112		(R)-5-(1-((6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)amino)ethyl)-2-(trifluoromethyl)pyridine 1-oxide formate

Example 113		6-(4-fluorophenyl)-8-methoxy-N-(2-morpholinoethyl)quinazolin-4-amine
Example 114		N-(((1r,4r)-4-aminocyclohexyl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 115		8-Methoxy-6-(5-methyl-1,3,4-thiadiazol-2-yl)-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 116		8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(5-methylpyridin-2-yl)quinazolin-4-amine
Example 117		6-(8-Methoxy-4-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-6-yl)nicotinonitrile
Example 118		6-(5-(difluoromethyl)pyridin-2-yl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 119		6-(8-Methoxy-4-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-6-yl)pyridin-3-ol
Example 120		6-(5-(difluoromethoxy)pyridin-2-yl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine

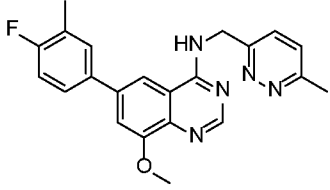
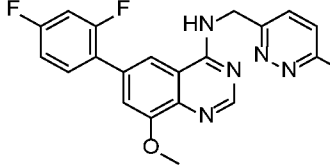
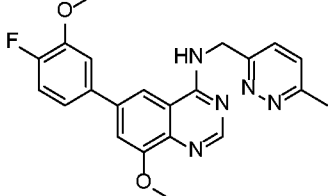
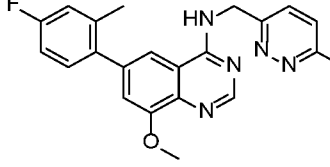
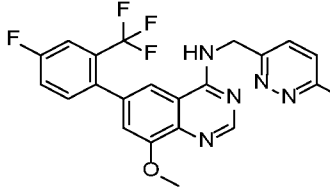
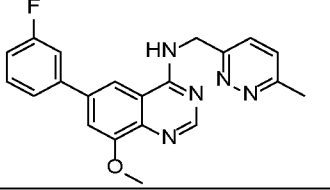
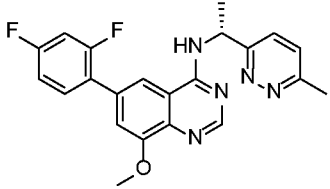
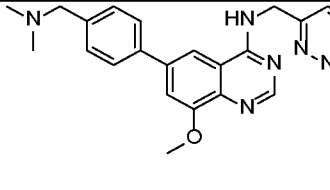
Example 121		8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(5-(methylsulfonyl)pyridin-2-yl)quinazolin-4-amine
Example 122		6-(8-Methoxy-4-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-6-yl)nicotinamide
Example 123		6-(8-Methoxy-4-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-6-yl)-N-methylnicotinamide
Example 124		8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(5-(trifluoromethoxy)pyridin-2-yl)quinazolin-4-amine
Example 125		6-[5-(Dimethylamino)-2-pyridyl]-8-methoxy-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine
Example 126		6-(5-Cyclopropylpyridin-2-yl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 127		6-(5-Chloropyridin-2-yl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 128		8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(6-methylpyridin-3-yl)quinazolin-4-amine
Example 129		8-Methoxy-6-(5-methyl-1,3,4-oxadiazol-2-yl)-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine

Example 130		8-Methoxy-6-(1-methyl-1H-pyrazol-3-yl)-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 131		6-(1,5-Dimethyl-1H-pyrazol-3-yl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 132		8-Methoxy-6-(6-methoxypyridazin-3-yl)-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 133		8-Methoxy-6-(6-methylpyridazin-3-yl)-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 134		8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(5-methylpyrimidin-2-yl)quinazolin-4-amine
Example 135		6-(5-Fluoro-2-pyridyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 136		6-(5-Fluoropyrimidin-2-yl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 137		6-[8-Methoxy-4-((6-methylpyridazin-3-yl)methylamino)quinazolin-6-yl]pyridazin-3-ol
Example 138		8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(5-(trifluoromethyl)pyridin-2-yl)quinazolin-4-amine

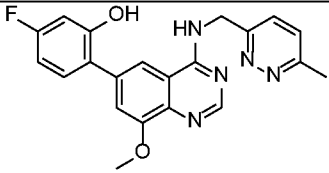
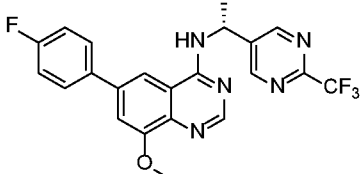
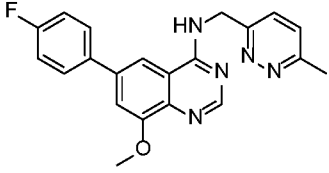
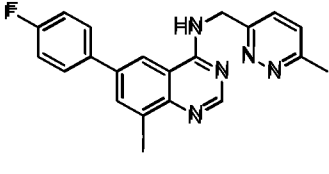
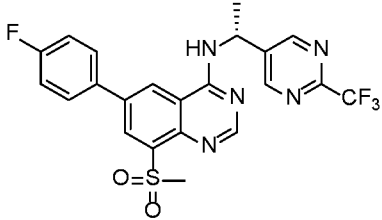
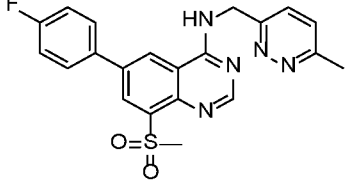
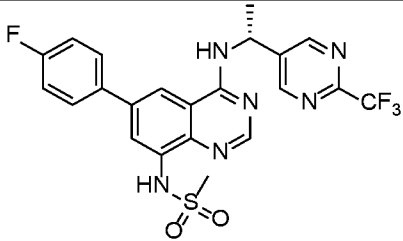
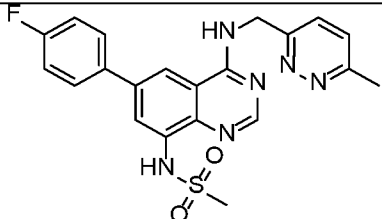
Example 139		8-Methoxy-6-(5-methoxypyridin-2-yl)-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 140		8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(5-methylthiazol-2-yl)quinazolin-4-amine
Example 141		8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(4-(trifluoromethyl)thiazol-2-yl)quinazolin-4-amine
Example 142		6-(1,3-Dimethyl-1H-pyrazol-4-yl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 143		8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(4-methylthiazol-2-yl)quinazolin-4-amine
Example 144		8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(2-methylthiazol-5-yl)quinazolin-4-amine
Example 145		(R)-5-(1-((8-Methoxy-6-(5-methyl-1,3,4-thiadiazol-2-yl)quinazolin-4-yl)amino)ethyl)-2-(trifluoromethyl)pyridine 1-oxide
Example 146		(R)-8-Methoxy-6-(5-methyl-1,3,4-thiadiazol-2-yl)-N-(1-(6-methylpyridazin-3-yl)ethyl)quinazolin-4-amine

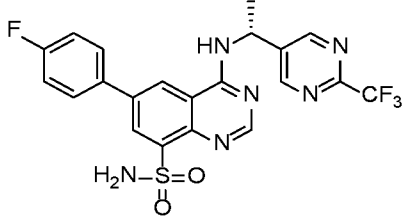
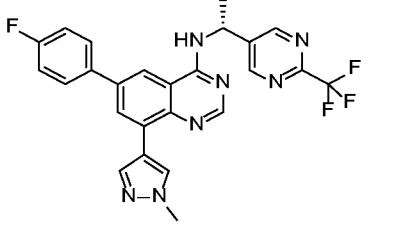
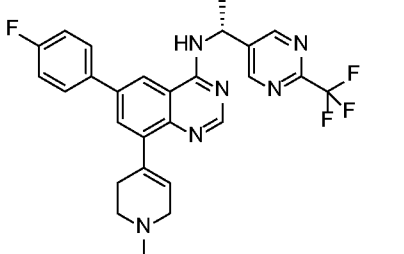
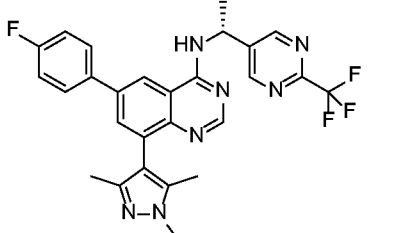
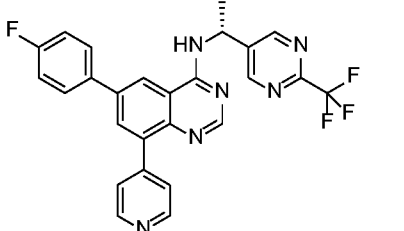
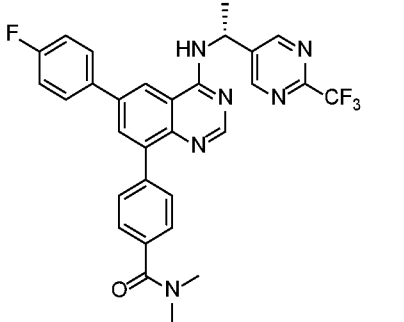
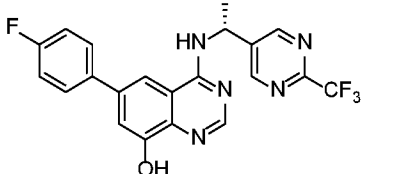
Example 147		(R)-8-Methoxy-6-(5-methyl-1,3,4-thiadiazol-2-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 148		8-Methoxy-6-(5-methylpyrimidin-2-yl)-N-[(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl]quinazolin-4-amine
Example 149		6-(5-Fluoropyrimidin-2-yl)-8-methoxy-N-[(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl]quinazolin-4-amine
Example 150		6-(5-Fluoro-2-pyridyl)-8-methoxy-N-[(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl]quinazolin-4-amine
Example 151		8-Methoxy-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-6-(5-methylpyrimidin-2-yl)quinazolin-4-amine
Example 152		8-Methoxy-6-(1-methylpyrazol-3-yl)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]quinazolin-4-amine
Example 153		6-[5-(Difluoromethyl)-2-pyridyl]-8-methoxy-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]quinazolin-4-amine
Example 154		8-Methoxy-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-6-(5-methyl-2-pyridyl)quinazolin-4-amine

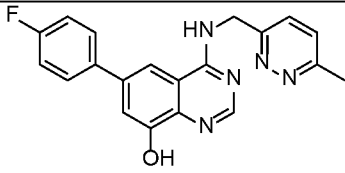
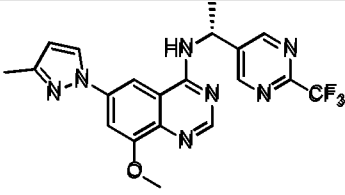
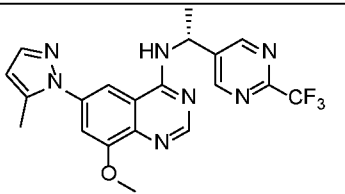
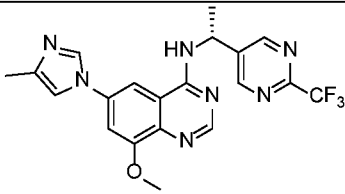
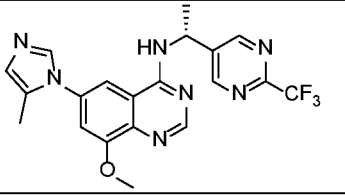
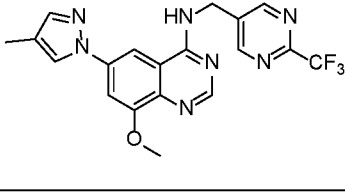
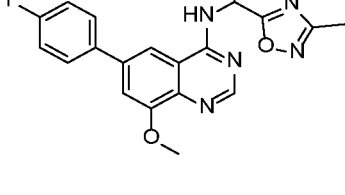
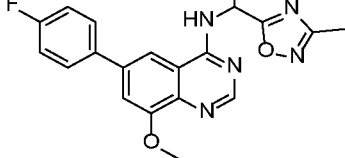
Example 155		6-(5-Fluoro-2-pyridyl)-8-methoxy-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]quinazolin-4-amine
Example 156		8-Methoxy-6-(3-methylisothiazol-5-yl)-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 157		(R)-8-methoxy-6-(5-methylpyridin-2-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 158		(R)-8-methoxy-6-(5-methylthiazol-2-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 159		(R)-8-methoxy-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazolin-6-ol
Example 160		(R)-8-methoxy-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 161		8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(5-(trifluoromethyl)thiazol-2-yl)quinazolin-4-amine
Example 163		8-Methoxy-6-(1-methyl-1H-pyrazol-4-yl)-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 163a		6-(4,5-Dimethylthiazol-2-yl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine

Example 164		6-(4-Fluoro-3-methylphenyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 165		6-(2,4-Difluorophenyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 166		6-(4-Fluoro-3-methoxyphenyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 167		6-(4-Fluoro-2-methylphenyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 168		6-(4-Fluoro-2-(trifluoromethyl)phenyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 169		6-(3-Fluorophenyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 170		6-(2,4-Difluorophenyl)-8-methoxy-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]quinazolin-4-amine
Example 171		6-[4-[(Dimethylamino)methyl]phenyl]-8-methoxy-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine formate

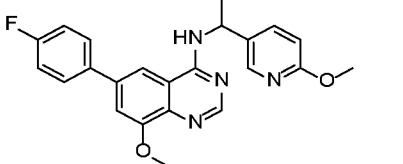
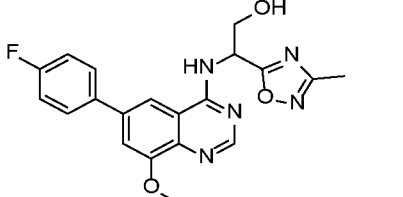
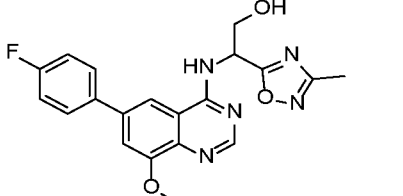
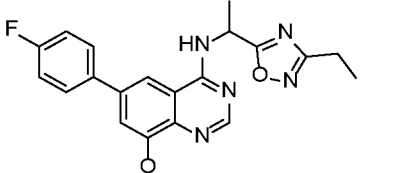
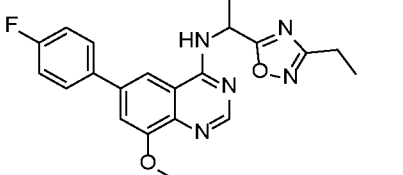
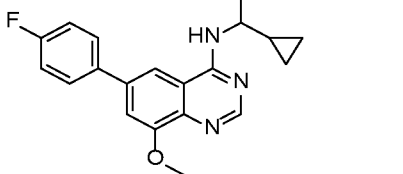
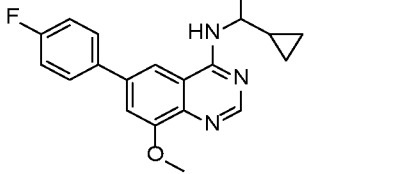
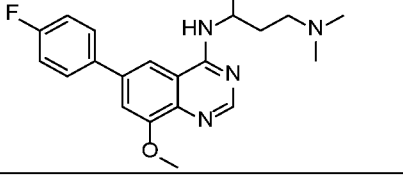
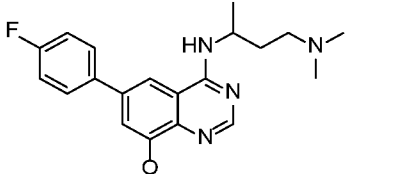
Example 172		4-[8-Methoxy-4-[(6-methylpyridazin-3-yl)methylamino]quinazolin-6-yl]-N,N-dimethyl-benzamide
Example 173		6-[4-(Dimethylamino)phenyl]-8-methoxy-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine
Example 174		8-Methoxy-6-(4-methoxyphenyl)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine
Example 175		6-(4-chlorophenyl)-8-methoxy-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine
Example 176		6-(3,4-Difluorophenyl)-8-methoxy-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine
Example 176a		6-(4-Fluoro-2-methoxyphenyl)-8-methoxy-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine
Example 177		8-Methoxy-N-[(6-methylpyridazin-3-yl)methyl]-6-(2,4,6-trifluorophenyl)quinazolin-4-amine
Example 178		2-(8-Methoxy-4-((6-methylpyridazin-3-yl)methyl)amino)quinazolin-6-yl)-5-methylbenzoyl nitrile
Example 179		5-Fluoro-2-(8-methoxy-4-((6-methylpyridazin-3-yl)methyl)amino)quinazolin-6-yl)benzoyl nitrile

Example 180		5-Fluoro-2-(8-methoxy-4-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-6-yl)phenol
Example 181		(R)-6-(4-fluorophenyl)-8-methoxy-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 182		6-(4-fluorophenyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 187		6-(4-fluorophenyl)-8-iodo-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 188		(R)-6-(4-fluorophenyl)-8-(methylsulfonyl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 189		6-(4-fluorophenyl)-N-((6-methylpyridazin-3-yl)methyl)-8-(methylsulfonyl)quinazolin-4-amine
Example 190		(R)-N-(6-(4-fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazolin-8-yl)methanesulfonamide
Example 191		N-(6-(4-fluorophenyl)-4-oxo-3,4-dihydroquinazolin-8-yl)methanesulfonamide

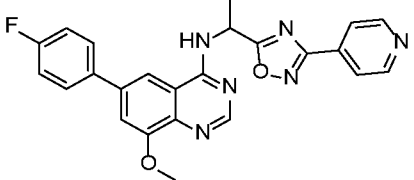
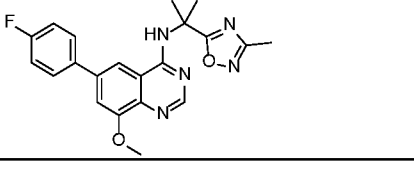
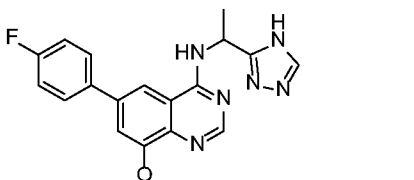
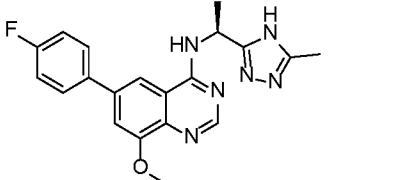
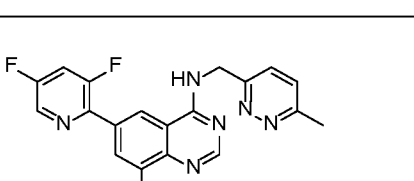
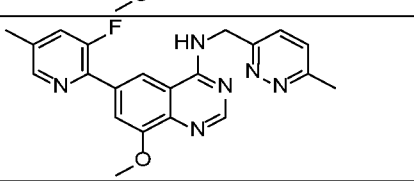
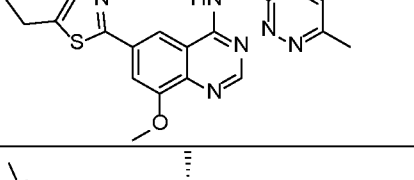
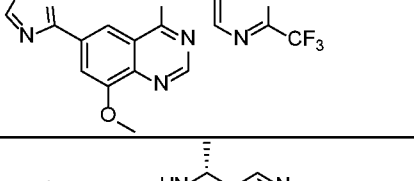
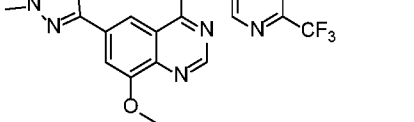
Example 192		(R)-6-(4-fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazolin-8-sulfonamide
Example 193		(R)-6-(4-fluorophenyl)-8-(1-methyl-1H-pyrazol-4-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 194		(R)-6-(4-Fluorophenyl)-8-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 195		(R)-6-(4-Fluorophenyl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)-8-(1,3,5-trimethyl-1H-pyrazol-4-yl)quinazolin-4-amine
Example 196		(R)-6-(4-Fluorophenyl)-8-(pyridin-4-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 197		(R)-4-(6-(4-Fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazolin-8-yl)-N,N-dimethylbenzamide
Example 198		(R)-6-(4-fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)-quinazolin-8-ol

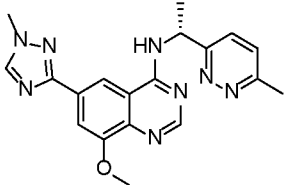
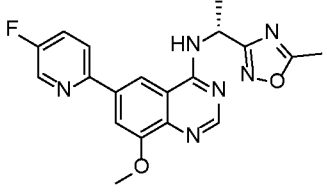
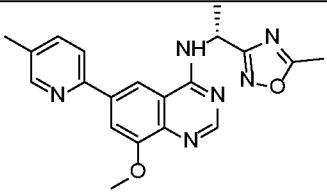
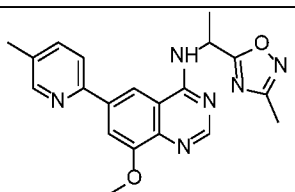
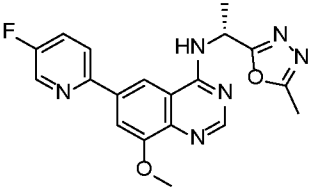
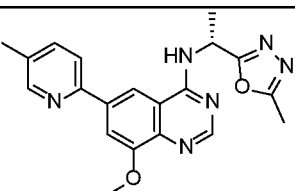
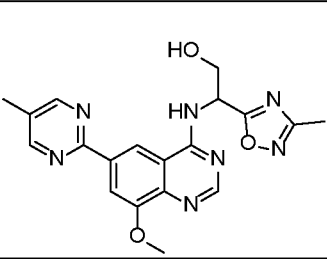
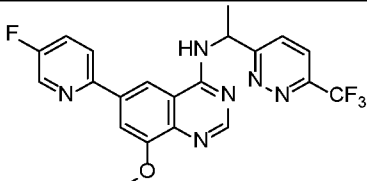
Example 199		6-(4-fluorophenyl)-4-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-8-ol
Example 223		((R)-8-methoxy-6-(3-methyl-1H-pyrazol-1-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 224		(R)-8-methoxy-6-(5-methyl-1H-pyrazol-1-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 225		(R)-8-Methoxy-6-(4-methyl-1H-imidazol-1-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 226		(R)-8-methoxy-6-(5-methyl-1H-imidazol-1-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 227		(R)-8-Methoxy-6-(4-methyl-1H-pyrazol-1-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 255		Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine
Example 256		Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine

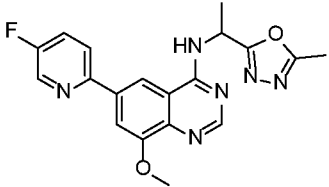
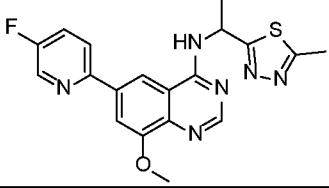
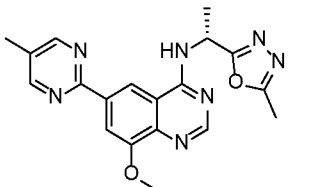
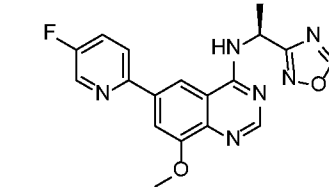
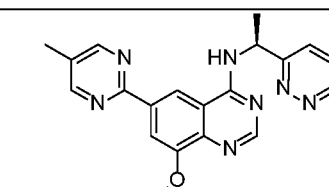
Example 257		Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine
Example 258		Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine
Example 259		Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(6-methylpyridin-3-yl)ethyl)quinazolin-4-amine
Example 260		Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(6-methylpyridin-3-yl)ethyl)quinazolin-4-amine
Example 261		Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine
Example 262		Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine
Example 263		Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)quinazolin-4-amine
Example 264		Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)quinazolin-4-amine
Example 265		Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(6-methoxypyridin-3-yl)ethyl)quinazolin-4-amine

Example 266		Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(6-methoxypyridin-3-yl)ethyl)quinazolin-4-amine
Example 267		Single enantiomer 1 of 2-((6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)amino)-2-(3-methyl-1,2,4-oxadiazol-5-yl)ethan-1-ol
Example 268		Single enantiomer 2 of 2-((6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)amino)-2-(3-methyl-1,2,4-oxadiazol-5-yl)ethan-1-ol
Example 269		Single enantiomer 1 of N-(1-(3-ethyl-1,2,4-oxadiazol-5-yl)ethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 270		Single enantiomer 2 of N-(1-(3-ethyl-1,2,4-oxadiazol-5-yl)ethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 271		Single enantiomer 1 of N-(1-cyclopropylethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 272		Single enantiomer 2 of N-(1-cyclopropylethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 273		Single enantiomer 1 of N3-(6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)-N1,N1-dimethylbutane-1,3-diamine
Example 274		Single enantiomer 2 of N3-(6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)-N1,N1-dimethylbutane-1,3-diamine

Example 275		Single enantiomer 1 of 3-((6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)amino)tetrahydrothiophene 1,1-dioxide
Example 276		Single enantiomer 2 of 3-((6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)amino)tetrahydrothiophene 1,1-dioxide
Example 277		Single enantiomer 1 of 6-(4-fluorophenyl)-N-[1-(3-isopropyl-1,2,4-oxadiazol-5-yl)ethyl]-8-methoxyquinazolin-4-amine
Example 278		Single enantiomer 2 of 6-(4-fluorophenyl)-N-[1-(3-isopropyl-1,2,4-oxadiazol-5-yl)ethyl]-8-methoxyquinazolin-4-amine
Example 279		Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-N-[2-methyl-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl]quinazolin-4-amine
Example 280		Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-N-[2-methyl-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl]quinazolin-4-amine
Example 281		Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,3,4-thiadiazol-2-yl)ethyl)quinazolin-4-amine
Example 282		Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,3,4-thiadiazol-2-yl)ethyl)quinazolin-4-amine

Example 291		6-(4-Fluorophenyl)-8-methoxy- <i>N</i> -(1-(3-(pyridin-4-yl)-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine
Example 293		6-(4-fluorophenyl)-8-methoxy- <i>N</i> -(2-(3-methyl-1,2,4-oxadiazol-5-yl)propan-2-yl)quinazolin-4-amine
Example 294		(<i>rac</i>)- <i>N</i> -(1-(4 <i>H</i> -1,2,4-triazol-3-yl)ethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 295		(<i>S</i>)-6-(4-fluorophenyl)-8-methoxy- <i>N</i> -(1-(5-methyl-4 <i>H</i> -1,2,4-triazol-3-yl)ethyl)quinazolin-4-amine
Example 296		6-(3,5-Difluoropyridin-2-yl)-8-methoxy- <i>N</i> -((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 297		6-(3-Fluoro-5-methyl-2-pyridyl)-8-methoxy- <i>N</i> -[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine
Example 298		6-(5-Ethylthiazol-2-yl)-8-methoxy- <i>N</i> -[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine
Example 299		(<i>R</i>)-8-methoxy-6-(1-methyl-1 <i>H</i> -1,2,4-triazol-3-yl)- <i>N</i> -(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 300		(<i>R</i>)-8-methoxy-6-(1-methyl-1 <i>H</i> -pyrazol-3-yl)- <i>N</i> -(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine

Example 301		(<i>R</i>)-8-methoxy-6-(1-methyl-1 <i>H</i> -1,2,4-triazol-3-yl)- <i>N</i> -(1-(6-methylpyridazin-3-yl)ethyl)quinazolin-4-amine
Example 315		(<i>R</i>)-6-(5-fluoropyridin-2-yl)-8-methoxy- <i>N</i> -(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine
Example 316		(<i>R</i>)-8-methoxy- <i>N</i> -(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)-6-(5-methylpyridin-2-yl)quinazolin-4-amine
Example 317		8-Methoxy- <i>N</i> -[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]-6-(5-methyl-2-pyridyl)quinazolin-4-amine
Example 318		6-(5-fluoro-2-pyridyl)-8-methoxy- <i>N</i> -[(1 <i>R</i>)-1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl]quinazolin-4-amine
Example 319		8-methoxy- <i>N</i> -[(1 <i>R</i>)-1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl]-6-(5-methyl-2-pyridyl)quinazolin-4-amine
Example 320		2-((8-methoxy-6-(5-methylpyrimidin-2-yl)quinazolin-4-yl)amino)-2-(3-methyl-1,2,4-oxadiazol-5-yl)ethan-1-ol
Example 321		6-(5-fluoro-2-pyridyl)-8-methoxy- <i>N</i> -[1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl]quinazolin-4-amine

Example 322		6-(5-fluoropyridin-2-yl)-8-methoxy- <i>N</i> -(1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)quinazolin-4-amine
Example 323		6-(5-fluoropyridin-2-yl)-8-methoxy- <i>N</i> -(1-(5-methyl-1,3,4-thiadiazol-2-yl)ethyl)quinazolin-4-amine
Example 324		8-methoxy- <i>N</i> -[(1R)-1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl]-6-(5-methylpyrimidin-2-yl)quinazolin-4-amine
Example 325		(<i>S</i>)-6-(5-fluoropyridin-2-yl)-8-methoxy- <i>N</i> -(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine
Example 326		8-Methoxy- <i>N</i> -[(1S)-1-(6-methylpyridazin-3-yl)ethyl]-6-(5-methylpyrimidin-2-yl)quinazolin-4-amine

In a further preferred embodiment, the invention is addressed to compound of formula (I) wherein

Z is aryl, wherein any of such aryl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, halo, CN,

5 **R₁** is H;

R₂ is selected from the group consisting of heteroaryl(C₁-C₄)alkyl-, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl-(C₁-C₆)alkyl-, wherein any of such alkyl, heteroaryl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, (C₁-C₆)haloalkyl, oxo, R^AO-, aryl, (R^AR^B)N- and

10 halo;

R^A and R^B are at each occurrence independently H or selected from the group consisting of (C₁-C₄)alkyl-, (C₁-C₆) haloalkyl;

Y is selected from the group consisting of -OR^D, R^CSO₂, halo and -NHSO₂R^C, heteroaryl, heterocycloalkyl, wherein any of such heteroaryl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, -C(O)N(R^AR^B);

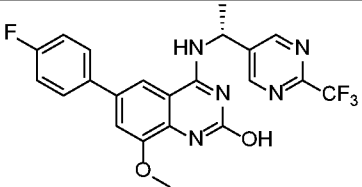
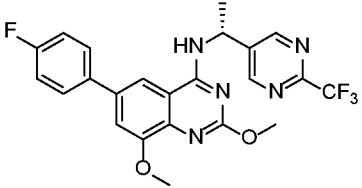
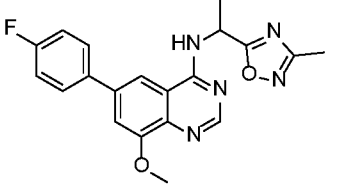
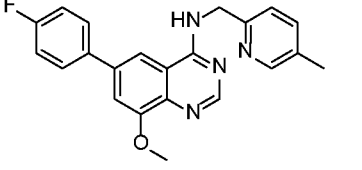
J is H or selected from the group consisting of OR^C;

R^C is H, or selected from the group consisting of (C₁-C₆)alkyl, (R^AR^B)N-;

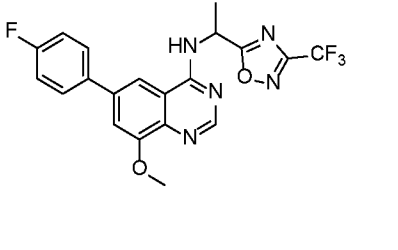
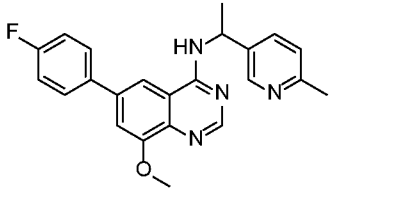
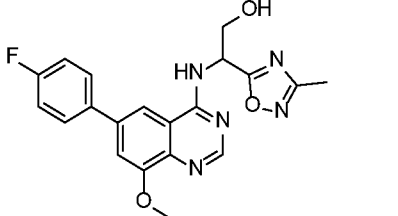
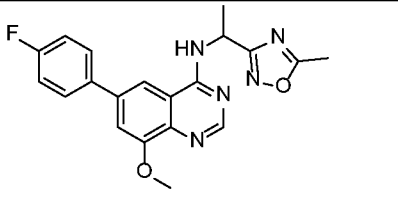
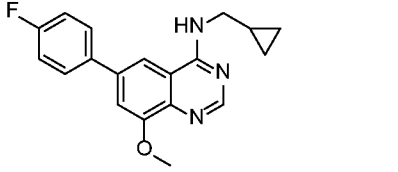
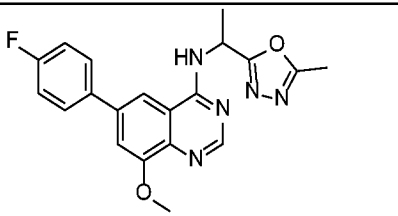
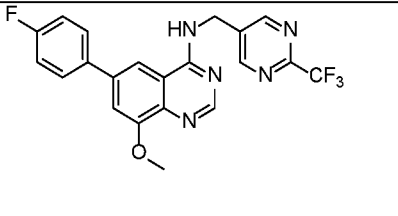
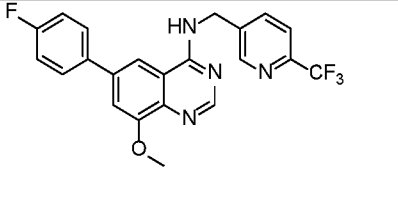
R^D is H or (C₁-C₆)alkyl.

According to a preferred embodiment, the invention refers to at least one compound of Table 5, selected from:

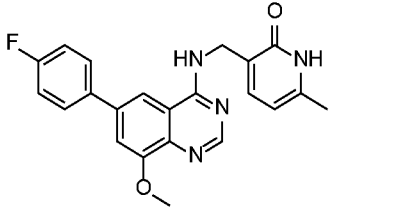
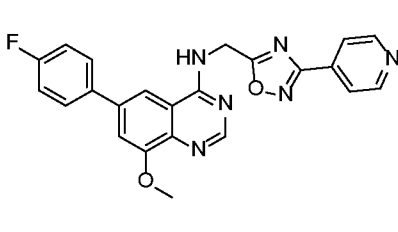
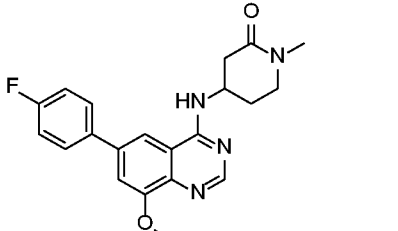
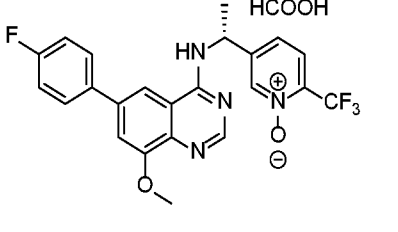
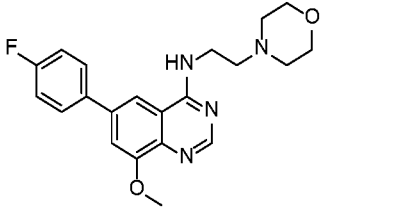
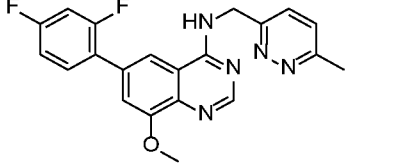
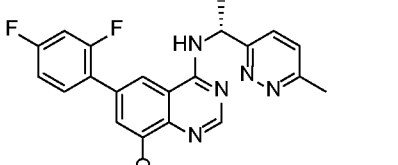
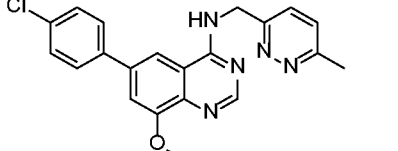
Table 5: List of preferred compounds having Formula (I)

Ex. N.	Structure	Chemical Name
Example 184		(R)-6-(4-Fluorophenyl)-8-methoxy-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)-amino)-quinazolin-2-ol
Example 185		(R)-6-(4-Fluorophenyl)-2,8-dimethoxy-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 1		6-(4-Fluorophenyl)-8-methoxy-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine
Example 2		6-(4-Fluorophenyl)-8-methoxy-N-((5-methylpyridin-2-yl)methyl)quinazolin-4-amine

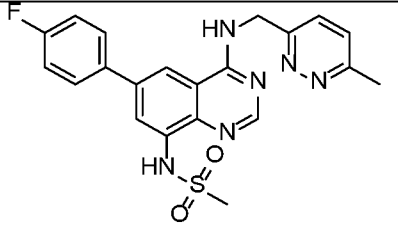
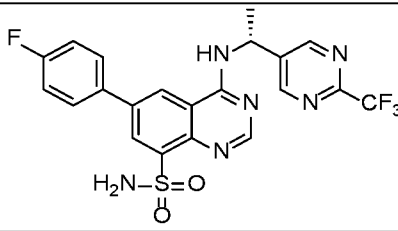
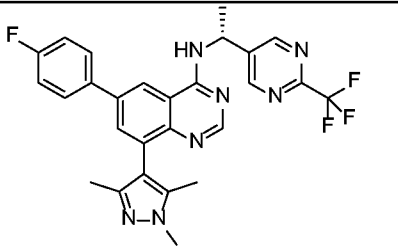
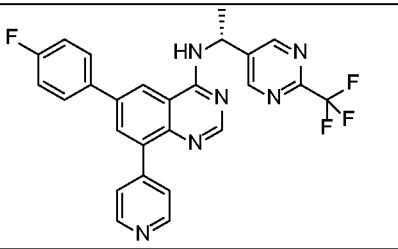
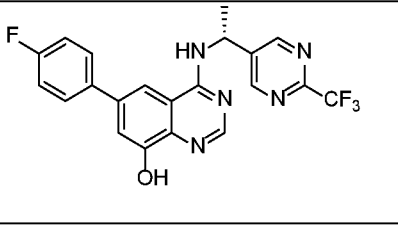
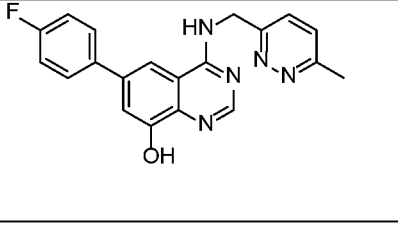
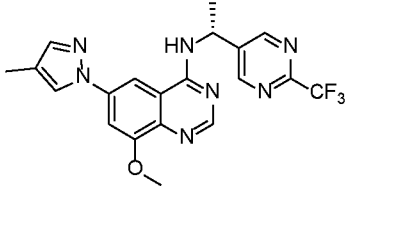
Example 3		N-((6-(Difluoromethoxy)pyridin-3-yl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 4		(R)-6-(4-Fluorophenyl)-8-methoxy-N-(1-(6-methylpyridazin-3-yl)ethyl)quinazolin-4-amine
Example 5		6-(4-Fluorophenyl)-8-methoxy-N-((6-methylpyridin-3-yl)methyl)quinazolin-4-amine
Example 6		4-(((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)methyl)-1-methylpyridin-2(1H)-one
Example 7		N-((2-(Dimethylamino)pyrimidin-5-yl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 8		N-((5-Chloropyrimidin-2-yl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 10		N-(1-(3-Ethyl-1,2,4-oxadiazol-5-yl)ethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 11		6-(4-Fluorophenyl)-8-methoxy-N-(1-(6-methoxypyridin-3-yl)ethyl)quinazolin-4-amine

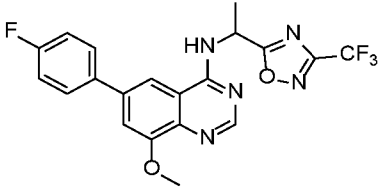
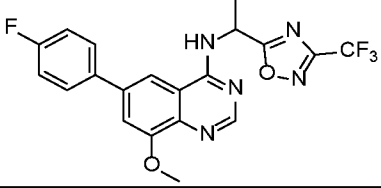
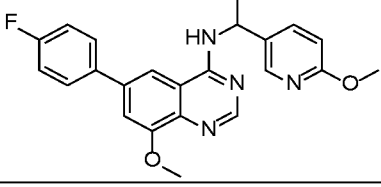
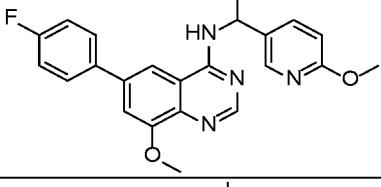
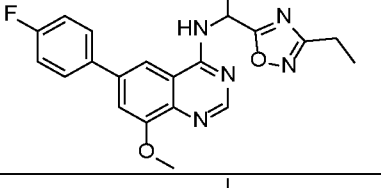
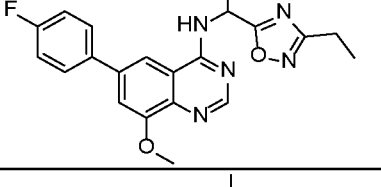
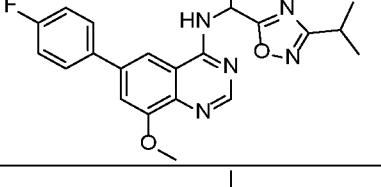
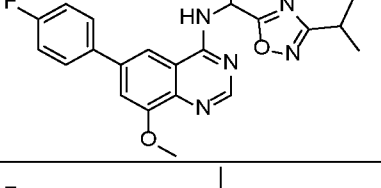
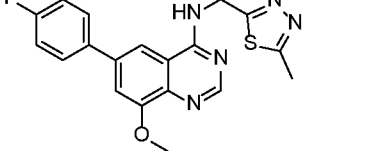
Example 12		6-(4-Fluorophenyl)-8-methoxy-N-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine
Example 14		6-(4-Fluorophenyl)-8-methoxy-N-(1-(6-methylpyridin-3-yl)ethyl)quinazolin-4-amine
Example 15		2-((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)-2-(3-methyl-1,2,4-oxadiazol-5-yl)ethan-1-ol
Example 16		6-(4-Fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine
Example 17		N-(Cyclopropylmethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 18		6-(4-Fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)quinazolin-4-amine
Example 19		6-(4-Fluorophenyl)-8-methoxy-N-((2-(trifluoromethyl)pyrimidin-5-yl)methyl)quinazolin-4-amine
Example 20		6-(4-Fluorophenyl)-8-methoxy-N-((6-(trifluoromethyl)pyridin-3-yl)methyl)quinazolin-4-amine

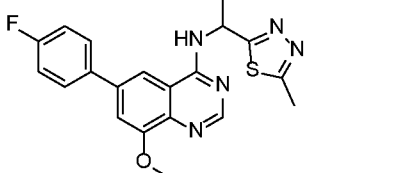
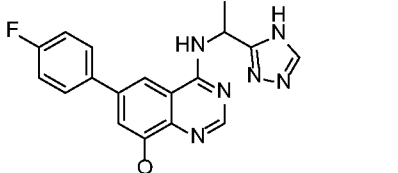
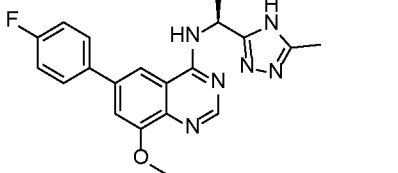
Example 21		6-(4-Fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,3,4-thiadiazol-2-yl)ethyl)quinazolin-4-amine
Example 22		6-(4-Fluorophenyl)-N-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)ethyl)-8-methoxyquinazolin-4-amine
Example 25		6-(4-Fluorophenyl)-8-methoxy-N-((tetrahydro-2H-pyran-4-yl)methyl)quinazolin-4-amine
Example 31		(S)-2-(((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)-2-(6-methoxypyridin-3-yl)ethan-1-ol
Example 33		6-(4-Fluorophenyl)-8-methoxy-N-(((6-methoxypyridin-3-yl)methyl)quinazolin-4-amine
Example 39		6-(4-Fluorophenyl)-8-methoxy-N-((1-methyl-1H-pyrazol-4-yl)methyl)quinazolin-4-amine
Example 45		6-(4-Fluorophenyl)-N-(imidazo[1,2-a]pyrimidin-6-ylmethyl)-8-methoxyquinazolin-4-amine
Example 48		N-([1,2,4]Triazolo[4,3-a]pyrimidin-3-ylmethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine

Example 49		3-(((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)methyl)-6-methylpyridin-2(1H)-one
Example 50		6-(4-Fluorophenyl)-8-methoxy-N-((3-(pyridin-4-yl)-1,2,4-oxadiazol-5-yl)methyl)quinazolin-4-amine
Example 64		4-[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]-1-methyl-piperidin-2-one
Example 112		(R)-5-(1-(((6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)amino)ethyl)-2-(trifluoromethyl)pyridine 1-oxide formate
Example 113		6-(4-fluorophenyl)-8-methoxy-N-(2-morpholinoethyl)quinazolin-4-amine
Example 165		6-(2,4-Difluorophenyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 170		6-(2,4-Difluorophenyl)-8-methoxy-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]quinazolin-4-amine
Example 175		6-(4-chlorophenyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine

Example 178		2-(8-Methoxy-4-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-6-yl)-5-methylbenzonitrile
Example 181		(R)-6-(4-fluorophenyl)-8-methoxy-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 182		6-(4-fluorophenyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 186		(R)-6-(4-Fluorophenyl)-8-iodo-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 187		6-(4-fluorophenyl)-8-iodo-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 188		(R)-6-(4-fluorophenyl)-8-(methylsulfonyl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 189		6-(4-fluorophenyl)-N-((6-methylpyridazin-3-yl)methyl)-8-(methylsulfonyl)quinazolin-4-amine
Example 190		(R)-N-(6-(4-fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazolin-8-yl)methanesulfonamide

Example 191		N-(6-(4-fluorophenyl)-4-oxo-3,4-dihydroquinazolin-8-yl)methanesulfonamide
Example 192		(R)-6-(4-fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazolin-8-sulfonamide
Example 195		(R)-6-(4-Fluorophenyl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)-8-(1,3,5-trimethyl-1H-pyrazol-4-yl)quinazolin-4-amine
Example 196		(R)-6-(4-Fluorophenyl)-8-(pyridin-4-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 198		(R)-6-(4-fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)-quinazolin-8-ol
Example 199		6-(4-fluorophenyl)-4-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-8-ol
Example 227		(R)-8-Methoxy-6-(4-methyl-1H-pyrazol-1-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine

Example 257		Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine
Example 258		Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine
Example 265		Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(6-methoxypyridin-3-yl)ethyl)quinazolin-4-amine
Example 266		Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(6-methoxypyridin-3-yl)ethyl)quinazolin-4-amine
Example 269		Single enantiomer 1 of N-(1-(3-ethyl-1,2,4-oxadiazol-5-yl)ethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 270		Single enantiomer 2 of N-(1-(3-ethyl-1,2,4-oxadiazol-5-yl)ethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 277		Single enantiomer 1 of 6-(4-fluorophenyl)-N-[1-(3-isopropyl-1,2,4-oxadiazol-5-yl)ethyl]-8-methoxyquinazolin-4-amine
Example 278		Single enantiomer 2 of 6-(4-fluorophenyl)-N-[1-(3-isopropyl-1,2,4-oxadiazol-5-yl)ethyl]-8-methoxyquinazolin-4-amine
Example 281		Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,3,4-thiadiazol-2-yl)ethyl)quinazolin-4-amine

Example 282		Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,3,4-thiadiazol-2-yl)ethyl)quinazolin-4-amine
Example 294		<i>(rac)</i> -N-(1-(4 <i>H</i> -1,2,4-triazol-3-yl)ethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine
Example 295		<i>(S)</i> -6-(4-fluorophenyl)-8-methoxy-N-(1-(5-methyl-4 <i>H</i> -1,2,4-triazol-3-yl)ethyl)quinazolin-4-amine

In a further preferred embodiment, the invention is addressed to compound of formula (I) wherein

Z is heteroaryl wherein any of such heteroaryl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, halo, CN, (C₁-C₆)haloalkyl;

5 **R₁** is H;

R₂ is selected from the group consisting of heteroaryl(C₁-C₄)alkyl-, wherein any of such alkyl, heteroaryl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, (C₁-C₆)haloalkyl and -oxo;

Y is -OR^D;

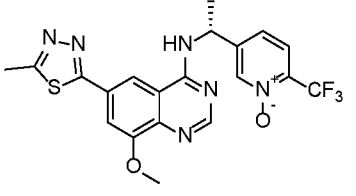
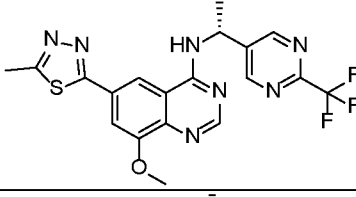
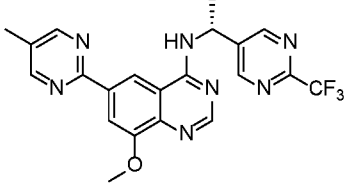
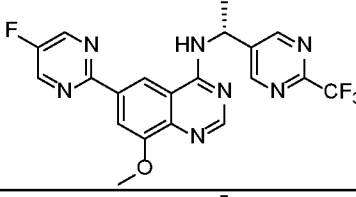
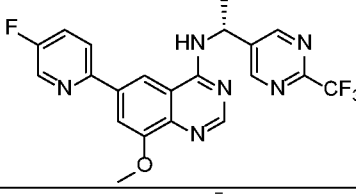
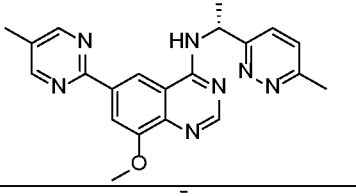
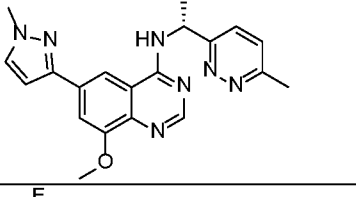
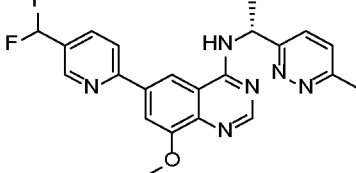
10 **J** is H;

R^D is (C₁-C₆)alkyl.

According to a preferred embodiment, the invention refers to at least one compound of Table 6, selected from:

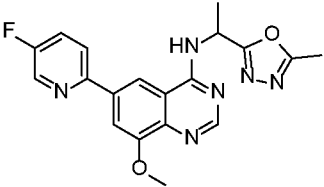
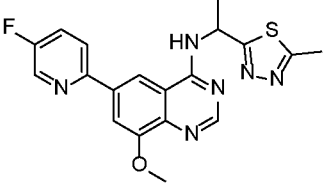
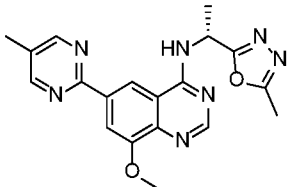
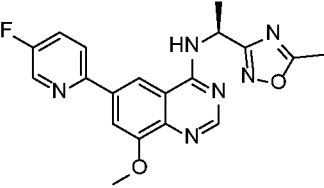
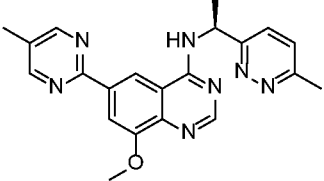
Table 6: List of preferred compounds having Formula (I)

Ex. N.	Structure	Chemical Name
Example 116		8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(5-methylpyridin-2-yl)quinazolin-4-amine
Example 118		6-(5-(Difluoromethyl)pyridin-2-yl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 127		6-(5-Chloropyridin-2-yl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 134		8-Methoxy-N-[(6-methylpyridazin-3-yl)methyl]-6-(5-methylpyrimidin-2-yl)quinazolin-4-amine
Example 135		6-(5-Fluoro-2-pyridyl)-8-methoxy-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine
Example 136		6-(5-Fluoropyrimidin-2-yl)-8-methoxy-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine
Example 140		8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(5-methylthiazol-2-yl)quinazolin-4-amine
Example 143		8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(4-methylthiazol-2-yl)quinazolin-4-amine

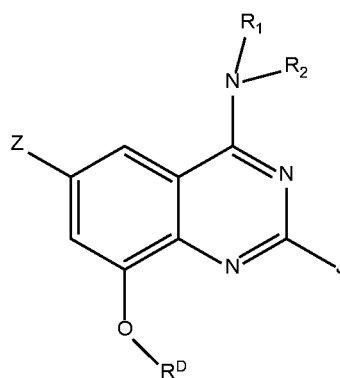
Example 145		(R)-5-(1-((8-Methoxy-6-(5-methyl-1,3,4-thiadiazol-2-yl)quinazolin-4-yl)amino)ethyl)-2-(trifluoromethyl)pyridine 1-oxide
Example 147		(R)-8-Methoxy-6-(5-methyl-1,3,4-thiadiazol-2-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 148		8-Methoxy-6-(5-methylpyrimidin-2-yl)-N-[(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl]quinazolin-4-amine
Example 149		6-(5-Fluoropyrimidin-2-yl)-8-methoxy-N-[(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl]quinazolin-4-amine
Example 150		6-(5-Fluoro-2-pyridyl)-8-methoxy-N-[(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl]quinazolin-4-amine
Example 151		8-Methoxy-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-6-(5-methylpyrimidin-2-yl)quinazolin-4-amine
Example 152		8-Methoxy-6-(1-methylpyrazol-3-yl)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]quinazolin-4-amine
Example 153		6-[5-(Difluoromethyl)-2-pyridyl]-8-methoxy-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]quinazolin-4-amine

Example 154		8-Methoxy-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-6-(5-methyl-2-pyridyl)quinazolin-4-amine
Example 155		6-(5-Fluoro-2-pyridyl)-8-methoxy-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]quinazolin-4-amine
Example 157		(R)-8-methoxy-6-(5-methylpyridin-2-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 158		(R)-8-methoxy-6-(5-methylthiazol-2-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 161		8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(5-(trifluoromethyl)thiazol-2-yl)quinazolin-4-amine
Example 296		6-(3,5-Difluoropyridin-2-yl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 297		6-(3-Fluoro-5-methyl-2-pyridyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 298		6-(5-Ethylthiazol-2-yl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine
Example 299		(R)-8-methoxy-6-(1-methyl-1H-1,2,4-triazol-3-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine

Example 300		(R)-8-methoxy-6-(1-methyl-1H-pyrazol-3-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine
Example 301		(R)-8-methoxy-6-(1-methyl-1H-1,2,4-triazol-3-yl)-N-(1-(6-methylpyridazin-3-yl)ethyl)quinazolin-4-amine
Example 315		(R)-6-(5-fluoropyridin-2-yl)-8-methoxy-N-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine
Example 316		(R)-8-methoxy-N-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)-6-(5-methylpyridin-2-yl)quinazolin-4-amine
Example 317		8-Methoxy-N-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]-6-(5-methyl-2-pyridyl)quinazolin-4-amine
Example 318		6-(5-fluoro-2-pyridyl)-8-methoxy-N-[(1R)-1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl]quinazolin-4-amine
Example 319		8-methoxy-N-[(1R)-1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl]-6-(5-methyl-2-pyridyl)quinazolin-4-amine
Example 321		6-(5-fluoro-2-pyridyl)-8-methoxy-N-[1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl]quinazolin-4-amine

Example 322		6-(5-fluoropyridin-2-yl)-8-methoxy- <i>N</i> -(1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)quinazolin-4-amine
Example 323		6-(5-fluoropyridin-2-yl)-8-methoxy- <i>N</i> -(1-(5-methyl-1,3,4-thiadiazol-2-yl)ethyl)quinazolin-4-amine
Example 324		8-methoxy- <i>N</i> -[(1R)-1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl]-6-(5-methylpyrimidin-2-yl)quinazolin-4-amine
Example 325		(<i>S</i>)-6-(5-fluoropyridin-2-yl)-8-methoxy- <i>N</i> -(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine
Example 326		8-Methoxy- <i>N</i> -[(1S)-1-(6-methylpyridazin-3-yl)ethyl]-6-(5-methylpyrimidin-2-yl)quinazolin-4-amine

In a further preferred embodiment, the invention is directed to a compound of formula (I) as defined above, wherein Y is -OR^D, represented by formula (Ia)



(Ia)

5 wherein

Z is selected from the group consisting of aryl, wherein any of such aryl may be optionally substituted by one or more groups selected from halo;

R₁ is H;

R₂ is selected from the group consisting of heteroaryl(C₁-C₄)alkyl-,
5 wherein any of such heteroaryl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, C₁-C₆haloalkyl;

R^A and **R^B** are at each occurrence independently H or selected from the group consisting of (C₁-C₄)alkyl-;

R^C is at each occurrence H or selected from the group consisting of (C₁-C₆)alkyl;

10 **R^D** is selected in the group consisting of H, (C₁-C₆)alkyl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl-, R^COC(O)(C₁-C₄)alkylene-, (R^AR^B)N(C₁-C₆)alkylene-, (C₃-C₈)heterocycloalkyl, R^CO(C₁-C₄)alkylene-, (R^AR^B)N(O)C(C₁-C₄)alkylene-, (C₃-C₈)cycloalkyl-(C₁-C₆)alkyl-, wherein any of such heterocycloalkyl may be optionally substituted by one or more groups selected from (C₁-
15 C₃)alkyl;

J is H.

In a further preferred embodiment, the invention is addressed to compound of formula (Ia) wherein

Z is H or selected from the group consisting of

20 aryl, preferably phenyl,
each of said aryl may be optionally substituted by one or more groups selected from halo, preferably fluorine,

R₁ is H;

R₂ is selected from the group consisting of

25 heteroaryl(C₁-C₄)alkyl-, (pyrimidinyl)ethyl, (pyridazinyl)methyl,
each of said heteroaryl is optionally further substituted by one or more groups

selected from

(C₁-C₃)alkyl, preferably methyl

trifluoromethyl,

R^D is H or selected in the group consisting of,

5 (C₁-C₆)alkyl, preferably methyl, propyl,

(C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl-, preferably (azetidiny)methyl,

(morpholinyl)methyl, (morpholinyl)ethyl, (oxetanyl)methyl,

R^COC(O)(C₁-C₄)alkylene-, wherein R^C is selected from the group of H and ethyl,

(R^AR^B)N(C₁-C₆)alkylene-, preferably dimethylaminopropyl,

10 (C₃-C₈)heterocycloalkyl, preferably tetrahydropyranyl,

R^CO(C₁-C₄)alkylene-, preferably selected from the group of methoxyethyl, propanolyl,

(R^AR^B)N(O)C(C₁-C₄)alkylene-, preferably dimethylacetamide,

tetrahydrofuranyl,

15 (C₃-C₈)cycloalkyl-(C₁-C₆)alkyl-, preferably (cyclopropyl)methyl,

each of said heterocycloalkyl may be optionally substituted by one or more groups selected from methyl, ethyl and propyl;

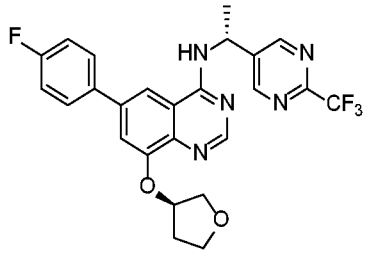
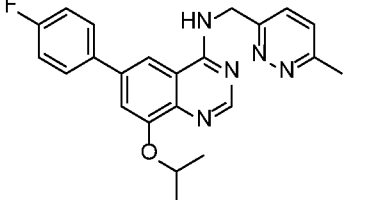
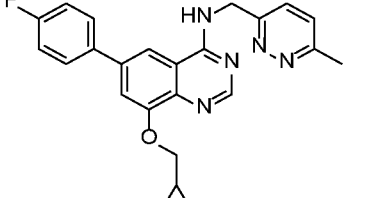
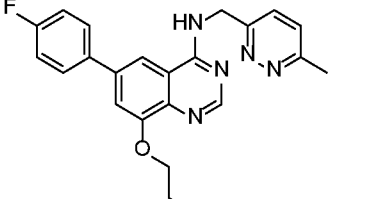
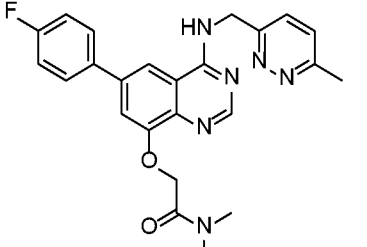
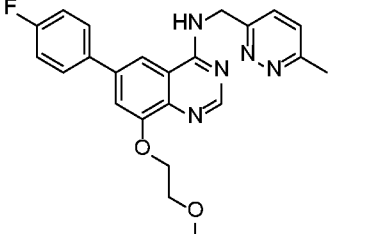
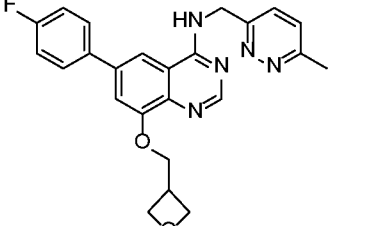
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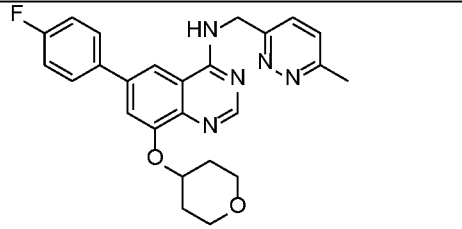
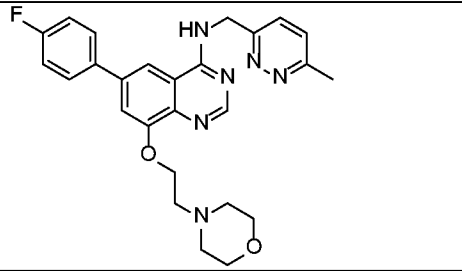
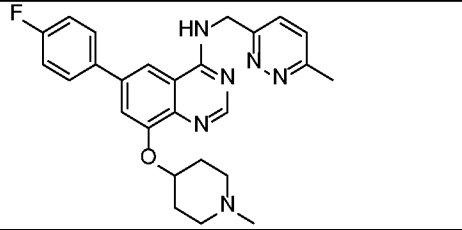
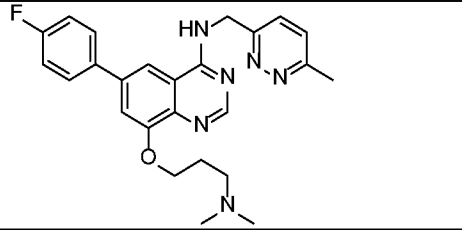
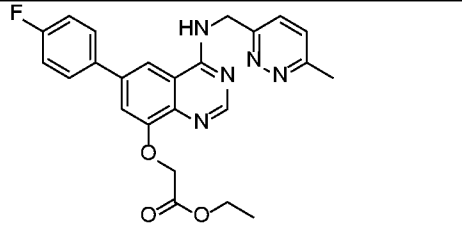
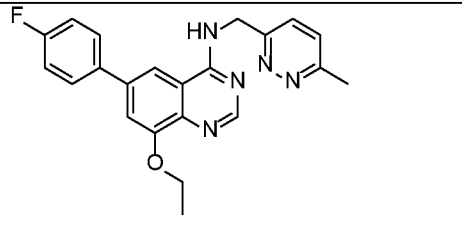
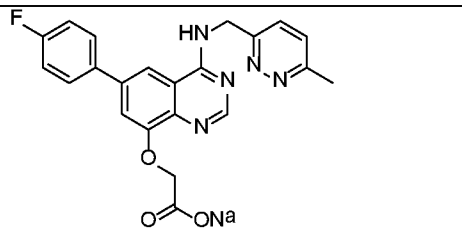
According to specific embodiments, the invention provides at least one compound

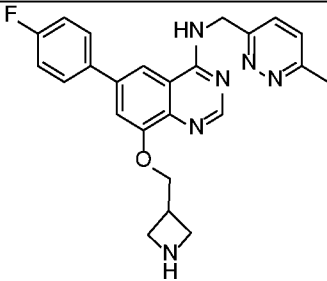
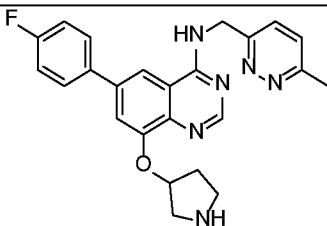
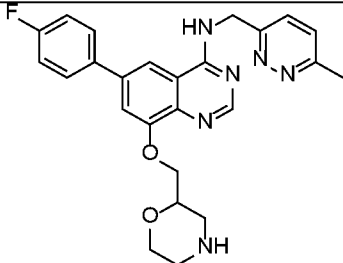
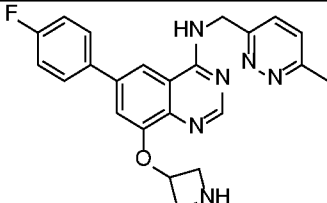
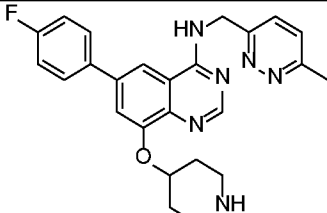
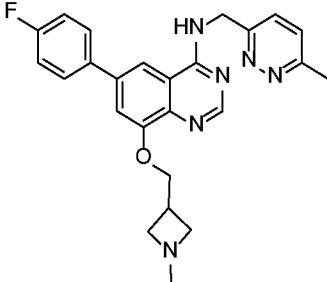
20 listed in the Table 7 below and pharmaceutical acceptable salts thereof.

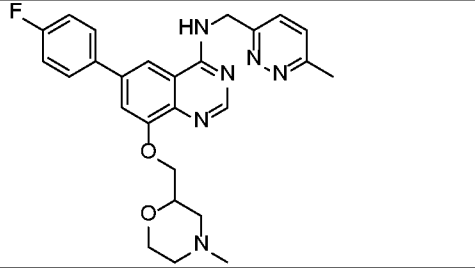
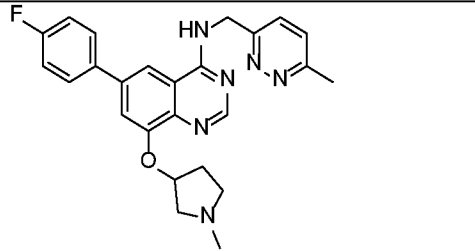
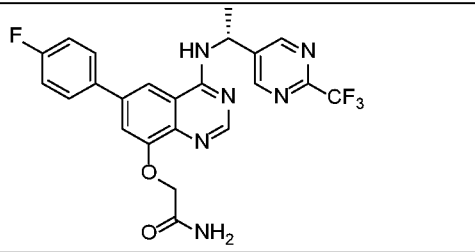
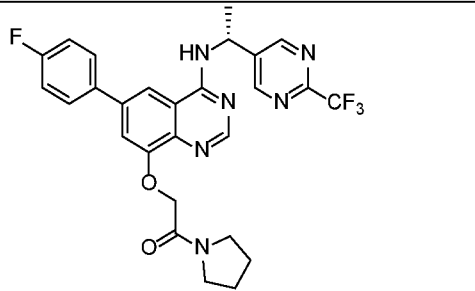
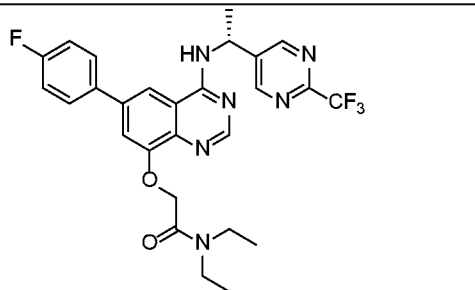
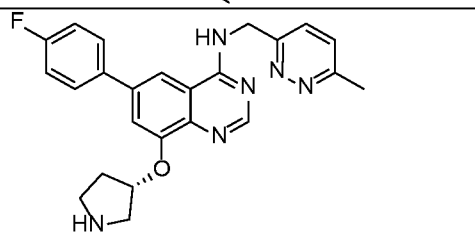
Table 7: List of preferred compounds having Formula (Ia)

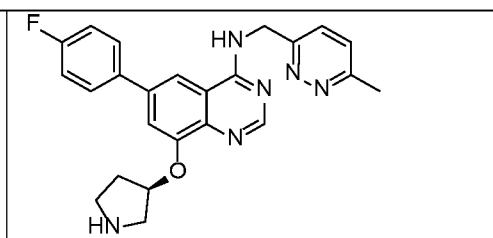
Ex. N.	Structure	Chemical name
Example 200		(R)-6-(4-Fluorophenyl)-8-((tetrahydro-2H-pyran-4-yl)oxy)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine

Example 201		(R)-4-(2-(1,1-dioxidothiomorpholino)ethyl)-8-(4-fluorophenyl)-3-oxo-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide
Example 202		6-(4-fluorophenyl)-8-isopropoxy-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine
Example 203		8-(cyclopropylmethoxy)-6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine
Example 204		2-[6-(4-fluorophenyl)-4-[(6-methylpyridazin-3-yl)methylamino]quinazolin-8-yl]oxyethanol
Example 205		2-[6-(4-fluorophenyl)-4-[(6-methylpyridazin-3-yl)methylamino]quinazolin-8-yl]oxy-N,N-dimethylacetamide
Example 206		6-(4-fluorophenyl)-8-(2-methoxyethoxy)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine
Example 207		6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-(oxetan-3-ylmethoxy)quinazolin-4-amine

Example 208		6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-tetrahydropyran-4-yloxy-quinazolin-4-amine
Example 209		6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-(2-morpholinoethoxy)quinazolin-4-amine
Example 210		6-(4-fluorophenyl)-8-[(1-methyl-4-piperidyl)oxy]-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine
Example 211		8-[3-(dimethylamino)propoxy]-6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine
Example 212		ethyl 2-[6-(4-fluorophenyl)-4-[(6-methylpyridazin-3-yl)methylamino]quinazolin-8-yl]oxyacetate
Example 213		8-ethoxy-6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine
Example 214		2-[6-(4-fluorophenyl)-4-[(6-methylpyridazin-3-yl)methylamino]quinazolin-8-yl]oxyacetic acid, sodium salt

Example 215		8-(azetidin-3-ylmethoxy)-6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine
Example 216		6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-pyrrolidin-3-yloxyquinazolin-4-amine
Example 217		6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-(morpholin-2-ylmethoxy)quinazolin-4-amine
Example 218		8-(azetidin-3-yloxy)-6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine
Example 219		6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-(4-piperidyloxy)quinazolin-4-amine
Example 220		6-(4-fluorophenyl)-8-[(1-methylazetidin-3-yl)methoxy]-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine

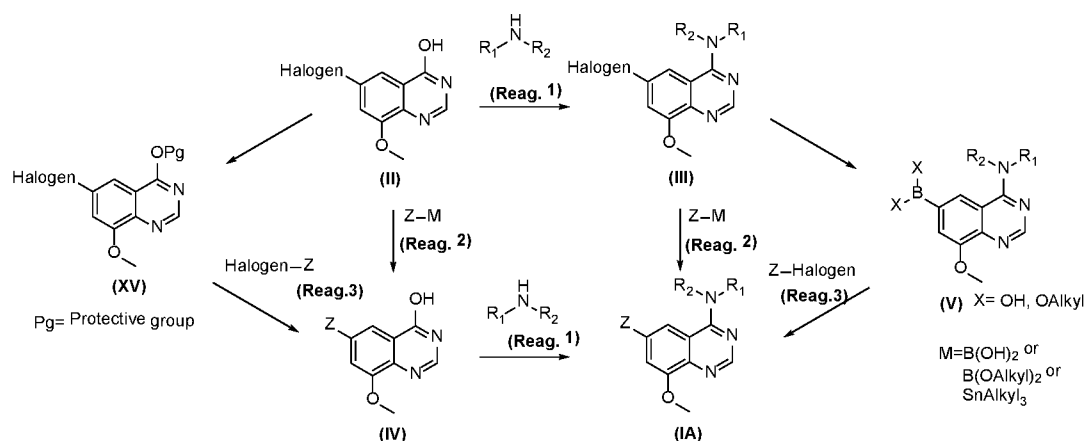
Example 221		6-(4-fluorophenyl)-8-[(4-methylmorpholin-2-yl)methoxy]-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine
Example 222		6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-(1-methylpyrrolidin-3-yl)oxy-quinazolin-4-amine
Example 310		<i>R</i> -2-((6-(4-fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazolin-8-yl)oxy)acetamide
Example 311		<i>R</i> -2-((6-(4-fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazolin-8-yl)oxy)-1-(pyrrolidin-1-yl)ethan-1-one
Example 312		<i>R</i> - <i>N,N</i> -diethyl-2-((6-(4-fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazolin-8-yl)oxy)acetamide
Example 313		6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-[(3 <i>S</i>)-pyrrolidin-3-yl]oxy-quinazolin-4-amine

Example 314		6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-[(3R)-pyrrolidin-3-yl]oxy-quinazolin-4-amine
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The compounds of formula (I) including all the compounds or at least one of the here above listed can be generally prepared according to the procedure outlined in detail in the Schemes shown below using generally known methods.

5

Scheme 1



In one embodiment of the present invention, compound (IA) may be prepared according to SCHEME 1 from compound (II). Compound (II) was prepared following the procedure described in *J. Med Chem.*, **2015**, 58 (8), 3548-3571.

Compound (III) may be prepared from Compound (II) by a deoxygenation reaction mediated by coupling reagents like PyBOP with a suitable amine (Reag. 1).

Compound (IA) may be prepared from Compound (III) by a metal-catalyzed cross coupling reactions like Stille or Suzuki or similars as described in "Transition Metals for Organic Synthesis", 2nd Ed, 1, 2004 with a suitable reagent like (Reag. 2).

Alternately Compound (V) may be prepared from Compound (III) by metal-catalyzed Miyaura borylation reaction.

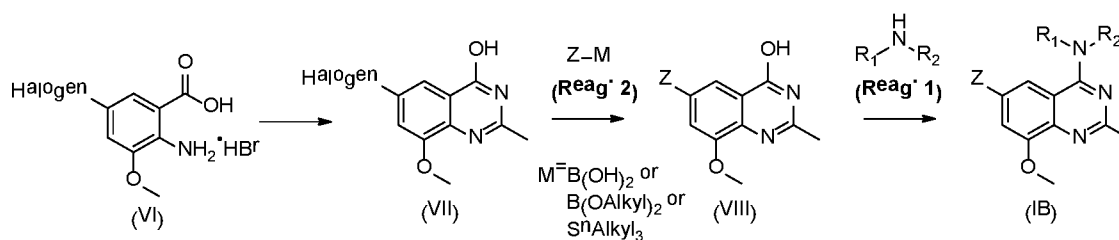
Compound (IA) may be prepared from Compound (V) by a metal-catalyzed cross coupling reactions like Stille, Suzuki or similar as described in "Transition Metals for Organic Synthesis", 2nd Ed, 1, 2004 with a suitable organohalogen compound like (Reag. 3).

5 In another embodiment, compound (IV) was prepared starting from compound (II) by a metal-catalyzed cross coupling reactions like Stille, Suzuki or similars as described in "Transition Metals for Organic Synthesis", 2nd Ed, 1, 2004 with a suitable Organometallic reagent like (Reag.2).

Compound (IA) may be prepared from Compound (V) by deoxyamination reaction
10 mediated by reagents like PyBOP or similar with a suitable amine (Reag. 1).

Some compounds (IA) may contain a protected hydroxyl or amino group which were then removed under well known procedures.

Scheme 2



15 In another embodiment of the present invention, compound (IB) may be prepared according to SCHEME 2 from compounds (VI).

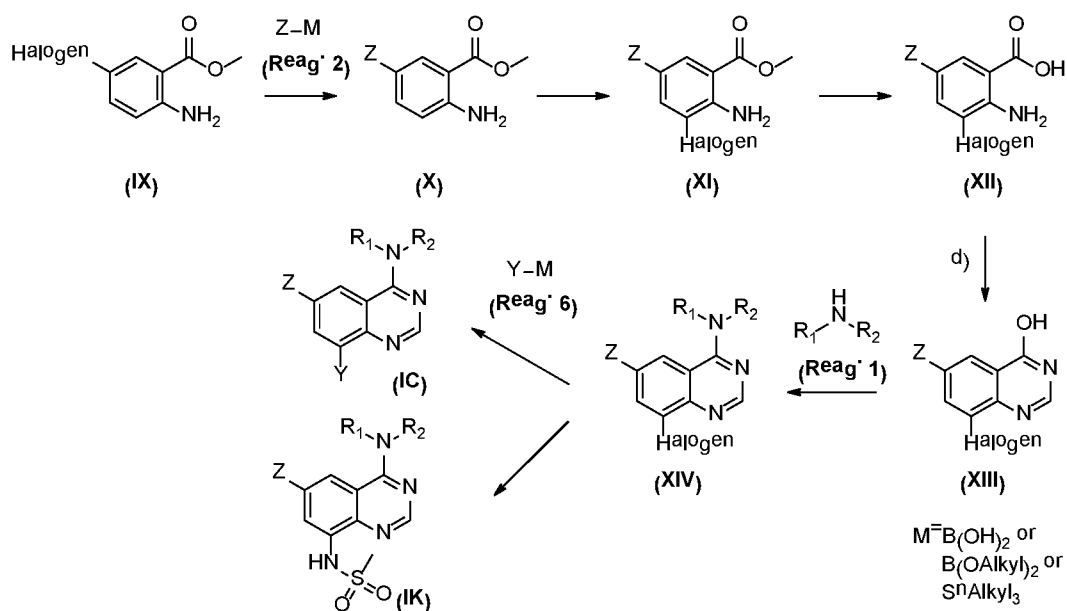
Compound (VII) may be prepared from Compound (VI) by means of a quinazoline ring construction reaction mediated by suitable reagents like triethylorthoacetate or similar.

20 Compound (VIII) may be prepared from Compound (VII) by metal-catalyzed cross coupling reactions like Stille, Suzuki or similar ones with suitable organometallic reagents (Reag.2) like, for example, organoboron compounds.

Compounds (IB) may be prepared from compound (VIII) by deoxyamination reaction mediated by reagents like PyBOP or similar in the presence of a suitable amine (Reag.1).

Some compounds (IB) may contain a protected hydroxyl or amino group which were then removed under well known procedures.

Scheme 3



In another embodiment of the present invention, compound (IC) may be prepared according to SCHEME 3 from compound (IX).

Compound (X) may be prepared from Compound (IX) by metal-catalyzed cross coupling reactions like Stille, Suzuki or similar ones with suitable organometallic reagents (Reag.2) like, for example, organoboron compounds.

Compound (XI) may be prepared from Compound (X) by Halogenation with suitable reagents like Bromine, NBS, NIS, Iodine, iodonium salts or similar.

Compound (XII) may be prepared from Compound (XI) by hydrolysis in a basic or acidic medium.

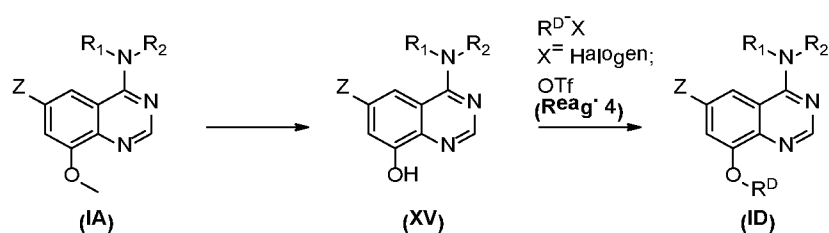
Compound (XIII) may be prepared from Compound (XII) by quinazoline ring construction reaction with suitable reagents like formamide or similars.

Compound (XIV) may be prepared from Compound (XIII) by deoxyamination reaction mediated by reagents like PyBOP or similar in the presence of a suitable amine (Reag. 1).

Compound (IC) may be prepared from Compound (XIV) by metal-catalyzed cross
5 coupling reactions like Stille, Suzuki or similar ones with suitable organometallic reagents (Reag. 6) like, for example, organoboron compounds. Some compounds (IC) may contain a protected hydroxyl or amino group which were then removed under well known procedures.

Compound (IK) may be prepared from Compound (XIV) by amination reactions in
10 the presence of a suitable reagent like, for example, methanesulfonamide. Some compounds (IK) may contain a protected hydroxyl or amino group which were then removed under well known procedures.

Scheme 4



15 In another embodiment of the present invention, compounds (ID) may be prepared according to SCHEME 4 from compounds (IA).

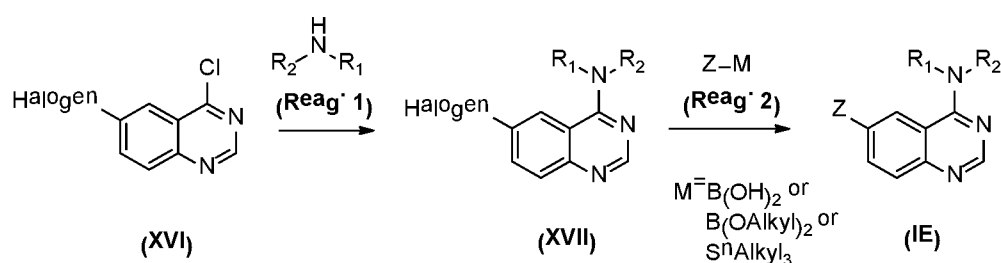
Compound (XV) may be prepared from Compound (IA) by means of dealkylation reactions mediated by strong Lewis acids like BBr₃ or similar.

Compounds (ID) were prepared from compounds (XV) by alkylation with a suitable
20 alkylating agent (Reag. 4) like, alkyl chlorides, bromides, iodides, mesylates, tosylates or similar.

Alternatively, compounds (ID) may be prepared from compounds (XV) and a suitable alcohol by Mitsunobu-like reactions mediated, for example, by DEAD/PPh₃, DIAD/PPh₃ or CMT.

Some compounds (ID) may contain a protected hydroxyl or amino group which were then removed under well-known procedures.

Scheme 5



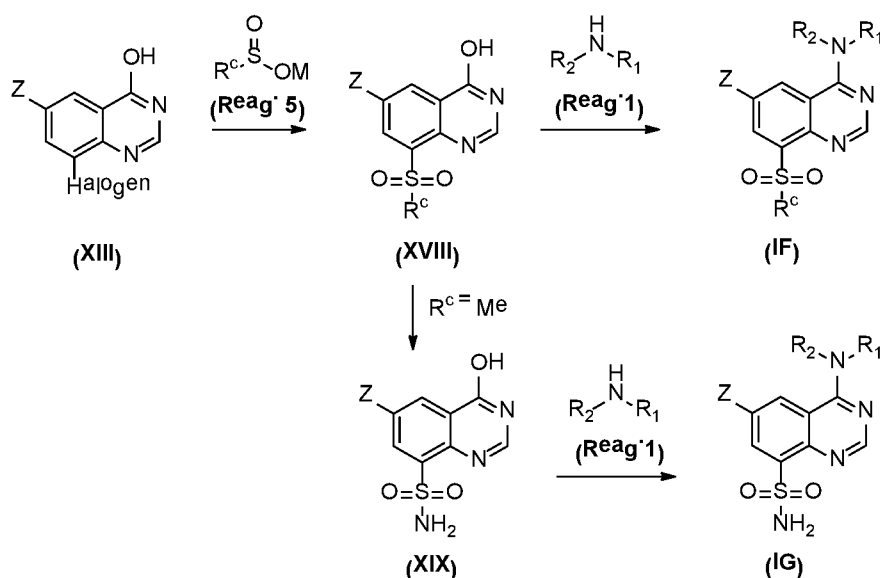
In another embodiment of the present invention, compound (IE) may be prepared according to SCHEME 5 from compounds (XVI).

Compound (XVII) may be prepared from Compound (XVI) by deoxygenation reaction mediated by reagents like PyBOP or similar in the presence of a suitable amine (Reag. 1).

Compounds (IE) were prepared from Compounds (XVII) by metal-catalyzed cross coupling reactions like Stille, Suzuki or similar ones with suitable organometallic reagents (Reag. 2) like, for example, organoboron compounds.

Some compounds (IE) may contain a protected hydroxyl or amino group which were then removed under well known procedures.

Scheme 6



In another embodiment of the present invention, compound (IF) and (IG) may be prepared according to SCHEME 6 from compounds (XIII).

- 5 Compound (XVIII) may be prepared from Compound (XIII) by metal catalyzed sulfenylation reaction with a suitable sulfinate (Reag. 5) like, for example, sodium methanesulfinate.

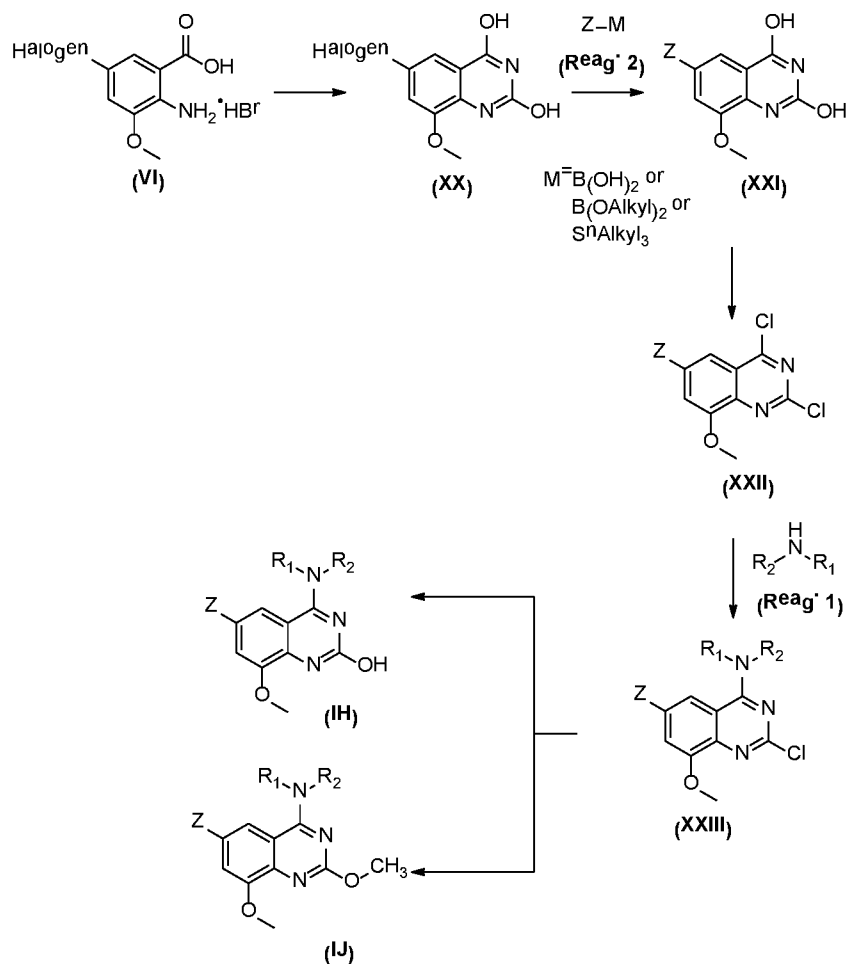
Compound (IF) may be prepared from Compound (XVIII) by deoxygenation reaction mediated by reagents like PyBOP or similar in the presence of a suitable amine
10 (Reag. 1). Some compounds (IF) may contain a protected hydroxyl or amino group which were then removed under well known procedures.

In another embodiment of the present invention Compound (XIX) may be prepared from Compound (XVIII) by amination with tributylborate and (aminooxy)sulfonic acid as described in *Tetr. Lett.* **1994**, 39, 7201

- 15 Compound (IG) may be prepared from Compound (XIX) by deoxygenation reaction mediated by reagents like PyBOP or similar in the presence of a suitable amine (Reag. 1).

Some compounds (IG) may contain a protected hydroxyl or amino group which were then removed under well known procedures.

Scheme 7



5 In another embodiment of the present invention, compound (IH) and (IJ) may be prepared according to SCHEME 7 from compounds (VI).

Compound (XX) may be prepared from Compound (VI) by quinazoline ring construction reaction with suitable reagents like Urea or similars.

10 Compound (XXI) may be prepared from Compound (XX) by metal-catalyzed cross coupling reactions like Stille, Suzuki or similar ones with suitable organometallic reagents (Reag. 2) like, for example, organoboron compounds.

Compound (XXII) may be prepared from Compound (XXI) by chlorination reaction with suitable reagents like phosphorous oxychloride or similar.

Compound (XXIII) may be prepared from Compound (XXII) by amination reaction in the presence of a suitable amine (Reag. 1).

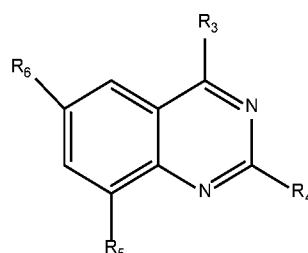
Compound (IH) may be prepared from Compound (XXIII) by hydrolysis with a suitable reagent like, for example, acetic acid.

5 Some compounds (IH) may contain a protected hydroxyl or amino group which were then removed under well known procedures.

In another embodiment of the present invention Compound (IJ) may be prepared from Compound (XXIII) by reaction with alkoxides, like, for example, Sodium Methoxide.

10 Some compounds (IJ) may contain a protected hydroxyl or amino group which were then removed under well known procedures.

In a specific aspect the present invention relates to compounds of formula (Ib)



(Ib)

15 wherein R₃ is OH or halo,

R₄ is H or OH;

R₅ is halo or -OMe;

R₆ is halo or Z;

Z is as defined above.

20 In a further aspect the present invention relates to the use of compounds of formula (Ib) as intermediate in the preparation of compounds of formula (I) as above described.

The compounds of the present invention have surprisingly been found to effectively inhibit P2X₃ receptor and said compounds are useful for the treatment of respiratory disease.

In one embodiment, representative compounds of formula (I) of the present invention have surprisingly been found to effectively and selectively inhibit P2X₃ receptor and said compounds are useful for the treatment of respiratory disease avoiding adverse effect, such as loss of taste response.

In a preferred embodiment, the compound of formula (I) are selective P2X₃ antagonist wherein the selective P2X₃ antagonist is at least 10-fold selective for P2X₃ homomeric receptor antagonism versus P2X_{2/3} heteromeric receptor antagonism.

In a further preferred embodiment, the selective P2X₃ antagonist is at least 30-fold selective for P2X₃ homomeric receptor antagonism versus P2X_{2/3} heteromeric receptor antagonism.

In a further preferred embodiment, the selective P2X₃ antagonist is at least 50-fold selective for P2X₃ homomeric receptor antagonism versus P2X_{2/3} heteromeric receptor antagonism.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof in admixture with one or more pharmaceutically acceptable carrier or excipient, either alone or in combination with one or more further active ingredient.

In one aspect, the invention refers to a compound of formula (I) according to the invention for use as a medicament.

In a further aspect, the invention refers to the use of a compound of formula (I) of the invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of disorders associated with P2X₃ receptors mechanism, preferably for the treatment of respiratory diseases.

Preferably, the invention refers to a compound of formula (I) for use in the prevention and /or treatment of respiratory diseases, preferably cough, sub-acute or chronic cough, treatment-resistant cough, idiopathic chronic cough, post-viral cough, iatrogenic cough, asthma, idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD) and cough associated with respiratory diseases such as COPD, asthma and bronchospasm.

More preferably, the invention refers to a compounds of formula (I) for use in the prevention and /or treatment of chronic cough and cough associated with respiratory diseases such as COPD, asthma and bronchospasm.

The invention also provides a method for the prevention and/or treatment of disorders associated with P2X₃ receptors mechanisms, said method comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of the invention.

In particular the invention refers to a method for the prevention and/or treatment wherein the disorder is cough, sub-acute or chronic cough, treatment-resistant cough, idiopathic chronic cough, post-viral cough, iatrogenic cough, asthma, idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD) and cough associated with respiratory diseases such as COPD, asthma and bronchospasm, wherein said method comprises the administration of a proper amount of a compound of formula (I) to a patient in the need thereof.

In a further preferred embodiment, the disorder is chronic cough.

The methods of treatment of the invention comprise administering a safe and effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof to a patient in need thereof. As used herein, "safe and effective amount" in reference to a compound of formula (I) or a pharmaceutically acceptable salt thereof or other pharmaceutically-active agent means an amount of the compound sufficient to treat

the patient's condition but low enough to avoid serious side effects and it can nevertheless be routinely determined by the skilled artisan. The compounds of formula (I) or pharmaceutically acceptable salts thereof may be administered once or according to a dosing regimen wherein a number of doses are administered at varying intervals of time
5 for a given period of time. Typical daily dosages may vary depending upon the particular route of administration chosen.

The invention also provides pharmaceutical compositions of compounds of formula (I) in admixture with one or more pharmaceutically acceptable carrier or excipient, for example those described in Remington's Pharmaceutical Sciences Handbook, XVII Ed.,
10 Mack Pub., N.Y., U.S.A.

Administration of the compounds of the invention and their pharmaceutical compositions may be accomplished according to patient needs, for example, orally, nasally, parenterally (subcutaneously, intravenously, intramuscularly, intrasternally and by infusion) and by inhalation.

15 Preferably the compounds of the present invention may be administered orally or by inhalation.

Various solid oral dosage forms can be used for administering compounds of the invention including such solid forms as tablets, gelcaps, capsules, caplets, granules, lozenges and bulk powders. The compounds of the invention can be administered alone
20 or combined with various pharmaceutically acceptable carriers, diluents (such as sucrose, mannitol, lactose, starches) and known excipients, including suspending agents, solubilizers, buffering agents, binders, disintegrants, preservatives, colorants, flavorants, lubricants and the like. Time release capsules, tablets and gels are also advantageous in administering the compounds of the invention.

25 Preferably the compounds of the invention are administered in forms of tablets.

Various liquid oral dosage forms can also be used for administering compounds of the invention, including aqueous and non-aqueous solutions, emulsions, suspensions, syrups, and elixirs. Such dosage forms can also contain suitable known inert diluents such as water and suitable known excipients such as preservatives, wetting agents, sweeteners, flavorants, as well as agents for emulsifying and/or suspending the compounds of the invention. The compounds of the invention may be injected, for example, intravenously, in the form of an isotonic sterile solution.

For the treatment of the diseases of the respiratory tract, the compounds according to the invention are preferably administered by inhalation.

Inhalable preparations include inhalable powders, propellant-containing metering aerosols or propellant-free inhalable formulations.

For administration as a dry powder, single- or multi-dose inhalers known from the prior art may be utilized. In that case the powder may be filled in gelatine, plastic or other capsules, cartridges or blister packs or in a reservoir.

A diluent or carrier chemically inert to the compounds of the invention, e.g. lactose or any other additive suitable for improving the respirable fraction may be added to the powdered compounds of the invention.

Inhalation aerosols containing propellant gas such as hydrofluoroalkanes may contain the compounds of the invention either in solution or in dispersed form. The propellant-driven formulations may also contain other ingredients such as co-solvents, stabilizers and optionally other excipients.

The propellant-free inhalable formulations comprising the compounds of the invention may be in form of solutions or suspensions in an aqueous, alcoholic or hydroalcoholic medium and they may be delivered by jet or ultrasonic nebulizers known from the prior art or by soft-mist nebulizers.

Preferably, the compound of the present invention are administered orally.

The compounds of the invention can be administered as the sole active agent or in combination with other pharmaceutical active ingredients.

Preferably, the compound of the present invention can be combined with therapeutic agents or active ingredients useful for the treatment of disease which are
5 related to or mediated by P2X₃ receptor.

The dosages of the compounds of the invention depend upon a variety of factors including among others the particular disease to be treated, the severity of the symptoms, the route of administration, and the like.

The invention is also directed to a device comprising a pharmaceutical composition
10 comprising a compound of formula (I) according to the invention, in form of a single- or multi-dose dry powder inhaler or a metered dose inhaler.

The various aspects of the invention described in this application are illustrated by the following examples which are not meant to limit the invention in any way. following examples illustrate the invention.

15 The example testing experiments described herein serve to illustrate the present invention and the invention is not limited to the examples given.

PREPARATIONS OF INTERMEDIATES AND EXAMPLES

Chemical names were generated using the Dotmatics software. In some cases generally accepted names of commercially available reagents were used in place of
20 Dotmatics software generated names.

All reagents, for which the synthesis is not described in the experimental part, are either commercially available, or are known compounds or may be formed from known compounds by known methods by a person skilled in the art.

(*R*)-1-(2-(trifluoromethyl)pyrimidin-5-yl)ethanamine HCl, (*R*)-1-(6-
25 methylpyridazin-3-yl)ethan-1-amine HCl were prepared accordingly to the procedure described in WO2016/091776.

Abbreviation – Meaning

Et₂O: diethyl ether;

Et₃N: triethyl amine;

TEA: triethyl amine;

5 DCC: N,N'-Dicyclohexylcarbodiimide;

PyBOP: (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate;

DMF: dimethylformamide;

EtOAc: Ethyl acetate;

RT: room temperature;

10 THF: tetrahydrofuran;

DCM: dichloromethane;

MeOH: methyl alcohol;

EtOH: ethylic alcohol;

TFA: Trifluoroacetic acid;

15 LC-MS: Liquid Chromatography/Mass Spectrometry;

HPLC: high pressure liquid chromatography;

MPLC: medium pressure liquid chromatography;

SFC: Supercritical Fluid Chromatography;

dppf: 1,1'- Bis(diphenylphosphino) ferrocene;

20 DIEA or DIPEA: N,N-Diisopropylethylamine;

MeCN: Acetonitrile;

MTBE: tert-Butyl methyl ether;

TBDMSCl: tert-Butyl(chloro)dimethylsilane;

DMSO: Dimethylsulfoxide;

25 Boc₂O: di-tert-butyl dicarbonate;

UPLC: Ultra Performance Liquid Chromatography.

General Experimental Details and methods

Analytical Methods

Liquid Chromatography-Mass Spectrometry

Method 1

5 UPLC-MS was performed on a Waters Acquity I-Class with Waters Diode Array
Detector coupled to a Waters SQD2 single quadrupole mass spectrometer using an Waters
HSS C18 column (1.8 μm , 100 \times 2.1 mm) being initially held at 5% acetonitrile/water
(with 0.1% formic acid in each mobile phase) for 1.2 minutes, followed by a linear
gradient of 5-100% within 3.5 minutes and then held at 100% for 1.5 minutes (F = 0.5
10 mL/min).

Method 2

UPLC-MS was performed on a Waters Acquity I-Class with Waters Diode Array
Detector coupled to a Waters SQD2 single quadrupole mass spectrometer using an Waters
BEH Shield RP18 column (1.7 μm , 100 \times 2.1 mm) being initially held at 5%
15 acetonitrile/water (with 10 mM ammonium bicarbonate in each mobile phase) for 1.2
minutes, followed by a linear gradient of 5-100% within 3.5 minutes and then held at
100% for 1.5 minutes (F = 0.5 mL/min).

Method 3

UPLC-MS was performed on a Waters DAD + Waters SQD2, single quadrupole
20 UPLC-MS spectrometer using an Acquity UPLC BEH Shield RP18 1.7 μm 100 \times 2.1mm
(Plus guard cartridge), maintained at temp column being initially held at 5%
acetonitrile/water (with 10 mM ammonium bicarbonate in each mobile phase) for 0.4
minutes, followed by a linear gradient of 5-95% within 6.4 minutes and then held at 95%
for 1.2 minutes (F = 0.4 mL/min).

25 Method 4

UPLC-MS was performed on a Waters DAD + Waters SQD2, single quadrupole

UPLC-MS spectrometer using an Acquity UPLC BEH Shield RP18 1.7 μ m 100 x 2.1mm (Plus guard cartridge), maintained at temp column being initially held at 5% Acetonitrile (Far UV grade) with 0.1% (V/V) formic acid / Water (High purity via PureLab Option unit) with 0.1% formic acid for 0.4 minutes, followed by a linear gradient of 5-95% within 5 6.4 minutes and then held at 95% for 1.2 minutes (F = 0.4 mL/min).

Method 5

Acquity UPLC - QDa Mass Spectrometer with a C18-reverse-phase column (50 x 2.1 mm Acquity CSH with 1.7 μ m particle size) maintained at 40 °C, elution with A: 95/5 water/acetonitrile + 0.05% formic acid; B: 95/5 acetonitrile/water + 0.05% formic acid.

10 Gradient:

Time [min]	Flow [ml/min]	Mobile phase A [%]	Mobile phase B [%]
0.0	1	99.0	1.0
1.50	1	0.1	99.9
1.90	1	0.1	99.9
2.00	1	99.0	1.0

Detection-MS, UV PDA

MS ionisation method-Electrospray (positive/negative ion).

Method 6

15 Acquity UPLC - QDa Mass Spectrometer with a C18-reverse-phase column (50 x 2.1 mm Acquity BEH with 1.7 μ m particle size) maintained at 40 °C, elution with A: 95/5 water/acetonitrile + 0.05% conc. ammonia; B: 95/5 acetonitrile/water + 0.05% conc. ammonia.

Gradient:

Time [min]	Flow [ml/min]	Mobile phase A [%]	Mobile phase B [%]
0.0	1	99.0	1.0
1.50	1	0.1	99.9
1.90	1	0.1	99.9
2.00	1	99.0	1.0

Detection-MS, UV PDA

MS ionisation method-Electrospray (positive/negative ion)

Method 7

- 5 Dionex UHPLC Ultimate 3000 with DAD detector/Thermo Scientific MSQ Pluse quipped with a Kinetex® 2.6 µm XB-C18 (4.6x50mm), 110A maintained at 25 °C, elution with A: 0.1 % v/v water solution of formic acid, B: 0.1 % v/v acetonitrile solution of formic acid

Gradient:

Time [min]	Flow [ml/min]	Mobile phase A [%]	Mobile phase B [%]
0.0	1.0	95	5
1.0	1.0	95	5
4.75	1.0	20	80
5.25	1.0	20	80
6.0	1.0	95	5
7.0	1.0	95	5

- 10 Detection-MS, UV PDA

MS ionisation method-Electrospray (positive/negative ion)

NMR

¹H Nuclear magnetic resonance (NMR) spectroscopy was carried out using a Bruker or Varian instruments operating at 300 or 400 MHz using the stated solvent at around room temperature unless otherwise stated. In all cases, NMR data were consistent
5 with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet; br, broad.

Preparative reverse-phase HPLC conditions

10 Preparative HPLC purification was performed by reverse phase HPLC using a Waters Fractionlynx preparative HPLC system (2525 pump, 2996/2998 UV/VIS detector, 2767 liquid handler) or an equivalent HPLC system such as a Gilson Trilution UV directed system. The Waters 2767 liquid handler acted as both auto-sampler and fraction collector. The columns used for the preparative purification of the compounds were a
15 Waters Sunfire OBD Phenomenex Luna Phenyl Hexyl or Waters Xbridge Phenyl at 10 μ m 19 \times 150 mm or Waters CSH Phenyl Hexyl, 19 \times 150, 5 μ m column. Appropriate focused gradients were selected based on acetonitrile and methanol solvent systems under either acidic or basic conditions. The modifiers used under acidic/basic conditions were formic acid or trifluoroacetic acid (0.1% V/V) and ammonium bicarbonate (10 mM)
20 respectively. The purification was controlled by Waters Fractionlynx software through monitoring at 210-400 nm, and triggered a threshold collection value at 260 nm and, when using the Fractionlynx, the presence of target molecular ion as observed under API conditions. Collected fractions were analysed by LCMS (Waters Acquity systems with Waters SQD).

25 Chiral Supercritical Fluid Chromatography (SFC) separation protocol

The diastereomeric separation of compounds was achieved by Supercritical Fluid Chromatography (SFC) using a Waters Thar Prep100 preparative SFC system (P200 CO2 pump, 2545 modifier pump, 2998 UV/VIS detector, 2767 liquid handler with Stacked Injection Module). The Waters 2767 liquid handler acted as both auto-sampler and
5 fraction collector. Appropriate isocratic methods were selected based on methanol, ethanol or isopropanol solvent systems under un-modified or basic conditions. The standard SFC method used was modifier, CO2, 100 mL/min, 120 Bar backpressure, 40 °C column temperature. The modifier used under basic conditions was diethylamine (0.1% V/V). The modifier used under acidic conditions was either formic acid (0.1%
10 V/V) or trifluoroacetic acid (0.1% V/V). The SFC purification was controlled by Waters Fractionlynx software through monitoring at 210-400 nm and triggered at a threshold collection value, typically 260 nm. Collected fractions were analysed by SFC (Waters/Thar SFC systems with Waters SQD). The fractions that contained the desired product were concentrated by vacuum centrifugation.

15 Supercritical Fluid Chromatography – Mass Spectrometry analytical conditions

Method 8

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a Lux Cellulose-3 column with a 15% methyl alcohol/CO₂ (with 0.1% diethylamine) isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

20 Method 9

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a Lux Cellulose-3 column with a 20% methyl alcohol/CO₂ (with 0.1% diethylamine) isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 10

25 SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a

Lux Cellulose-4 column with a 55% ethyl alcohol/CO₂ (with 0.1% diethylamine) isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 11

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
5 Lux Cellulose-4 column with a 20% *iso*-propyl alcohol/CO₂ (with 0.1% diethylamine)
isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 12

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
Lux Cellulose-4 column with a 30% *iso*-propyl alcohol/CO₂ (with 0.1% diethylamine)
10 isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 13

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
Lux Cellulose-4 column with a 50% *iso*-propyl alcohol/CO₂ (with 0.1% diethylamine)
isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

15 Method 14

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
Lux Cellulose-4 column with a 25% methyl alcohol/CO₂ (with 0.1% diethylamine)
isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 15

20 SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
YMC Amylose-C column with a 15% ethyl alcohol/CO₂ (with 0.1% diethylamine)
isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 16

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a

YMC Amylose-C column with a 25% *iso*-propyl alcohol/CO₂ (with 0.1% diethylamine) isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 17

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
5 YMC Amylose-C column with a 35% *iso*-propyl alcohol/CO₂ (with 0.1% diethylamine) isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 18

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
YMC Amylose-C column with a 55% *iso*-propyl alcohol/CO₂ (with 0.1% diethylamine)
10 isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 19

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
YMC Amylose-C column with a 15% methyl alcohol/CO₂ (with 0.1% diethylamine)
isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

15 Method 20

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
YMC Amylose-C column with a 20% methyl alcohol/CO₂ (with 0.1% diethylamine)
isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 21

20 SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
YMC Cellulose-C column with a 15% *iso*-propyl alcohol/CO₂ (with 0.1% diethylamine)
isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 22

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a

YMC Cellulose-C column with a 15% methyl alcohol/CO₂ (with 0.1% diethylamine) isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 23

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
5 YMC Cellulose-C column with a 25% methyl alcohol/CO₂ (with 0.1% diethylamine) isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 24

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
10 YMC Cellulose-SC column with a 55% *iso*-propyl alcohol/CO₂ (with 0.1% diethylamine) isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 25

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
Lux Cellulose-3 column with a 10% methyl alcohol/CO₂ (with 0.1% diethylamine) isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

15 Method 26

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
Lux Cellulose-3 column with a 25% methyl alcohol/CO₂ (with 0.1% diethylamine) isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 27

20 SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
Lux Cellulose-3 column with a 30% methyl alcohol/CO₂ (with 0.1% diethylamine) isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 28

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a

Lux Cellulose-4 column with a 40% iso-propyl alcohol/CO₂ (with 0.1% diethylamine) isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 29

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
5 Lux Cellulose-4 column with a 40% methyl alcohol/CO₂ (with 0.1% diethylamine) isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 30

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
Lux Cellulose-4 column with a 50% methyl alcohol/CO₂ (with 0.1% diethylamine)
10 isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 31

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
Lux Cellulose-4 column with a 55% iso-propyl alcohol/CO₂ (with 0.1% diethylamine)
isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

15 Method 32

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
Lux Cellulose-4 column with a 55% methyl alcohol/CO₂ (with 0.1% diethylamine)
isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 33

20 SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
YMC Amylose-C column with a 20% ethyl alcohol/CO₂ (with 0.1% diethylamine)
isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 34

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a

YMC Amylose-C column with a 30% iso-propyl alcohol/CO₂ (with 0.1% diethylamine) isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 35

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
5 YMC Amylose-C column with a 30% methyl alcohol/CO₂ (with 0.1% diethylamine) isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 36

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
YMC Amylose-C column with a 40% methyl alcohol/CO₂ (with 0.1% diethylamine)
10 isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 37

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
YMC Amylose-C column with a 55% methyl alcohol/CO₂ (with 0.1% diethylamine)
isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

15 Method 38

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
YMC Cellulose-C column with a 20% methyl alcohol/CO₂ (with 0.1% diethylamine)
isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 39

20 SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a
YMC Cellulose-SC column with a 35% iso-propyl alcohol/CO₂ (with 0.1% diethylamine)
isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

Method 40

SFC-MS was performed on a Waters/Thar SFC systems with Waters SQD using a

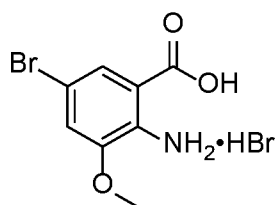
YMC Cellulose-SC column with a 45% iso-propyl alcohol/CO₂ (with 0.1% diethylamine)isocratic run at 5 mL/min, 120 Bar backpressure, 40 °C column temperature.

PREPARATION OF INTERMEDIATES AND EXAMPLES

5 Example 1

6-(4-Fluorophenyl)-8-methoxy-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine

Preparation of Intermediate 1, 2-Amino-5-bromo-3-methoxybenzoic acid hydrobromide



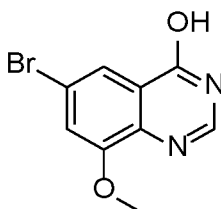
10

A solution of bromine (6.0 g, 1.9 mL, 37.70 mmol) in chloroform (15 mL) was added dropwise over a period of one hour to a suspension of 2-amino-3-methoxybenzoic acid (6.0 g, 35.90 mmol) in chloroform (180 mL) at 0 °C. The reaction was stirred for a further five hours and slowly allowed to warm to room temperature. The solvent was removed *in vacuo* and the residue was triturated with diethyl ether. The reaction was filtered to give the title compound as a beige solid (11.3 g, 96%).

15

LCMS (Method 4): [MH⁺] = 247 at 4.07 min.

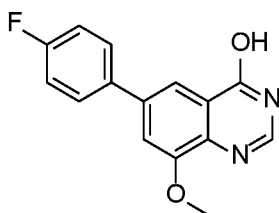
Preparation of Intermediate 2 6-Bromo-8-methoxyquinazolin-4-ol



A solution 2-amino-5-bromo-3-methoxybenzoic acid hydrobromide (Intermediate 1) (10.0 g, 30.60 mmol) in formamide (40 mL) was heated to 165 °C for 18 hours. After return to room temperature, the reaction was diluted with water (100 mL) and poured into ice water (400 mL) and filtered. The solid was washed with water (200 mL) and diethyl
5 ether (200 mL) to give the title compound as a light brown solid (5.9 g, 76%).

LCMS (Method 4): [MH⁺] = 255 at 3.07 min.

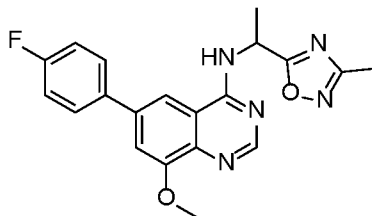
Preparation of Intermediate 3, 6-(4-Fluorophenyl)-8-methoxyquinazolin-4-ol



Nitrogen was bubbled for 5 min through a mixture of 6-bromo-8-
10 methoxyquinazolin-4-ol (Intermediate 2) (1.18 g, 4.63 mmol), 4-fluorophenylboronic acid (710 mg, 5.09 mmol) and cesium carbonate (5.73 g, 17.58 mmol) in 1,4-dioxane (30 mL) and water (7.5 mL), then [1,1'-
bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (190 mg, 0.23 mmol) was added and the reaction was heated to 110 °C for 5 hours. After
15 return to room temperature, the reaction was diluted with water (20 mL), filtered and the solid was washed with 10% methanol in diethyl ether then with diethyl ether to give the title compound (1.0 g, 80%) as a beige solid.

LCMS (Method 5): [MH⁺] = 271.1 at 0.81 min.

**6-(4-Fluorophenyl)-8-methoxy-N-(1-(3-methyl-1,2,4-oxadiazol-5-
20 yl)ethyl)quinazolin-4-amine**

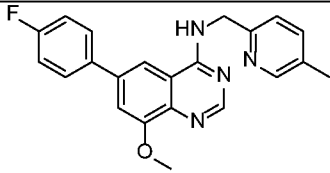
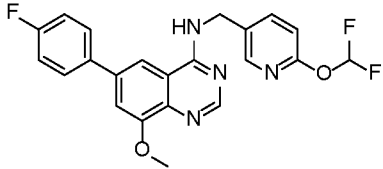
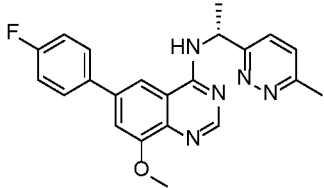
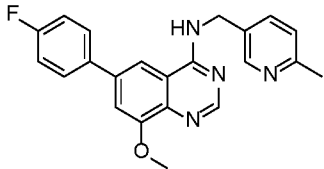


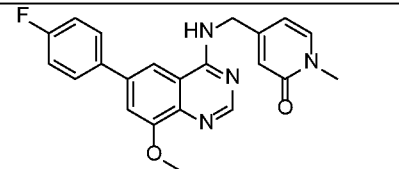
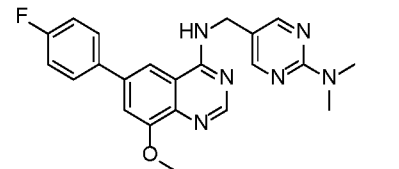
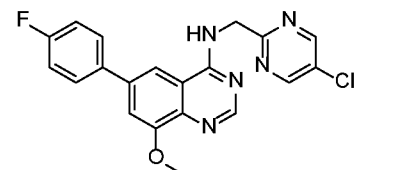
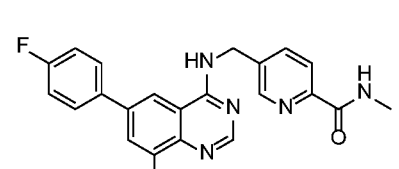
To a solution of 6-(4-fluorophenyl)-8-methoxyquinazolin-4-ol (Intermediate 3) (100 mg, 0.37 mmol) in *N,N*-dimethylformamide (2 mL) was successively added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (212 mg, 0.41 mmol) and di-*isopropylethylamine* (0.32 mL, 1.85 mmol). The resulting mixture was heated to 40 °C and stirred for 20 min, 1-(3-methyl-1,2,4-oxadiazol-5-yl)ethan-1-amine (67 mg, 0.41 mmol) was then added and the heating was maintained at 40 °C for 18 hours. After return to room temperature, the mixture was diluted with ethyl acetate (50 mL) and water (20 mL). The organic phase was washed with brine (2 × 20 mL), passed through a hydrophobic frit and the solvent was removed *in vacuo*. The residue was purified by preparative HPLC to give the title compound (43 mg, 31%) as a white solid.

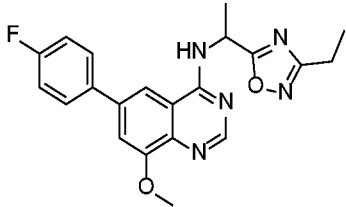
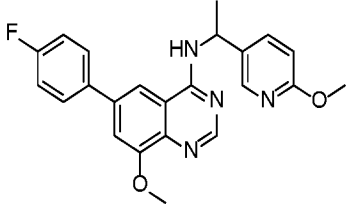
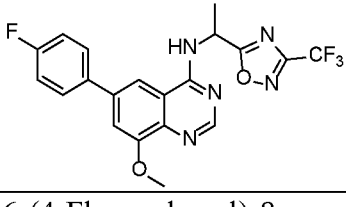
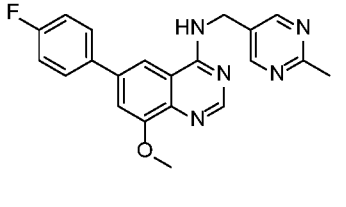
¹H NMR (400 MHz, DMSO): δ 8.85 (d, J = 6.8 Hz, 1 H), 8.49 (s, 1 H), 8.24 (s, 1 H), 7.99 (dd, J = 5.6, 8.6 Hz, 2 H), 7.61 (s, 1 H), 7.44 (dd, J = 8.8, 8.8 Hz, 2 H), 5.88-5.82 (m, 1 H), 4.08 (s, 3 H), 2.37 (s, 3 H), 1.78 (d, J = 7.1 Hz, 3 H). LCMS (Method 4): [MH⁺] = 375 at 3.29 min.

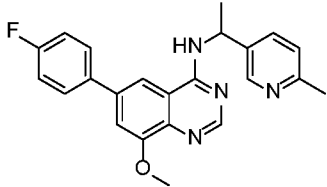
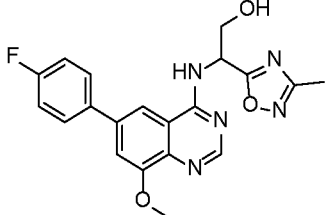
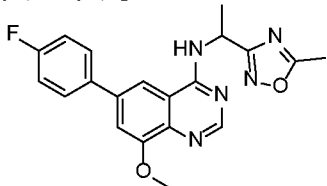
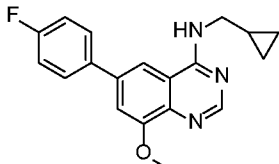
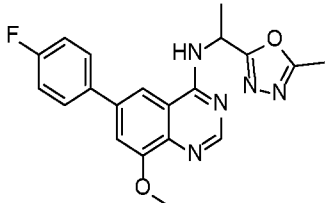
The compounds reported in the table below were synthesised following the same procedure described for the preparation of 6-(4-Fluorophenyl)-8-methoxy-*N*-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine.

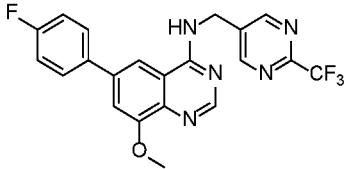
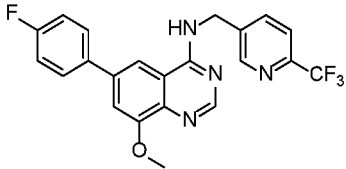
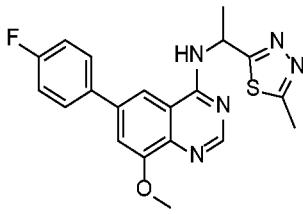
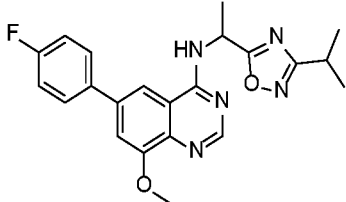
Example No.	Chemical Name Structure	Analytical Data ¹ H NMR LC-MS
Example 2	6-(4-Fluorophenyl)-8-methoxy- <i>N</i> -((5-methylpyridin-2-yl)methyl)quinazolin-4-amine	¹ H NMR (400 MHz, DMSO): δ 8.94 (dd, J = 5.9, 5.9 Hz, 1 H), 8.40 (s, 1 H), 8.37 (d, J = 1.8 Hz, 1 H), 8.20 (d, J = 1.8 Hz, 1 H), 7.97-7.92 (m, 2 H), 7.56-7.53 (m, 2 H), 7.39

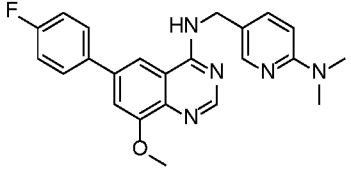
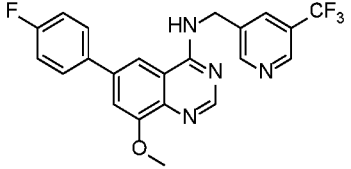
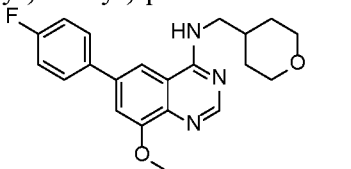
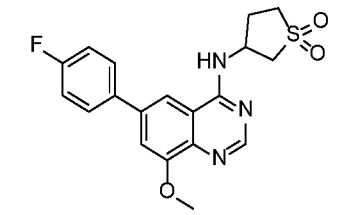
		(dd, J = 8.9, 8.9 Hz, 2 H), 7.26 (d, J = 8.0 Hz, 1 H), 4.85 (d, J = 5.9 Hz, 2 H), 4.02 (s, 3 H), 2.28 (s, 3 H). LCMS (Method 4): [MH ⁺] = 375 at 3.10 min.
Example 3	<p><i>N</i>-((6-(Difluoromethoxy)pyridin-3-yl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine</p> 	¹ H NMR (400 MHz, DMSO): δ 8.90 (dd, J = 5.4, 5.4 Hz, 1 H), 8.47 (s, 1 H), 8.33 (d, J = 2.0 Hz, 1 H), 8.11 (d, J = 1.6 Hz, 1 H), 7.97-7.90 (m, 3 H), 7.69 (t, J = 73.0 Hz, 1 H), 7.53 (d, J = 1.7 Hz, 1 H), 7.38 (dd, J = 8.9, 8.9 Hz, 2 H), 7.07 (d, J = 8.8 Hz, 1 H), 4.80 (d, J = 5.6 Hz, 2 H), 4.02 (s, 3 H). LCMS (Method 3): [MH ⁺] = 427 at 4.72 min.
Example 4	<p>(<i>R</i>)-6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-(1-(6-methylpyridazin-3-yl)ethyl)quinazolin-4-amine</p> 	¹ H NMR (400 MHz, DMSO): δ 9.18-9.18 (m, 1 H), 8.47 (s, 1 H), 8.36 (d, J = 1.4 Hz, 1 H), 8.00-7.95 (m, 2 H), 7.65 (d, J = 8.7 Hz, 2 H), 7.53 (d, J = 8.7 Hz, 1 H), 7.42 (dd, J = 8.8, 8.8 Hz, 2 H), 5.88-5.79 (m, 1 H), 4.06 (s, 3 H), 2.60 (s, 3 H), 1.74 (d, J = 7.2 Hz, 3 H). LCMS (Method 3): [MH ⁺] = 390 at 4.13 min.
Example 5	<p>6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-((6-methylpyridin-3-yl)methyl)quinazolin-4-amine</p> 	¹ H NMR (400 MHz, DMSO): δ 8.85 (dd, J = 5.7, 5.7 Hz, 1 H), 8.50 (d, J = 1.9 Hz, 1 H), 8.45 (s, 1 H), 8.12 (d, J = 1.6 Hz, 1 H), 7.92 (ddd, J = 3.1, 5.4, 12.1 Hz, 2 H), 7.68 (dd, J = 2.3, 8.0 Hz, 1 H), 7.52 (d, J = 1.6 Hz, 1 H), 7.38 (dd, J = 8.9, 8.9 Hz, 2 H), 7.21 (d, J = 7.9 Hz, 1 H), 4.77 (d, J = 5.5 Hz, 2 H), 2.44 (s, 3 H). LCMS (Method 4): [MH ⁺] = 375 at 2.40 min.
Example 6	<p>4-(((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)methyl)-1-methylpyridin-2(1H)-one</p>	¹ H NMR (400 MHz, DMSO): δ 9.03-8.96 (m, 1 H), 8.46 (s, 1 H), 8.18-8.14 (m, 1 H), 7.95 (ddd, J = 3.2, 5.3, 12.1 Hz, 2 H), 7.63 (d, J = 6.9 Hz, 1 H), 7.58 (d, J = 1.4 Hz, 1 H), 7.40 (dd, J = 8.9, 8.9 Hz, 2 H), 6.27 (s, 1 H), 6.23 (dd, J = 1.9, 7.0 Hz, 1 H), 4.64 (d, J = 5.6 Hz, 2 H), 4.04 (s, 3 H), 3.38 (s, 3 H).

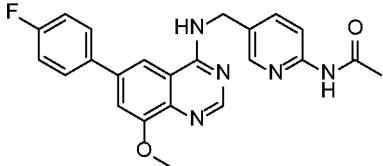
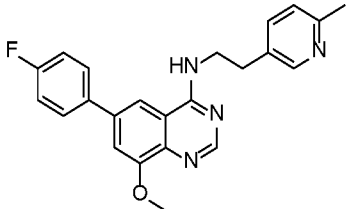
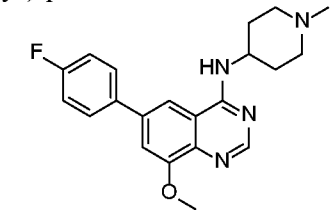
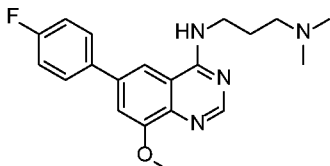
		LCMS (Method 4): [MH ⁺] = 391 at 2.97 min.
Example 7	<i>N</i> -((2-(Dimethylamino)pyrimidin-5-yl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.71 (dd, J = 5.1, 5.1 Hz, 1 H), 8.42 (s, 1 H), 8.36 (s, 2 H), 7.99 (d, J = 1.6 Hz, 1 H), 7.83 (ddd, J = 3.2, 5.3, 12.1 Hz, 2 H), 7.44 (d, J = 1.5 Hz, 1 H), 7.29 (dd, J = 8.9, 8.9 Hz, 2 H), 4.51 (d, J = 5.4 Hz, 2 H), 3.94 (s, 3 H), 3.02 (s, 6 H). LCMS (Method 4): [MH ⁺] = 405 at 3.24 min.
Example 8	<i>N</i> -((5-Chloropyrimidin-2-yl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 9.14-9.06 (m, 1 H), 8.89 (s, 2 H), 8.35 (s, 1 H), 8.21 (d, J = 1.6 Hz, 1 H), 7.97-7.93 (m, 2 H), 7.56 (d, J = 1.5 Hz, 1 H), 7.40 (dd, J = 8.8, 8.8 Hz, 2 H), 4.98 (d, J = 5.9 Hz, 2 H), 4.03 (s, 3 H). LCMS (Method 4): [MH ⁺] = 396 at 3.30 min.
Example 9	5-(((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)methyl)- <i>N</i> -methylpicolinamide 	¹ H NMR (400 MHz, DMSO): δ 9.18-9.11 (m, 1 H), 8.74-8.69 (m, 2 H), 8.49 (s, 1 H), 8.17-8.15 (m, 2 H), 8.01-7.91 (m, 4 H), 7.58 (d, J = 1.3 Hz, 1 H), 7.39 (dd, J = 8.8, 8.8 Hz, 2 H), 4.92 (d, J = 5.5 Hz, 2 H), 4.04 (s, 3 H), 2.82 (d, J = 4.9 Hz, 3 H). LCMS (Method 4): [MH ⁺] = 418 at 3.19 min.
Example 10	<i>N</i> -(1-(3-Ethyl-1,2,4-oxadiazol-5-yl)ethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine	¹ H NMR (400 MHz, DMSO): δ 8.85 (d, J = 6.8 Hz, 1 H), 8.46 (s, 1 H), 8.21 (d, J = 1.6 Hz, 1 H), 7.95 (ddd, J = 3.2, 5.3, 12.1 Hz, 2 H), 7.58 (d, J = 1.5 Hz, 1 H), 7.40 (dd, J = 8.9, 8.9 Hz, 2 H), 5.86-5.81 (m, 1 H), 4.04 (s, 3 H), 2.71 (q, J = 7.6 Hz, 2 H), 1.74 (d, J = 7.2 Hz, 3 H), 1.22 (dd, J = 7.5, 7.5 Hz, 3 H).

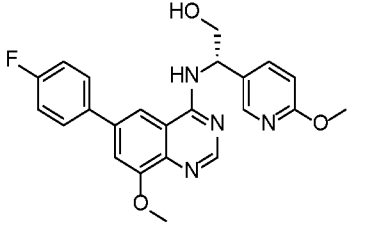
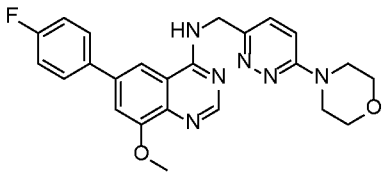
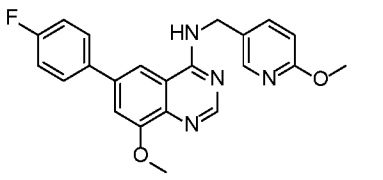
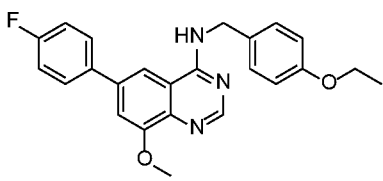
		LCMS (Method 4): [MH ⁺] = 394 at 3.49 min.
Example 11	<p>6-(4-Fluorophenyl)-8-methoxy-N-(1-(6-methoxypyridin-3-yl)ethyl)quinazolin-4-amine</p> 	¹ H NMR (400 MHz, DMSO): δ 8.45 (d, J = 7.7 Hz, 1 H), 8.42 (s, 1 H), 8.26 (d, J = 2.5 Hz, 1 H), 8.20 (d, J = 1.6 Hz, 1 H), 7.93 (ddd, J = 3.2, 5.5, 12.1 Hz, 2 H), 7.80 (dd, J = 2.5, 8.7 Hz, 1 H), 7.51 (d, J = 1.5 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 6.80 (d, J = 8.9 Hz, 1 H), 5.63-5.58 (m, 1 H), 4.01 (s, 3 H), 3.82 (s, 3 H), 1.63 (d, J = 7.0 Hz, 3 H). LCMS (Method 4): [MH ⁺] = 405 at 3.55 min.
Example 12	<p>6-(4-Fluorophenyl)-8-methoxy-N-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine</p> 	¹ H NMR (400 MHz, DMSO): δ 8.91 (d, J = 6.8 Hz, 1 H), 8.44 (s, 1 H), 8.17 (d, J = 1.6 Hz, 1 H), 7.97-7.92 (m, 2 H), 7.58 (d, J = 1.5 Hz, 1 H), 7.40 (dd, J = 8.8, 8.8 Hz, 2 H), 5.94-5.89 (m, 1 H), 4.04 (s, 3 H), 1.81 (d, J = 7.2 Hz, 3 H). LCMS (Method 4): [MH ⁺] = 434 at 3.90 min.
Example 13	<p>6-(4-Fluorophenyl)-8-methoxy-N-((2-methylpyrimidin-5-yl)methyl)quinazolin-4-amine</p> 	¹ H NMR (400 MHz, DMSO): δ 8.97 (dd, J = 5.8, 5.8 Hz, 1 H), 8.59 (s, 2 H), 8.34 (s, 1 H), 8.21 (d, J = 1.5 Hz, 1 H), 7.98-7.93 (m, 2 H), 7.54 (d, J = 1.3 Hz, 1 H), 7.39 (dd, J = 8.8, 8.8 Hz, 2 H), 4.93 (d, J = 5.6 Hz, 2 H), 4.03 (s, 3 H), 2.25 (s, 3 H). LCMS (Method 4): [MH ⁺] = 376 at 3.08 min.
Example 14	<p>6-(4-Fluorophenyl)-8-methoxy-N-(1-(6-methylpyridin-3-yl)ethyl)quinazolin-4-amine</p>	¹ H NMR (400 MHz, DMSO): δ 8.61-8.54 (m, 2 H), 8.42 (s, 1 H), 8.24 (d, J = 1.5 Hz, 1 H), 7.97-7.92 (m, 2 H), 7.74 (dd, J = 2.3, 8.1 Hz, 1 H), 7.53 (d, J = 1.5 Hz, 1 H), 7.40 (dd, J = 8.8, 8.8 Hz, 2 H), 7.21 (d, J

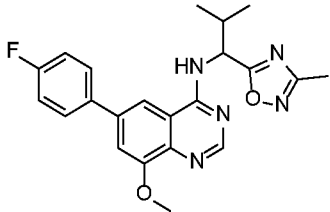
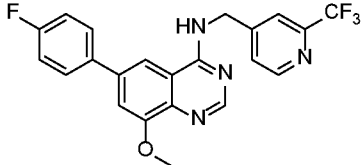
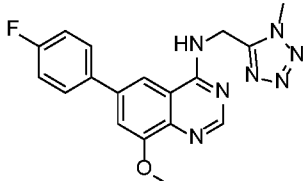
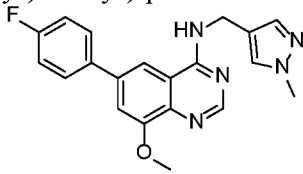
		<p>= 8.0 Hz, 1 H), 5.66-5.57 (m, 1 H), 4.02 (s, 3 H), 2.43 (s, 3 H), 1.64 (d, J = 7.0 Hz, 3 H). LCMS (Method 4): [MH⁺] = 389 at 2.65 min.</p>
Example 15	<p>2-((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)-2-(3-methyl-1,2,4-oxadiazol-5-yl)ethan-1-ol</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.92-8.92 (m, 1 H), 8.50 (s, 1 H), 8.28 (d, J = 1.4 Hz, 1 H), 7.99-7.94 (m, 2 H), 7.61 (d, J = 1.1 Hz, 1 H), 7.41 (dd, J = 8.9, 8.9 Hz, 2 H), 5.80 (q, J = 6.7 Hz, 1 H), 5.41 (s, 1 H), 4.05 (s, 6 H), 2.34 (s, 3 H). LCMS (Method 4): [MH⁺] = 396 at 2.96 min.</p>
Example 16	<p>6-(4-Fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.65 (d, J = 7.7 Hz, 1 H), 8.45 (s, 1 H), 8.23 (d, J = 1.6 Hz, 1 H), 7.97-7.93 (m, 2 H), 7.55 (d, J = 1.5 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 5.79-5.74 (m, 1 H), 4.03 (s, 3 H), 1.68 (d, J = 7.2 Hz, 3 H). LCMS (Method 4): [MH⁺] = 380 at 3.32 min.</p>
Example 17	<p>N-(Cyclopropylmethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.43 (s, 2 H), 8.11 (d, J = 1.6 Hz, 1 H), 7.95-7.90 (m, 2 H), 7.50 (d, J = 1.5 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 4.01 (s, 3 H), 3.44 (dd, J = 6.1, 6.1 Hz, 2 H), 1.27-1.18 (m, 1 H), 0.53-0.47 (m, 2 H), 0.34-0.29 (m, 2 H). LCMS (Method 4): [MH⁺] = 324 at 3.57 min.</p>
Example 18	<p>6-(4-Fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.33-9.33 (m, 1 H), 8.61 (s, 1 H), 8.24 (s, 1 H), 7.95 (ddd, J = 3.2, 5.3, 12.1 Hz, 2 H), 7.69 (s, 1 H), 7.41 (dd, J = 8.8, 8.8 Hz, 2 H), 5.99-5.91 (m, 1 H), 4.09 (s, 3 H), 1.75 (d, J = 7.0 Hz, 3 H). LCMS (Method 4): [MH⁺] = 380 at 3.08 min.</p>
Example 19	<p>6-(4-Fluorophenyl)-8-methoxy-N-((2-</p>	<p>¹H NMR (400 MHz, DMSO): δ 9.12 (s, 2 H), 8.96 (dd, J = 5.6, 5.6</p>

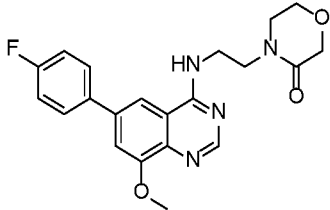
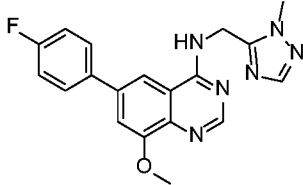
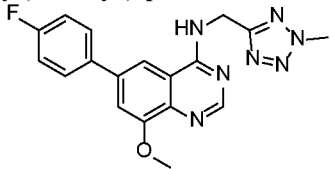
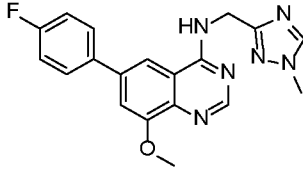
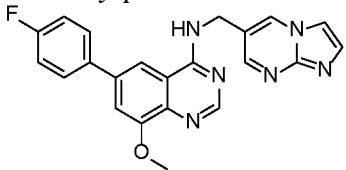
	(trifluoromethyl)pyrimidin-5-yl)methyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.47 (s, 1 H), 8.10 (d, J = 1.6 Hz, 1 H), 7.92 (ddd, J = 3.2, 5.3, 12.1 Hz, 2 H), 7.54 (d, J = 1.6 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 4.91 (d, J = 5.4 Hz, 2 H), 4.03 (s, 3 H). LCMS (Method 4): [MH ⁺] = 430 at 4.71 min.
Example 20	6-(4-Fluorophenyl)-8-methoxy- <i>N</i> -((6-(trifluoromethyl)pyridin-3-yl)methyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.97 (dd, J = 5.8, 5.8 Hz, 1 H), 8.84 (d, J = 1.5 Hz, 1 H), 8.45 (s, 1 H), 8.13 (d, J = 1.8 Hz, 1 H), 8.06 (dd, J = 1.5, 8.0 Hz, 1 H), 7.95-7.87 (m, 3 H), 7.54 (d, J = 1.6 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 4.92 (d, J = 5.5 Hz, 2 H), 4.03 (s, 3 H). LCMS (Method 3): [MH ⁺] = 429 at 4.62 min.
Example 21	6-(4-Fluorophenyl)-8-methoxy- <i>N</i> -(1-(5-methyl-1,3,4-thiadiazol-2-yl)ethyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.81 (d, J = 7.7 Hz, 1 H), 8.50 (s, 1 H), 8.20 (d, J = 1.6 Hz, 1 H), 7.94 (ddd, J = 3.2, 5.4, 12.1 Hz, 2 H), 7.56 (d, J = 1.6 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 5.99-5.95 (m, 1 H), 4.03 (s, 3 H), 2.66 (s, 3 H), 1.81 (d, J = 7.2 Hz, 3 H). LCMS (Method 4): [MH ⁺] = 396 at 3.13 min.
Example 22	6-(4-Fluorophenyl)- <i>N</i> -(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)ethyl)-8-methoxyquinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.81 (d, J = 7.3 Hz, 1 H), 8.45 (s, 1 H), 8.20 (d, J = 1.8 Hz, 1 H), 7.97-7.93 (m, 2 H), 7.57 (d, J = 1.6 Hz, 1 H), 7.40 (dd, J = 8.8, 8.8 Hz, 2 H), 5.86-5.81 (m, 1 H), 4.04 (s, 3 H), 3.09-3.01 (m, 1 H), 1.74 (d, J = 7.2 Hz, 3 H), 1.25 (dd, J = 1.4, 6.9 Hz, 6 H). LCMS (Method 4): [MH ⁺] = 408 at 3.67 min.

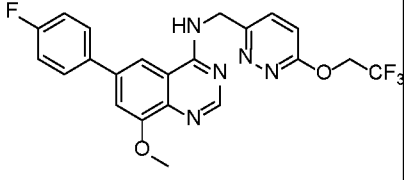
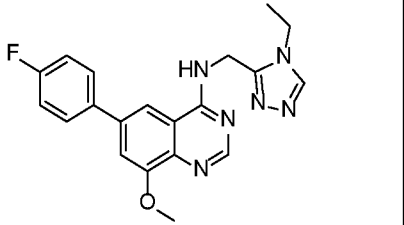
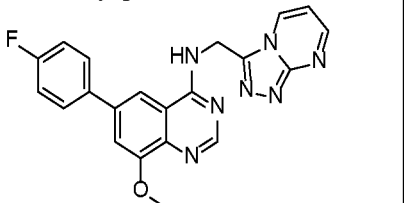
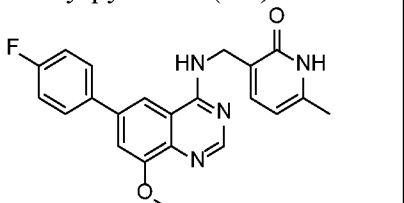
<p>Example 23</p>	<p><i>N</i>-((6-(Dimethylamino)pyridin-3-yl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.70 (dd, J = 5.6, 5.6 Hz, 1 H), 8.46 (s, 1 H), 8.16 (d, J = 2.0 Hz, 1 H), 8.10 (d, J = 1.8 Hz, 1 H), 7.94-7.89 (m, 2 H), 7.57 (dd, J = 2.4, 8.7 Hz, 1 H), 7.50 (d, J = 1.5 Hz, 1 H), 7.37 (dd, J = 8.9, 8.9 Hz, 2 H), 6.62 (d, J = 8.4 Hz, 1 H), 4.64 (d, J = 5.5 Hz, 2 H), 4.01 (s, 3 H), 2.99 (s, 6 H). LCMS (Method 4): [MH⁺] = 404 at 2.41 min.</p>
<p>Example 24</p>	<p>6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-[[5-(trifluoromethyl)-3-pyridyl]methyl]quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.94 (dd, J = 2.2, 2.2 Hz, 2 H), 8.89 (d, J = 1.1 Hz, 1 H), 8.46 (s, 1 H), 8.21 (dd, J = 2.2, 2.2 Hz, 1 H), 8.11 (d, J = 1.6 Hz, 1 H), 7.95-7.90 (m, 2 H), 7.54 (d, J = 1.5 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 4.92 (d, J = 5.6 Hz, 2 H), 4.02 (s, 3 H). LCMS (Method 4): [MH⁺] = 429 at 3.55 min.</p>
<p>Example 25</p>	<p>6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-((tetrahydro-2<i>H</i>-pyran-4-yl)methyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.46 (s, 2 H), 8.12 (d, J = 1.6 Hz, 1 H), 7.94-7.90 (m, 2 H), 7.52 (d, J = 1.4 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 4.02 (s, 3 H), 3.87 (dd, J = 2.5, 11.4 Hz, 2 H), 3.48 (dd, J = 6.3, 6.3 Hz, 2 H), 3.28 (dt, J = 2.0, 11.8 Hz, 2 H), 2.05-1.96 (m, 1 H), 1.67 (dd, J = 1.8, 12.7 Hz, 2 H), 1.34-1.22 (m, 2 H). LCMS (Method 3): [MH⁺] = 368 at 4.04 min.</p>
<p>Example 26</p>	<p>3-((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)tetrahydrothiophene 1,1-dioxide</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.53 (s, 1 H), 8.38 (d, J = 6.5 Hz, 1 H), 8.09 (d, J = 1.6 Hz, 1 H), 7.94-7.89 (m, 2 H), 7.54 (d, J = 1.6 Hz, 1 H), 7.40 (dd, J = 8.9, 8.9 Hz, 2 H), 5.10 (dd, J = 6.7, 15.6 Hz, 1 H), 4.03 (s, 3 H), 3.69 (dd, J = 8.2, 13.4 Hz, 1 H), 3.50-3.38 (m, 1 H), 3.31-3.23 (m, 1 H), 3.15 (dd, J = 8.1, 13.2 Hz, 1 H), 2.65-2.55 (m, 1 H), 2.41-2.30 (m, 1 H). LCMS (Method 3): [MH⁺] = 388 at 3.77 min.</p>

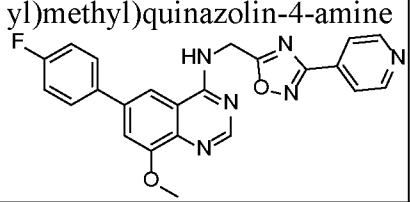
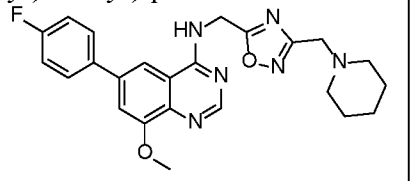
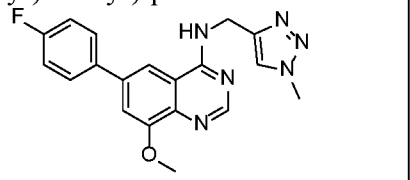
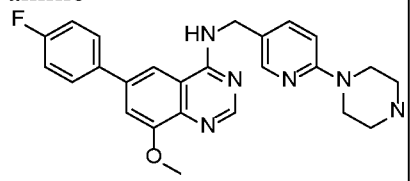
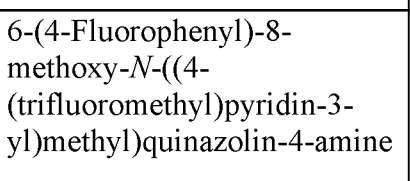
<p>Example 27</p>	<p><i>N</i>-(5-(((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)methyl)pyridin-2-yl)acetamide</p> 	<p>¹H NMR (400 MHz, DMSO): δ 10.47 (s, 1 H), 8.82 (dd, J = 5.7, 5.7 Hz, 1 H), 8.46 (s, 1 H), 8.35 (d, J = 1.9 Hz, 1 H), 8.12 (d, J = 1.5 Hz, 1 H), 8.04 (d, J = 8.5 Hz, 1 H), 7.94-7.90 (m, 2 H), 7.80 (dd, J = 2.3, 8.6 Hz, 1 H), 7.52 (d, J = 1.4 Hz, 1 H), 7.38 (dd, J = 8.9, 8.9 Hz, 2 H), 4.76 (d, J = 5.5 Hz, 2 H), 4.02 (s, 3 H), 2.08 (s, 3 H). LCMS (Method 3): [MH⁺] = 418 at 3.76 min.</p>
<p>Example 28</p>	<p>6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-(2-(6-methylpyridin-3-yl)ethyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.47 (s, 1 H), 8.43 (dd, J = 5.5, 5.5 Hz, 1 H), 8.34 (d, J = 1.9 Hz, 1 H), 8.04 (d, J = 1.6 Hz, 1 H), 7.92-7.88 (m, 2 H), 7.57 (dd, J = 2.3, 7.8 Hz, 1 H), 7.51 (d, J = 1.5 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 7.18 (d, J = 7.8 Hz, 1 H), 4.02 (s, 3 H), 3.82-3.75 (m, 2 H), 2.97 (dd, J = 7.1, 7.1 Hz, 2 H), 2.42 (s, 3 H). LCMS (Method 4): [MH⁺] = 389 at 2.40 min.</p>
<p>Example 29</p>	<p>6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-(1-methylpiperidin-4-yl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.43 (s, 1 H), 8.12 (d, J = 1.6 Hz, 1 H), 7.98-7.90 (m, 3 H), 7.49 (d, J = 1.5 Hz, 1 H), 7.38 (dd, J = 8.9, 8.9 Hz, 2 H), 4.22-4.13 (m, 1 H), 4.01 (s, 3 H), 2.85 (dd, J = 2.8, 8.8 Hz, 2 H), 2.21 (s, 3 H), 2.03-1.89 (m, 4 H), 1.74-1.62 (m, 2 H). LCMS (Method 4): [MH⁺] = 367 at 2.20 min.</p>
<p>Example 30</p>	<p><i>N</i>¹-(6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)-<i>N</i>³,<i>N</i>³-dimethylpropane-1,3-diamine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.43 (s, 1 H), 8.37 (dd, J = 5.4, 5.4 Hz, 1 H), 8.03 (d, J = 1.6 Hz, 1 H), 7.93-7.89 (m, 2 H), 7.49 (d, J = 1.6 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 4.01 (s, 3 H), 3.57 (dd, J = 6.6, 13.1 Hz, 2 H), 2.33 (dd, J = 7.0, 7.0 Hz, 2 H), 2.17 (s, 6 H), 1.85-1.76 (m, 2 H). LCMS (Method 4): [MH⁺] = 355 at 2.19 min.</p>

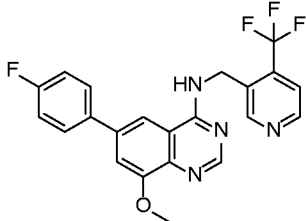
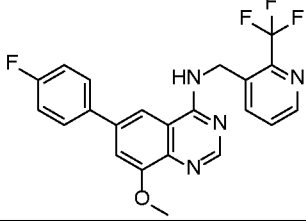
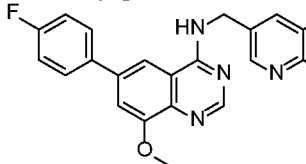
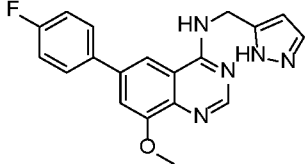
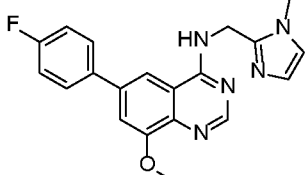
<p>Example 31</p>	<p>(<i>S</i>)-2-((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)-2-(6-methoxypyridin-3-yl)ethan-1-ol</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.50 (d, J = 7.5 Hz, 1 H), 8.43 (s, 1 H), 8.25 (dd, J = 1.9, 9.0 Hz, 2 H), 7.97-7.93 (m, 2 H), 7.81 (dd, J = 2.5, 8.7 Hz, 1 H), 7.53 (d, J = 1.4 Hz, 1 H), 7.41 (dd, J = 8.8, 8.8 Hz, 2 H), 6.80 (d, J = 8.5 Hz, 1 H), 5.57-5.49 (m, 1 H), 5.11 (dd, J = 5.5, 5.5 Hz, 1 H), 4.02 (s, 3 H), 3.93-3.87 (m, 1 H), 3.82 (s, 3 H), 3.81-3.75 (m, 1 H). LCMS (Method 3): [MH⁺] = 421 at 4.15 min.</p>
<p>Example 32</p>	<p>6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-((6-morpholinopyridazin-3-yl)methyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.95-8.94 (m, 1 H), 8.38 (s, 1 H), 8.10-8.06 (m, 2 H), 7.88-7.83 (m, 2 H), 7.47 (d, J = 1.4 Hz, 1 H), 7.37 (d, J = 9.4 Hz, 1 H), 7.30 (dd, J = 8.9, 8.9 Hz, 2 H), 7.17 (d, J = 9.4 Hz, 1 H), 4.85 (d, J = 5.6 Hz, 2 H), 3.95 (s, 3 H), 3.66-3.63 (m, 4 H), 3.45-3.42 (m, 4 H). LCMS (Method 3): [MH⁺] = 447 at 4.05 min.</p>
<p>Example 33</p>	<p>6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-((6-methoxypyridin-3-yl)methyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.83 (dd, J = 5.4, 5.4 Hz, 1 H), 8.50 (s, 1 H), 8.27 (d, J = 1.5 Hz, 1 H), 8.14 (s, 1 H), 7.95 (dd, J = 5.3, 8.6 Hz, 2 H), 7.79 (dd, J = 2.1, 8.5 Hz, 1 H), 7.55 (s, 1 H), 7.41 (dd, J = 8.8, 8.8 Hz, 2 H), 6.84 (d, J = 8.6 Hz, 1 H), 4.77 (d, J = 5.6 Hz, 2 H), 4.06 (s, 3 H), 3.87 (s, 3 H). LCMS (Method 4): [MH⁺] = 398 at 3.38 min.</p>
<p>Example 34</p>	<p><i>N</i>-(4-ethoxybenzyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.80 (dd, J = 5.9, 5.9 Hz, 1 H), 8.44 (s, 1 H), 8.22 (s, 1 H), 8.14 (d, J = 1.6 Hz, 1 H), 7.92 (ddd, J = 3.2, 5.4, 12.1 Hz, 2 H), 7.52 (d, J = 1.5 Hz, 1 H), 7.37 (dd, J = 8.8, 8.8 Hz, 2 H), 7.31 (d, J = 8.8 Hz, 2 H), 6.88 (d, J = 8.7 Hz, 2 H), 4.74 (d, J = 5.6 Hz, 2 H), 4.02-3.98 (m, 6 H), 1.31 (dd, J = 7.0, 7.0 Hz, 3 H). LCMS (Method 3): [MH⁺] = 404 at 5.1 min.</p>

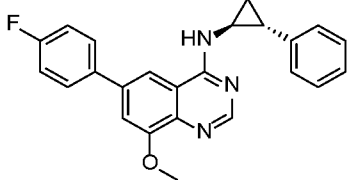
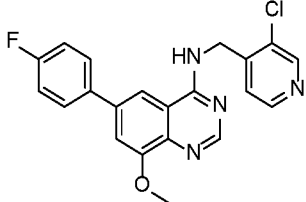
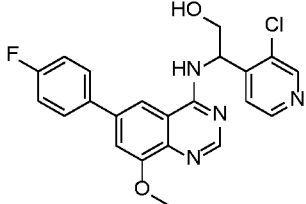
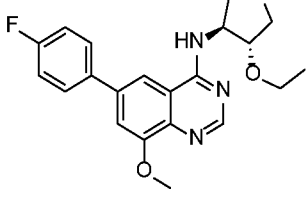
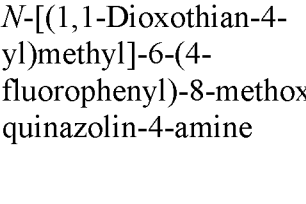
<p>Example 35</p>	<p>6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-(2-methyl-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.68 (d, J = 7.9 Hz, 1 H), 8.44 (s, 1 H), 8.31 (d, J = 1.6 Hz, 1 H), 7.99-7.94 (m, 2 H), 7.56 (d, J = 1.5 Hz, 1 H), 7.41 (dd, J = 8.9, 8.9 Hz, 2 H), 5.53 (dd, J = 8.5, 8.5 Hz, 1 H), 4.02 (s, 3 H), 2.34 (s, 3 H), 1.13 (d, J = 6.7 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 3 H). LCMS (Method 3): [MH⁺] = 408 at 4.74 min.</p>
<p>Example 36</p>	<p>6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-[[2-(trifluoromethyl)-4-pyridyl]methyl]quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.00 (dd, J = 5.8, 5.8 Hz, 1 H), 8.70 (d, J = 5.0 Hz, 1 H), 8.42 (s, 1 H), 8.16 (d, J = 1.6 Hz, 1 H), 7.97-7.90 (m, 3 H), 7.69 (d, J = 5.0 Hz, 1 H), 7.56 (d, J = 1.5 Hz, 1 H), 7.40 (dd, J = 8.9, 8.9 Hz, 2 H), 4.94 (d, J = 5.8 Hz, 2 H), 4.03 (s, 3 H). LCMS (Method 4): [MH⁺] = 429 at 3.57 min.</p>
<p>Example 38</p>	<p>6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-((1-methyl-1<i>H</i>-tetrazol-5-yl)methyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.17-9.16 (m, 1 H), 8.49 (s, 1 H), 8.15 (d, J = 1.6 Hz, 1 H), 7.96-7.91 (m, 2 H), 7.58 (d, J = 1.3 Hz, 1 H), 7.40 (dd, J = 8.9, 8.9 Hz, 2 H), 5.05 (d, J = 5.4 Hz, 2 H), 4.19 (s, 3 H), 4.04 (s, 3 H). LCMS (Method 4): [MH⁺] = 366 at 2.86 min.</p>
<p>Example 39</p>	<p>6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-((1-methyl-1<i>H</i>-pyrazol-4-yl)methyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.61 (dd, J = 5.5, 5.5 Hz, 1 H), 8.48 (s, 1 H), 8.10 (d, J = 1.8 Hz, 1 H), 7.94-7.89 (m, 2 H), 7.68 (s, 1 H), 7.50 (d, J = 1.6 Hz, 1 H), 7.44 (s, 1 H), 7.37 (dd, J = 8.9, 8.9 Hz, 2 H), 4.60 (d, J = 5.5 Hz, 2 H), 4.01 (s, 3 H), 3.38-3.34 (m, 3 H). LCMS (Method 4): [MH⁺] = 364 at 3.02 min.</p>
<p>Example 41</p>	<p>4-(2-((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)ethyl)morpholin-3-one</p>	<p>¹H NMR (400 MHz, DMSO): δ 8.46 (s, 1 H), 8.03 (d, J = 1.6 Hz, 1 H), 7.91 (ddd, J = 3.2, 5.3, 12.1 Hz, 2 H), 7.51 (d, J = 1.5 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 4.01 (d, J</p>

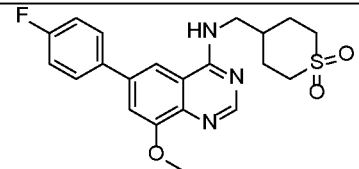
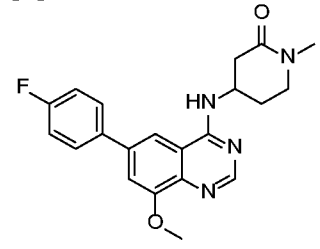
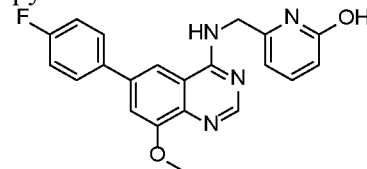
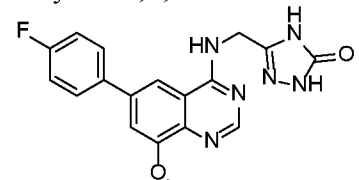
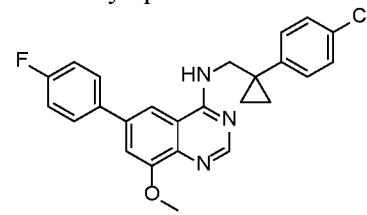
		= 7.5 Hz, 2 H), 3.81-3.72 (m, 4 H), 3.62 (dd, J = 6.2, 6.2 Hz, 2 H), 3.42 (dd, J = 5.1, 5.1 Hz, 2 H). LCMS (Method 4): [MH ⁺] = 397 at 2.87 min.
Example 42	<p>6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-((1-methyl-1<i>H</i>-1,2,4-triazol-5-yl)methyl)quinazolin-4-amine</p> 	¹ H NMR (400 MHz, DMSO): δ 9.23-9.23 (m, 1 H), 8.53 (s, 1 H), 8.19 (d, J = 1.6 Hz, 1 H), 7.96-7.91 (m, 2 H), 7.85 (s, 1 H), 7.60 (d, J = 1.3 Hz, 1 H), 7.40 (dd, J = 8.9, 8.9 Hz, 2 H), 4.93 (d, J = 5.4 Hz, 2 H), 4.05 (s, 3 H), 3.98 (s, 3 H). LCMS (Method 3): [MH ⁺] = 365 at 3.77 min.
Example 43	<p>6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-((2-methyl-2<i>H</i>-tetrazol-5-yl)methyl)quinazolin-4-amine</p> 	¹ H NMR (400 MHz, DMSO): δ 8.99 (dd, J = 5.6, 5.6 Hz, 1 H), 8.44 (s, 1 H), 8.17-8.15 (m, 2 H), 7.96-7.91 (m, 2 H), 7.55 (d, J = 1.5 Hz, 1 H), 7.39 (dd, J = 8.8, 8.8 Hz, 2 H), 5.03 (d, J = 5.6 Hz, 2 H), 4.33 (s, 3 H), 4.03 (s, 3 H). LCMS (Method 4): [MH ⁺] = 366 at 4.01 min.
Example 44	<p>6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-((1-methyl-1<i>H</i>-1,2,4-triazol-3-yl)methyl)quinazolin-4-amine</p> 	¹ H NMR (400 MHz, DMSO): δ 8.81 (dd, J = 5.6, 5.6 Hz, 1 H), 8.43 (s, 1 H), 8.38 (s, 1 H), 8.18 (d, J = 1.6 Hz, 1 H), 7.94 (ddd, J = 3.2, 5.4, 12.1 Hz, 2 H), 7.53 (d, J = 1.5 Hz, 1 H), 7.38 (dd, J = 8.9, 8.9 Hz, 2 H), 4.81 (d, J = 5.8 Hz, 2 H), 4.02 (s, 3 H), 3.82 (s, 3 H). LCMS (Method 3): [MH ⁺] = 365 at 3.65 min.
Example 45	<p>6-(4-Fluorophenyl)-<i>N</i>-(imidazo[1,2-<i>a</i>]pyrimidin-6-ylmethyl)-8-methoxyquinazolin-4-amine</p> 	¹ H NMR (400 MHz, DMSO): δ 9.02 (d, J = 2.0 Hz, 1 H), 8.90 (dd, J = 5.1, 5.1 Hz, 1 H), 8.70 (d, J = 2.3 Hz, 1 H), 8.53 (s, 1 H), 8.14 (s, 1 H), 7.99-7.92 (m, 3 H), 7.75 (d, J = 1.0 Hz, 1 H), 7.57 (s, 1 H), 7.42 (dd, J = 8.8, 8.8 Hz, 2 H), 4.89 (d, J = 5.1 Hz, 2 H), 4.06 (s, 3 H). LCMS (Method 4): [MH ⁺] = 401 at 3.51 min.

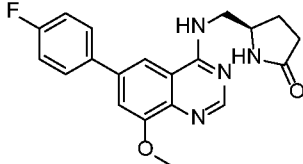
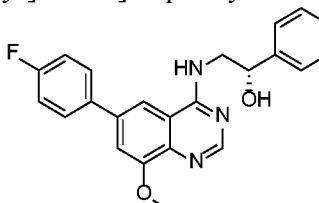
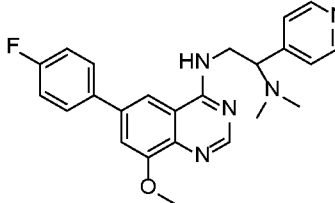
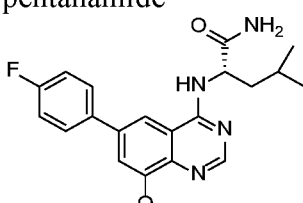
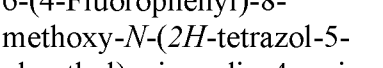
<p>Example 46</p>	<p>6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-((6-(2,2,2-trifluoroethoxy)pyridazin-3-yl)methyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.06 (dd, J = 5.6, 5.6 Hz, 1 H), 8.47 (s, 1 H), 8.20 (s, 1 H), 7.97 (dd, J = 5.3, 8.6 Hz, 2 H), 7.78 (d, J = 9.1 Hz, 1 H), 7.58 (s, 1 H), 7.42 (dd, J = 8.7, 8.7 Hz, 3 H), 5.22 (q, J = 8.9 Hz, 2 H), 5.05 (d, J = 5.6 Hz, 2 H), 4.07 (s, 3 H). LCMS (Method 4): [MH⁺] = 460 at 3.66 min.</p>
<p>Example 47</p>	<p><i>N</i>-((4-Ethyl-4<i>H</i>-1,2,4-triazol-3-yl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.90 (dd, J = 4.7, 4.7 Hz, 1 H), 8.58 (s, 1 H), 8.53 (s, 1 H), 8.21 (d, J = 7.3 Hz, 1 H), 7.96 (dd, J = 5.4, 8.7 Hz, 2 H), 7.58 (s, 1 H), 7.41 (dd, J = 8.7, 8.7 Hz, 2 H), 5.00 (d, J = 5.1 Hz, 2 H), 4.15 (q, J = 7.2 Hz, 2 H), 4.06 (s, 3 H), 1.34 (dd, J = 7.2, 7.2 Hz, 3 H). LCMS (Method 3): [MH⁺] = 379 at 3.42 min.</p>
<p>Example 48</p>	<p><i>N</i>-([1,2,4]Triazolo[4,3-α]pyrimidin-3-ylmethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.40 (dd, J = 1.5, 6.6 Hz, 1 H), 9.07 (dd, J = 5.3, 5.3 Hz, 1 H), 8.91-8.88 (m, 1 H), 8.46 (s, 1 H), 8.26 (s, 1 H), 7.99 (dd, J = 5.7, 8.5 Hz, 2 H), 7.59 (s, 1 H), 7.46-7.36 (m, 3 H), 5.11 (d, J = 5.3 Hz, 2 H), 4.07 (s, 3 H). LCMS (Method 3): [MH⁺] = 402 at 3.46 min.</p>
<p>Example 49</p>	<p>3-(((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)methyl)-6-methylpyridin-2(1<i>H</i>)-one</p> 	<p>¹H NMR (400 MHz, DMSO): δ 11.71-11.68 (m, 1 H), 8.66 (dd, J = 5.4, 5.4 Hz, 1 H), 8.45 (s, 1 H), 8.21 (s, 1 H), 7.98 (dd, J = 5.4, 8.7 Hz, 2 H), 7.56 (s, 1 H), 7.42 (dd, J = 8.8, 8.8 Hz, 2 H), 7.25 (d, J = 6.8 Hz, 1 H), 5.98 (d, J = 7.1 Hz, 1 H), 4.55 (d, J = 5.1 Hz, 2 H), 4.06 (s, 3 H), 2.20 (s, 3 H). LCMS (Method 3): [MH⁺] = 391 at 3.88 min.</p>
<p>Example 50</p>	<p>6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-((3-(pyridin-4-yl)-1,2,4-oxadiazol-5-</p>	<p>¹H NMR (400 MHz, DMSO): δ 9.28 (dd, J = 4.9, 4.9 Hz, 1 H), 8.83 (d, J = 5.8 Hz, 2 H), 8.48 (s, 1 H), 8.22 (s, 1 H), 8.20 (s, 1 H), 8.03-7.95 (m, 4 H), 7.62 (s, 1 H), 7.45 (dd, J = 8.8, 8.8 Hz, 2 H), 5.19 (d, J</p>

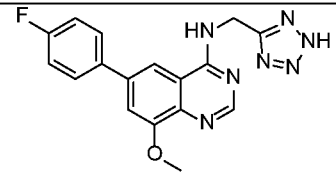
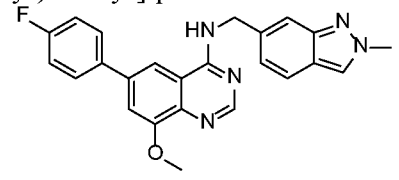
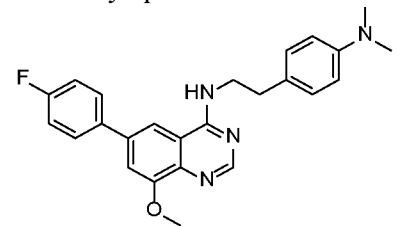
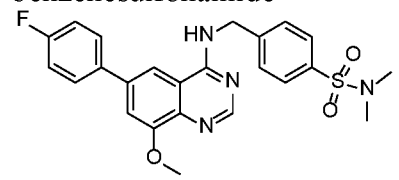
	<p>yl)methyl)quinazolin-4-amine</p> 	<p>= 5.1 Hz, 2 H), 4.08 (s, 3 H). LCMS (Method 3): [MH⁺] = 429 at 4.31 min.</p>
Example 51	<p>6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-((3-(piperidin-1-ylmethyl)-1,2,4-oxadiazol-5-yl)methyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.16 (dd, J = 5.4, 5.4 Hz, 1 H), 8.46 (s, 1 H), 8.19 (s, 1 H), 7.98 (dd, J = 5.6, 8.6 Hz, 2 H), 7.61 (s, 1 H), 7.44 (dd, J = 8.7, 8.7 Hz, 2 H), 5.07 (d, J = 5.6 Hz, 2 H), 4.07 (s, 3 H), 3.60 (s, 2 H), 2.42 (dd, J = 4.9, 4.9 Hz, 4 H), 1.54-1.45 (m, 4 H), 1.38 (d, J = 4.8 Hz, 2 H). LCMS (Method 3): [MH⁺] = 449 at 4.57 min.</p>
Example 52	<p>6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-((1-methyl-1<i>H</i>-1,2,3-triazol-4-yl)methyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.81 (dd, J = 5.6, 5.6 Hz, 1 H), 8.47 (s, 1 H), 8.11 (d, J = 1.6 Hz, 1 H), 7.97 (s, 1 H), 7.91 (ddd, J = 3.2, 5.3, 12.1 Hz, 2 H), 7.51 (d, J = 1.6 Hz, 1 H), 7.36 (dd, J = 8.9, 8.9 Hz, 2 H), 4.79 (d, J = 5.5 Hz, 2 H), 4.00 (s, 3 H), 3.99 (s, 3 H). LCMS (Method 4): [MH⁺] = 365 at 2.89 min.</p>
Example 53	<p>6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)methyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.73 (dd, J = 5.6, 5.6 Hz, 1 H), 8.46 (s, 1 H), 8.26 (s, 1 H), 8.19 (d, J = 2.1 Hz, 1 H), 8.10 (d, J = 1.6 Hz, 1 H), 7.94-7.89 (m, 2 H), 7.59 (dd, J = 2.4, 8.7 Hz, 1 H), 7.51 (d, J = 1.6 Hz, 1 H), 7.37 (dd, J = 8.9, 8.9 Hz, 2 H), 6.81 (d, J = 8.7 Hz, 1 H), 4.65 (d, J = 5.5 Hz, 2 H), 4.01 (s, 3 H), 2.38 (dd, J = 5.0, 5.0 Hz, 4 H), 2.21 (s, 3 H), 1.07 (d, J = 6.7 Hz, 3 H). LCMS (Method 4): [MH⁺] = 458.5 at 2.40 min.</p>
Example 54	<p>6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-((4-(trifluoromethyl)pyridin-3-yl)methyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.80-8.75 (m, 2 H), 8.42 (s, 1 H), 8.13 (d, J = 8.5 Hz, 2 H), 7.90 (dd, J = 5.5, 8.4 Hz, 2 H), 7.77 (d, J = 5.1 Hz, 1 H), 7.53 (s, 1 H), 7.36 (dd, J = 8.8, 8.8 Hz, 2 H), 4.99 (s, 2 H), 4.01 (s, 3 H). LCMS (Method 4): [MH⁺] = 428.4 at 3.50 min.</p>

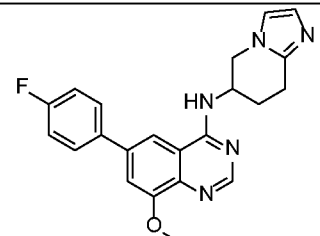
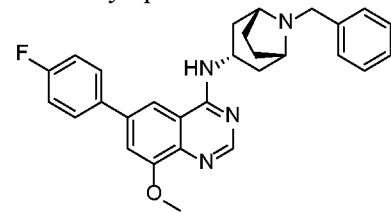
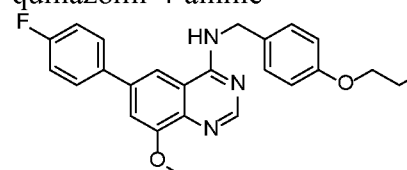
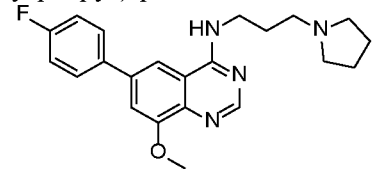
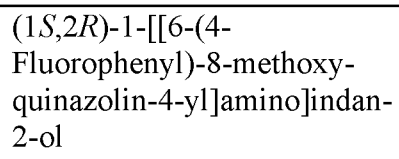
		
Example 55	6-(4-Fluorophenyl)-8-methoxy- <i>N</i> -((2-(trifluoromethyl)pyridin-3-yl)methyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 9.28-9.28 (m, 1 H), 8.66 (d, J = 4.4 Hz, 1 H), 8.50 (s, 1 H), 8.22 (d, J = 1.5 Hz, 1 H), 8.01 (d, J = 8.0 Hz, 1 H), 7.97-7.93 (m, 2 H), 7.70-7.63 (m, 2 H), 7.41 (dd, J = 8.8, 8.8 Hz, 2 H), 5.04 (d, J = 4.8 Hz, 2 H), 4.07 (s, 3 H). LCMS (Method 3): [MH ⁺] = 429.2 at 4.76 min.
Example 56	<i>N</i> -((5,6-Dimethylpyridin-3-yl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.99 (s, 1 H), 8.48 (s, 1 H), 8.33 (d, J = 1.9 Hz, 1 H), 8.14 (d, J = 1.6 Hz, 1 H), 7.93 (ddd, J = 3.2, 5.4, 12.1 Hz, 2 H), 7.55 (dd, J = 1.5, 8.8 Hz, 2 H), 7.38 (dd, J = 8.9, 8.9 Hz, 2 H), 4.77 (d, J = 5.5 Hz, 2 H), 4.03 (s, 3 H), 2.40 (s, 3 H), 2.23 (s, 3 H). LCMS (Method 4): [MH ⁺] = 389.3 at 2.46 min.
Example 57		¹ H NMR (400 MHz, DMSO): δ 8.74 (dd, J = 5.6, 5.6 Hz, 1 H), 8.47 (s, 1 H), 8.15 (d, J = 1.6 Hz, 1 H), 7.95-7.91 (m, 2 H), 7.58 (s, 1 H), 7.52 (d, J = 1.6 Hz, 1 H), 7.37 (dd, J = 8.9, 8.9 Hz, 2 H), 6.22 (d, J = 2.1 Hz, 1 H), 4.79 (d, J = 5.5 Hz, 2 H), 4.02 (s, 3 H). LCMS (Method 4): [MH ⁺] = 350 at 2.96 min.
Example 58	6-(4-Fluorophenyl)-8-methoxy- <i>N</i> -[(1-methylimidazol-2-yl)methyl]quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.75 (dd, J = 5.1, 5.1 Hz, 1 H), 8.48 (s, 1 H), 8.20-8.17 (m, 1 H), 7.95-7.90 (m, 2 H), 7.53 (d, J = 1.6 Hz, 1 H), 7.37 (dd, J = 8.9, 8.9 Hz, 2 H), 7.12 (s, 1 H), 6.83 (s, 1 H), 4.82 (d, J = 5.1 Hz, 2 H), 4.02 (s, 3 H), 3.71 (s, 3 H). LCMS (Method 4): [MH ⁺] = 364 at 2.23 min.
Example 59	6-(4-Fluorophenyl)-8-methoxy- <i>N</i> -(2-	¹ H NMR (400 MHz, DMSO): δ 8.50-8.47 (m, 2 H), 8.09 (d, J = 1.8 Hz, 1 H), 7.95-7.90 (m, 2 H), 7.51

	phenylcyclopropyl)quinazolin-4-amine 	(d, J = 1.6 Hz, 1 H), 7.39 (dd, J = 8.8, 8.8 Hz, 2 H), 7.35-7.30 (m, 2 H), 7.27-7.20 (m, 3 H), 4.02 (s, 3 H), 3.32-3.25 (m, 1 H), 2.22-2.16 (m, 1 H), 1.50-1.34 (m, 2 H). LCMS (Method 3): [MH ⁺] = 386 at 5.1 min.
Example 60	<i>N</i> -[(3-Chloro-4-pyridyl)methyl]-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.97 (dd, J = 5.7, 5.7 Hz, 1 H), 8.64 (s, 1 H), 8.45-8.41 (m, 2 H), 8.20 (d, J = 1.5 Hz, 1 H), 7.98-7.93 (m, 2 H), 7.57 (d, J = 1.5 Hz, 1 H), 7.43-7.35 (m, 3 H), 4.87 (d, J = 5.6 Hz, 2 H), 4.04 (s, 3 H). LCMS (Method 3): [MH ⁺] = 395 at 4.48 min.
Example 61	2-(3-Chloro-4-pyridyl)-2-[[6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl]amino]ethanol 	¹ H NMR (400 MHz, DMSO): δ 8.76 (s, 1 H), 8.66 (d, J = 6.5 Hz, 1 H), 8.45-8.42 (m, 2 H), 8.30 (d, J = 1.5 Hz, 1 H), 7.97 (ddd, J = 3.1, 5.4, 12.0 Hz, 2 H), 7.56 (d, J = 5.4 Hz, 2 H), 7.41 (dd, J = 8.9, 8.9 Hz, 2 H), 5.90-5.83 (m, 1 H), 5.32 (dd, J = 5.8, 5.8 Hz, 1 H), 4.03 (s, 3 H), 3.92-3.85 (m, 2 H). LCMS (Method 3): [MH ⁺] = 425 at 4 min.
Example 62	<i>N</i> -[(3 <i>S</i> ,4 <i>R</i>)-4-Ethoxytetrahydrofuran-3-yl]-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.50 (s, 1 H), 8.25 (d, J = 6.7 Hz, 1 H), 8.19 (d, J = 1.6 Hz, 1 H), 7.95-7.91 (m, 2 H), 7.52 (d, J = 1.5 Hz, 1 H), 7.38 (dd, J = 8.9, 8.9 Hz, 2 H), 4.74 (dd, J = 5.6, 5.6 Hz, 1 H), 4.16-4.12 (m, 1 H), 4.10 (dd, J = 5.9, 9.5 Hz, 1 H), 4.04-3.99 (m, 4 H), 3.85-3.70 (m, 3 H), 3.58 (ddd, J = 7.0, 9.5, 14.0 Hz, 1 H), 1.17 (dd, J = 7.0, 7.0 Hz, 3 H). LCMS (Method 3): [MH ⁺] = 384 at 4.45 min.
Example 63	<i>N</i> -[(1,1-Dioxothian-4-yl)methyl]-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.45 (s, 2 H), 8.09 (d, J = 1.6 Hz, 1 H), 7.92 (ddd, J = 3.2, 5.4, 12.1 Hz, 2 H), 7.51 (d, J = 1.6 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 4.01 (s, 3 H), 3.51 (dd, J = 6.1, 6.1 Hz, 2 H), 3.20-3.01 (m, 4 H), 2.16-2.08 (m, 3

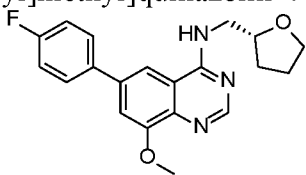
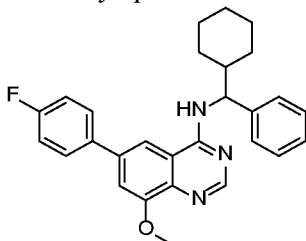
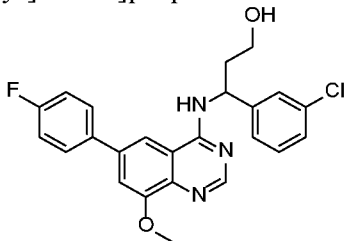
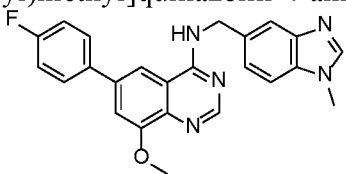
		H), 1.77-1.66 (m, 2 H). LCMS (Method 3): [MH ⁺] = 416 at 3.99 min.
Example 64	4-[[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]-1-methyl-piperidin-2-one 	¹ H NMR (400 MHz, DMSO): δ 8.47 (s, 1 H), 8.12-8.08 (m, 2 H), 7.91 (ddd, J = 3.2, 5.4, 12.1 Hz, 2 H), 7.50 (d, J = 1.6 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 4.67-4.56 (m, 1 H), 4.02 (s, 3 H), 2.87 (s, 3 H), 2.75-2.68 (m, 1 H), 2.45 (dd, J = 9.7, 16.9 Hz, 1 H), 2.19 (ddd, J = 1.8, 3.3, 12.8 Hz, 1 H), 2.01-1.89 (m, 1 H). LCMS (Method 4): [MH ⁺] = 381 at 2.9 min.
Example 65	6-[[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]methyl]-1 <i>H</i> -pyridin-2-one 	¹ H NMR (400 MHz, DMSO): δ 8.81 (dd, J = 5.7, 5.7 Hz, 1 H), 8.46 (s, 1 H), 8.14 (d, J = 1.6 Hz, 1 H), 7.96-7.92 (m, 2 H), 7.55 (d, J = 1.5 Hz, 1 H), 7.42-7.32 (m, 3 H), 6.21 (d, J = 9.2 Hz, 1 H), 6.10 (d, J = 5.5 Hz, 1 H), 4.63 (d, J = 5.5 Hz, 2 H), 4.03 (s, 3 H). LCMS (Method 4): [MH ⁺] = 377 at 2.84 min.
Example 66	3-[[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]methyl]-1,4-dihydro-1,2,4-triazol-5-one 	¹ H NMR (400 MHz, DMSO): δ 11.11 (s, 1 H), 8.99 (s, 1 H), 8.44 (s, 1 H), 8.15 (d, J = 1.6 Hz, 1 H), 7.95-7.90 (m, 2 H), 7.52 (d, J = 1.5 Hz, 1 H), 7.38 (dd, J = 8.9, 8.9 Hz, 2 H), 4.55 (s, 2 H), 4.02 (s, 3 H). LCMS (Method 4): [MH ⁺] = 367 at 2.62 min.
Example 67	<i>N</i> -[[1-(4-Chlorophenyl)cyclopropyl]methyl]-6-(4-fluorophenyl)-8-methoxy-quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.38 (s, 1 H), 8.19 (dd, J = 5.7, 5.7 Hz, 1 H), 8.07 (d, J = 1.6 Hz, 1 H), 7.91-7.87 (m, 2 H), 7.48 (d, J = 1.5 Hz, 1 H), 7.41-7.35 (m, 4 H), 7.31-7.28 (m, 2 H), 4.00 (s, 3 H), 3.90 (d, J = 5.6 Hz, 2 H), 1.11-1.06 (m, 2 H), 0.85-0.80 (m, 2 H). LCMS (Method 4): [MH ⁺] = 434 at 4.17 min.

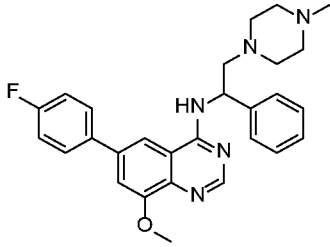
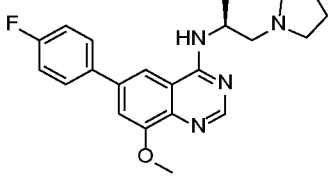
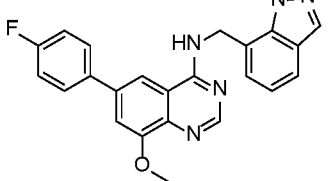
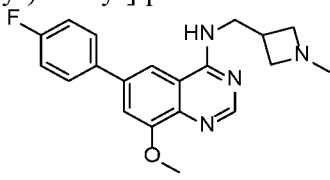
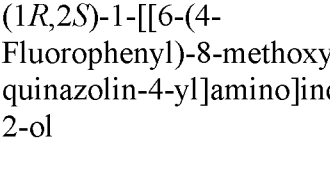
Example 68	<p>(5<i>R</i>)-5-[[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]methyl]pyrrolidin-2-one</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.84-8.84 (m, 1 H), 8.53 (s, 1 H), 8.14 (d, J = 1.6 Hz, 1 H), 7.96-7.91 (m, 2 H), 7.87 (s, 1 H), 7.61 (s, 1 H), 7.41 (dd, J = 8.9, 8.9 Hz, 2 H), 4.06 (s, 3 H), 3.96-3.88 (m, 1 H), 3.68-3.61 (m, 2 H), 2.28-2.10 (m, 3 H), 1.89-1.81 (m, 1 H). LCMS (Method 4): [MH⁺] = 367 at 2.78 min.</p>
Example 69	<p>(1<i>S</i>)-2-[[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]-1-phenyl]-ethanol</p> 	<p>¹H NMR (400 MHz, DMSO) δ 8.52 (dd, J=5.3, 5.3 Hz, 1H), 8.47 (s, 1H), 8.16 - 8.13 (m, 2H), 7.96 - 7.91 (m, 2H), 7.52 (d, J=1.5 Hz, 1H), 7.44 - 7.34 (m, 6H), 7.27 (dd, J=7.2, 7.2 Hz, 1H), 4.98 (dd, J=4.3, 8.2 Hz, 1H), 4.02 (s, 3H), 3.86 - 3.78 (m, 1H), 3.61 - 3.52 (m, 1H). LCMS (Method 3): [MH⁺] = 390 at 4.47 min.</p>
Example 70	<p><i>N'</i>-[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]-<i>N,N</i>-dimethyl-1-(4-pyridyl)ethane-1,2-diamine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.51 (d, J = 5.9 Hz, 2 H), 8.45 (s, 1 H), 8.23 (dd, J = 5.3, 5.3 Hz, 1 H), 7.95 (d, J = 1.6 Hz, 1 H), 7.87 (ddd, J = 3.2, 5.3, 12.1 Hz, 2 H), 7.48 (d, J = 1.5 Hz, 1 H), 7.38 (dd, J = 8.8, 8.8 Hz, 2 H), 7.32 (d, J = 5.9 Hz, 2 H), 4.16-4.08 (m, 1 H), 4.00 (s, 3 H), 3.96-3.84 (m, 2 H), 2.20 (s, 6 H). LCMS (Method 3): [MH⁺] = 418 at 4.05 min.</p>
Example 71	<p>(2<i>S</i>)-2-[[[6-(4-fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]-4-methyl-pentanamide</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.41 (s, 1 H), 8.25 (d, J = 1.6 Hz, 1 H), 8.18 (d, J = 8.0 Hz, 1 H), 7.98-7.94 (m, 2 H), 7.55-7.51 (m, 2 H), 7.39 (dd, J = 8.8, 8.8 Hz, 2 H), 7.01 (s, 1 H), 4.87 (ddd, J = 4.4, 7.9, 10.8 Hz, 1 H), 4.02 (s, 3 H), 1.92-1.62 (m, 3 H), 0.92 (dd, J = 6.5, 26.6 Hz, 6 H). LCMS (Method 4): [MH⁺] = 383 at 3.31 min.</p>
Example 72	<p>6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-(2<i>H</i>-tetrazol-5-ylmethyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.09 (s, 1 H), 8.46 (s, 1 H), 8.15 (d, J = 1.5 Hz, 2 H), 7.96-7.92 (m, 2</p>

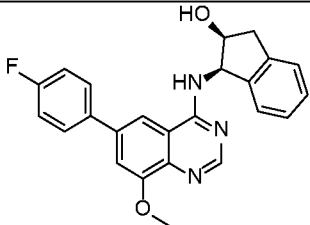
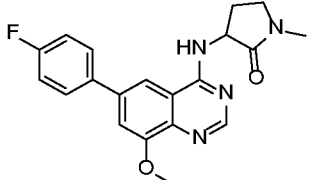
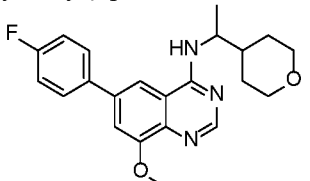
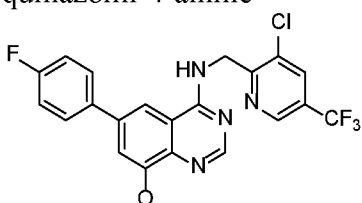
		H), 7.58 (d, J = 1.3 Hz, 2 H), 7.40 (dd, J = 8.8, 8.8 Hz, 2 H), 5.07 (d, J = 5.5 Hz, 2 H), 4.04 (s, 3 H), 2.56 (s, 1 H), 1.28-1.17 (m, 1 H). LCMS (Method 4): [MH ⁺] = 352 at 2.81 min.
Example 73	6-(4-Fluorophenyl)-8-methoxy- <i>N</i> -[(2-methylindazol-6-yl)methyl]quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.86 (dd, J = 5.6, 5.6 Hz, 1 H), 8.46 (s, 1 H), 8.43 (s, 1 H), 8.22-8.18 (m, 1 H), 7.95-7.91 (m, 2 H), 7.54-7.48 (m, 2 H), 7.37 (dd, J = 8.8, 8.8 Hz, 2 H), 7.18 (dd, J = 6.8, 8.7 Hz, 1 H), 7.00 (d, J = 6.8 Hz, 1 H), 5.05 (d, J = 5.4 Hz, 2 H), 4.17 (s, 3 H), 4.03 (s, 3 H). LCMS (Method 4): [MH ⁺] = 414 at 3.29 min.
Example 74	<i>N</i> -[2-[4-(Dimethylamino)phenyl]ethyl]-6-(4-fluorophenyl)-8-methoxy-quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.47 (s, 1 H), 8.39 (dd, J = 5.5, 5.5 Hz, 1 H), 8.07 (d, J = 1.6 Hz, 1 H), 7.94-7.89 (m, 2 H), 7.50 (d, J = 1.6 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 7.10 (d, J = 8.8 Hz, 2 H), 6.69 (d, J = 8.7 Hz, 2 H), 4.01 (s, 3 H), 3.71 (dd, J = 5.9, 14.7 Hz, 2 H), 2.88 (app d, J = 8.0 Hz, 2 H), 2.85 (s, 6 H). LCMS (Method 4): [MH ⁺] = 417 at 2.97 min.
Example 75	4-[[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]methyl]- <i>N,N</i> -dimethylbenzenesulfonamide 	¹ H NMR (400 MHz, DMSO): δ 8.97 (dd, J = 5.8, 5.8 Hz, 1 H), 8.44 (s, 1 H), 8.17 (d, J = 1.3 Hz, 1 H), 7.94 (dd, J = 5.5, 8.8 Hz, 2 H), 7.73 (d, J = 8.3 Hz, 2 H), 7.64 (d, J = 8.4 Hz, 2 H), 7.55 (d, J = 1.1 Hz, 1 H), 7.39 (dd, J = 8.8, 8.8 Hz, 2 H), 4.93 (d, J = 5.8 Hz, 2 H), 4.03 (s, 3 H), 2.60 (s, 6 H). LCMS (Method 4): [MH ⁺] = 467 at 3.51 min.
Example 76	6-(4-Fluorophenyl)-8-methoxy- <i>N</i> -(5,6,7,8-tetrahydroimidazo[1,2- <i>α</i>]pyridin-6-yl)quinazolin-4-amine	¹ H NMR (400 MHz, DMSO): δ 8.52 (s, 1 H), 8.22 (d, J = 6.8 Hz, 1 H), 8.13 (d, J = 2.1 Hz, 1 H), 7.94-7.89 (m, 2 H), 7.53 (d, J = 1.5 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 7.12 (s, 1 H), 6.96 (s, 1 H), 4.84-4.78 (m, 1 H), 4.47 (dd, J = 5.2, 12.2 Hz, 1 H), 4.03 (s, 3 H), 3.94 (dd, J = 9.0, 12.2 Hz, 1 H), 3.09-2.87 (m, 2 H), 2.28-2.11 (m, 2

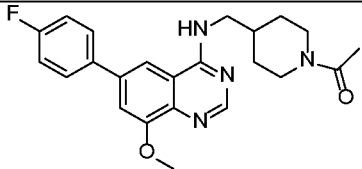
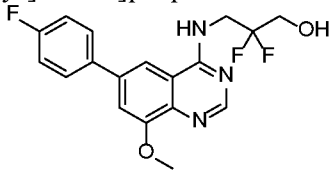
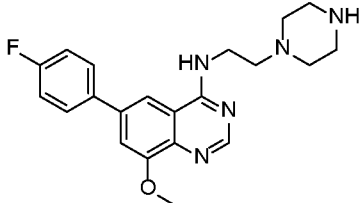
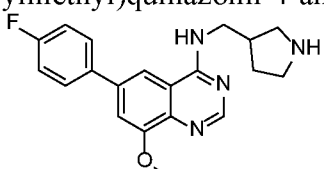
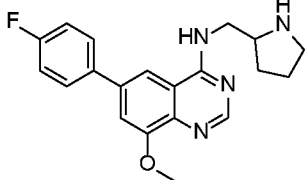
		H). LCMS (Method 4): [MH ⁺] = 390 at 2.27 min.
Example 77	<i>N</i> -[(1 <i>R</i> ,5 <i>S</i>)-8-Benzyl-8-azabicyclo[3.2.1]octan-3-yl]-6-(4-fluorophenyl)-8-methoxy-quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.43 (s, 1 H), 8.11 (d, J = 1.6 Hz, 1 H), 7.96-7.90 (m, 3 H), 7.48 (d, J = 1.5 Hz, 1 H), 7.42-7.32 (m, 6 H), 7.25 (dd, J = 7.2, 7.2 Hz, 1 H), 4.75-4.67 (m, 1 H), 4.00 (s, 3 H), 3.59 (s, 2 H), 3.24 (s, 2 H), 2.12-2.04 (m, 2 H), 1.85-1.79 (m, 4 H), 1.76-1.68 (m, 2 H). LCMS (Method 4): [MH ⁺] = 469 at 2.67 min.
Example 78	<i>N</i> -[[4-[2-(dimethylamino)ethoxy]phenyl]methyl]-6-(4-fluorophenyl)-8-methoxy-quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.84 (dd, J = 5.8, 5.8 Hz, 1 H), 8.48 (s, 1 H), 8.28 (s, 1 H), 8.18 (d, J = 1.5 Hz, 1 H), 7.99-7.94 (m, 2 H), 7.55 (d, J = 1.5 Hz, 1 H), 7.44-7.34 (m, 4 H), 6.96-6.92 (m, 2 H), 4.78 (d, J = 5.8 Hz, 2 H), 4.06 (s, 6 H), 2.65 (dd, J = 5.8, 5.8 Hz, 2 H), 2.25 (s, 6 H). LCMS (Method 4): [MH ⁺] = 447 at 2.58 min.
Example 79	6-(4-Fluorophenyl)-8-methoxy- <i>N</i> -(3-pyrrolidin-1-ylpropyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.48 (s, 1 H), 8.44 (dd, J = 5.2, 5.2 Hz, 1 H), 8.28 (s, 1 H), 8.07 (d, J = 1.8 Hz, 1 H), 7.97-7.93 (m, 2 H), 7.53 (d, J = 1.5 Hz, 1 H), 7.42 (dd, J = 8.8, 8.8 Hz, 2 H), 4.05 (s, 3 H), 3.64 (ddd, J = 6.5, 6.5, 6.5 Hz, 2 H), 2.74-2.65 (m, 6 H), 1.98-1.88 (m, 2 H), 1.81-1.74 (m, 4 H). LCMS (Method 4): [MH ⁺] = 381 at 2.24 min.
Example 80	(1 <i>S</i> ,2 <i>R</i>)-1-[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]indan-2-ol 	¹ H NMR (400 MHz, DMSO): δ 8.48 (s, 1 H), 8.36-8.32 (m, 2 H), 7.98-7.93 (m, 2 H), 7.52 (d, J = 1.5 Hz, 1 H), 7.35-7.20 (m, 6 H), 5.93 (dd, J = 4.9, 8.2 Hz, 1 H), 5.05 (d, J = 3.8 Hz, 1 H), 4.65 (d, J = 3.8 Hz, 1 H), 4.02 (s, 3 H), 3.16 (dd, J = 4.9, 16.3 Hz, 1 H), 2.92 (d, J = 15.9

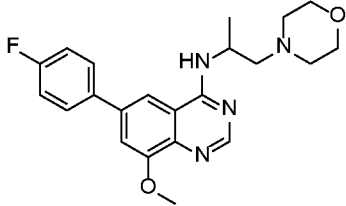
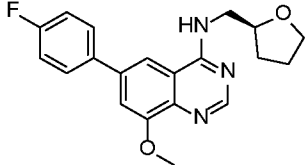
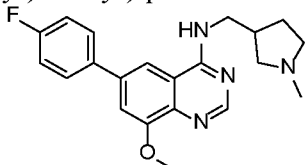
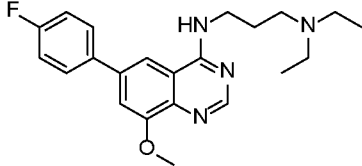
		Hz, 1 H). LCMS (Method 4): [MH ⁺] = 402 at 3.56 min.
Example 81	6-(4-Fluorophenyl)-8-methoxy- <i>N</i> -[(4-methyl-2,3-dihydro-1,4-benzoxazin-7-yl)methyl]quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.69 (dd, J = 5.7, 5.7 Hz, 1 H), 8.42 (s, 1 H), 8.14-8.11 (m, 1 H), 7.93-7.88 (m, 2 H), 7.49 (d, J = 1.5 Hz, 1 H), 7.35 (dd, J = 9.0, 9.0 Hz, 2 H), 6.81 (dd, J = 2.0, 8.1 Hz, 1 H), 6.71 (d, J = 2.0 Hz, 1 H), 6.63 (d, J = 8.3 Hz, 1 H), 4.62 (d, J = 5.6 Hz, 2 H), 4.20-4.17 (m, 2 H), 4.00 (s, 3 H), 3.18-3.15 (m, 2 H), 2.78 (s, 3 H). LCMS (Method 4): [MH ⁺] = 431 at 3.7 min.
Example 82	<i>N</i> -[(6-Chloroimidazo[1,2- <i>α</i>]pyridin-2-yl)methyl]-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.88 (dd, J = 5.8, 5.8 Hz, 1 H), 8.74 (d, J = 1.3 Hz, 1 H), 8.44 (s, 1 H), 8.17 (d, J = 1.8 Hz, 1 H), 7.95-7.90 (m, 2 H), 7.82 (s, 1 H), 7.56-7.51 (m, 2 H), 7.36 (dd, J = 9.0, 9.0 Hz, 2 H), 7.24 (dd, J = 2.0, 9.6 Hz, 1 H), 4.89 (d, J = 5.6 Hz, 2 H), 4.01 (s, 3 H). LCMS (Method 4): [MH ⁺] = 434 at 3.04 min.
Example 83	<i>N</i> -[(4-Benzyloxyphenyl)methyl]-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.77 (dd, J = 5.9, 5.9 Hz, 1 H), 8.42 (s, 1 H), 8.12 (d, J = 1.5 Hz, 1 H), 7.93-7.88 (m, 2 H), 7.50 (d, J = 1.5 Hz, 1 H), 7.44-7.29 (m, 9 H), 6.98-6.94 (m, 2 H), 5.07 (s, 2 H), 4.72 (d, J = 5.8 Hz, 2 H), 4.00 (s, 3 H). LCMS (Method 4): [MH ⁺] = 466 at 4.23 min.
Example 84	<i>N</i> -[(1-Benzylazetid-3-yl)methyl]-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine 	¹ H NMR (400 MHz, MeOD): δ 8.52 (s, 1 H), 8.11 (s, 1 H), 8.02-7.99 (m, 1 H), 7.82-7.77 (m, 2 H), 7.64 (d, J = 1.6 Hz, 1 H), 7.41-7.31 (m, 4 H), 7.28-7.23 (m, 3 H), 4.41 (dd, J = 2.2, 13.0 Hz, 1 H), 4.09 (s, 3 H), 4.09-3.84 (m, 3 H), 3.52-3.38 (m, 1 H), 2.84-2.78 (m, 1 H).

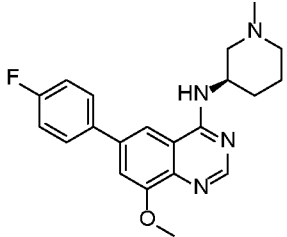
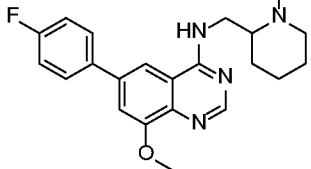
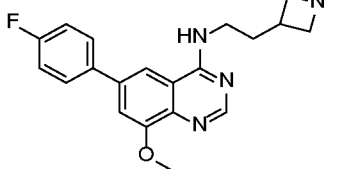
		LCMS (Method 4): [MH ⁺] = 429 at 2.41 min.
Example 85	6-(4-Fluorophenyl)-8-methoxy- <i>N</i> -[[<i>(2R)</i> -tetrahydrofuran-2-yl]methyl]quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.41 (s, 2 H), 8.15-8.12 (m, 1 H), 7.94-7.90 (m, 2 H), 7.49 (d, J = 1.8 Hz, 1 H), 7.36 (dd, J = 8.8, 8.8 Hz, 2 H), 4.19-4.11 (m, 1 H), 4.00 (s, 3 H), 3.84-3.78 (m, 1 H), 3.68-3.58 (m, 3 H), 2.00-1.77 (m, 3 H), 1.68-1.58 (m, 1 H). LCMS (Method 3): [MH ⁺] = 354 at 4.36 min.
Example 86	<i>N</i> -[Cyclohexyl(phenyl)methyl]-6-(4-fluorophenyl)-8-methoxy-quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO) d 8.36 (s, 2H), 8.22 (d, J=1.5 Hz, 1H), 7.94 - 7.89 (m, 2H), 7.49 - 7.45 (m, 3H), 7.39 (dd, J=8.8, 8.8 Hz, 2H), 7.31 (dd, J=7.6, 7.6 Hz, 2H), 7.20 (dd, J=7.3, 7.3 Hz, 1H), 5.22 (dd, J=9.5, 9.5 Hz, 1H), 4.08 (q, J=5.2 Hz, 1H), 3.97 (s, 3H), 3.17 (d, J=5.1 Hz, 2H), 2.07 (s, 2H), 2.01 - 1.91 (m, 1H), 1.70 (d, J=10.6 Hz, 1H), 1.61 (dd, J=9.1, 9.1 Hz, 2H), 1.29 - 0.88 (m, 6H). LCMS (Method 4): [MH ⁺] = 442 at 4.49 min.
Example 87	3-(3-Chlorophenyl)-3-[[6-(4-fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]propan-1-ol 	¹ H NMR (400 MHz, DMSO): δ 8.48 (d, J = 7.9 Hz, 1 H), 8.38 (s, 1 H), 8.22 (d, J = 1.5 Hz, 1 H), 7.97-7.92 (m, 2 H), 7.51 (s, 2 H), 7.45-7.35 (m, 4 H), 7.29 (d, J = 8.2 Hz, 1 H), 5.61 (dd, J = 8.3, 14.2 Hz, 1 H), 4.01 (s, 3 H), 3.58-3.44 (m, 2 H), 2.25-2.14 (m, 1 H), 2.09-1.98 (m, 1 H). LCMS (Method 4): [MH ⁺] = 438 at 3.69 min.
Example 88	6-(4-Fluorophenyl)-8-methoxy- <i>N</i> -[(1-methylbenzimidazol-5-yl)methyl]quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.92 (dd, J = 5.7, 5.7 Hz, 1 H), 8.46 (s, 1 H), 8.18 (d, J = 1.6 Hz, 1 H), 8.15 (s, 1 H), 7.95-7.91 (m, 2 H), 7.67 (s, 1 H), 7.54-7.51 (m, 2 H), 7.40-7.33 (m, 3 H), 4.93 (d, J = 5.8 Hz, 2 H), 4.02 (s, 3 H), 3.82 (s, 3 H). LCMS (Method 4): [MH ⁺] = 414 at 2.51 min.
Example 89	6-(4-Fluorophenyl)-8-methoxy- <i>N</i> -[2-(4-methylpiperazin-1-yl)-1-	¹ H NMR (400 MHz, DMSO): δ 8.45 (d, J = 8.2 Hz, 1 H), 8.38 (s, 1 H), 8.25 (d, J = 1.5 Hz, 1 H), 8.18

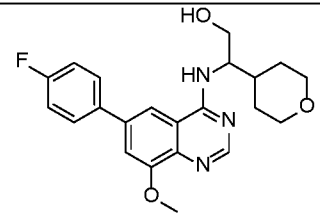
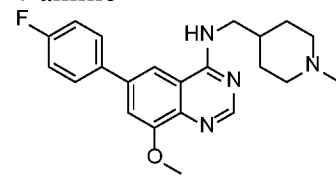
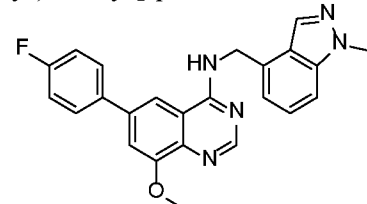
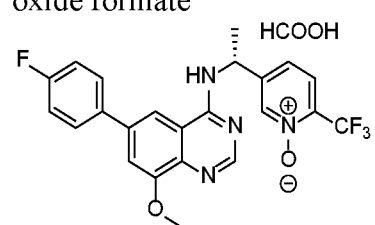
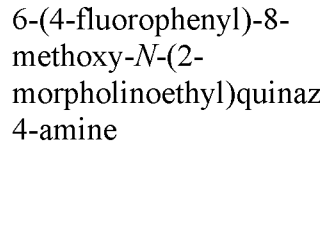
	phenyl-ethyl]quinazolin-4-amine 	(s, 1 H), 7.97-7.93 (m, 2 H), 7.50 (d, J = 7.7 Hz, 3 H), 7.41 (dd, J = 8.9, 8.9 Hz, 2 H), 7.34 (dd, J = 7.5, 7.5 Hz, 2 H), 7.24 (dd, J = 7.3, 7.3 Hz, 1 H), 5.80-5.72 (m, 1 H), 4.01 (s, 3 H), 3.02 (dd, J = 9.8, 12.7 Hz, 1 H), 2.68 (dd, J = 5.2, 12.7 Hz, 1 H), 2.58 (br s, 3 H), 2.35-2.35 (m, 4 H), 2.16 (s, 3 H). LCMS (Method 4): [MH ⁺] = 472 at 2.77 min.
Example 90	6-(4-Fluorophenyl)-8-methoxy- <i>N</i> -[(1 <i>S</i>)-1-methyl-2-pyrrolidin-1-yl-ethyl]quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.43 (s, 1 H), 8.09 (d, J = 1.6 Hz, 1 H), 7.99-7.89 (m, 3 H), 7.49 (d, J = 1.5 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 4.75-4.66 (m, 1 H), 4.01 (s, 3 H), 2.81 (dd, J = 7.6, 12.0 Hz, 1 H), 2.73-2.62 (m, 5 H), 1.70 (s, 4 H), 1.28 (d, J = 6.5 Hz, 3 H). LCMS (Method 4): [MH ⁺] = 381 at 2.34 min.
Example 91	6-(4-Fluorophenyl)-8-methoxy- <i>N</i> -[(1-methylindazol-7-yl)methyl]quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.81 (dd, J = 5.0, 5.0 Hz, 1 H), 8.49 (s, 1 H), 8.24 (d, J = 1.6 Hz, 1 H), 8.07 (s, 1 H), 7.94-7.89 (m, 2 H), 7.71 (d, J = 8.0 Hz, 1 H), 7.54 (d, J = 1.5 Hz, 1 H), 7.38-7.32 (m, 3 H), 7.12-7.07 (m, 1 H), 5.27 (d, J = 4.9 Hz, 2 H), 4.27 (s, 3 H), 4.03 (s, 3 H). LCMS (Method 3): [MH ⁺] = 414 at 4.48 min.
Example 92	6-(4-Fluorophenyl)-8-methoxy- <i>N</i> -[(1-methylazetidin-3-yl)methyl]quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.22 (s, 1 H), 7.88 (d, J = 1.8 Hz, 1 H), 7.79 (dd, J = 5.4, 8.8 Hz, 2 H), 7.67 (s, 1 H), 7.39 (d, J = 1.9 Hz, 1 H), 7.32 (dd, J = 8.8, 8.8 Hz, 2 H), 4.11-4.07 (m, 1 H), 3.95 (s, 3 H), 3.76-3.66 (m, 2 H), 3.36-3.29 (m, 1 H), 2.73-2.68 (m, 2 H), 2.46 (s, 3 H), 2.22-2.19 (m, 1 H). LCMS (Method 4): [MH ⁺] = 353 at 2.14 min.
Example 93	(1 <i>R</i> ,2 <i>S</i>)-1-[[6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl]amino]indan-2-ol 	¹ H NMR (400 MHz, DMSO): δ 8.50 (s, 1 H), 8.40-8.36 (m, 2 H), 8.00-7.96 (m, 2 H), 7.54 (d, J = 1.5 Hz, 1 H), 7.37-7.21 (m, 6 H), 5.95 (dd, J = 5.0, 8.2 Hz, 1 H), 5.07 (d, J = 3.6 Hz, 1 H), 4.68 (d, J = 3.3 Hz,

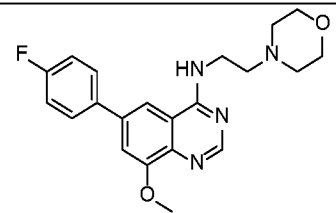
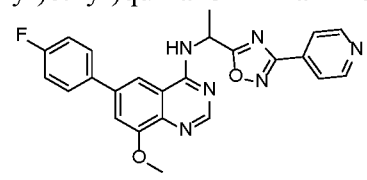
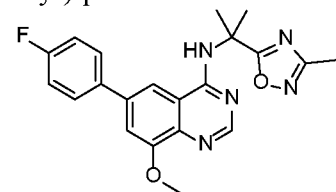
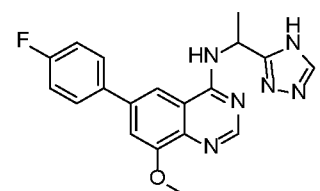
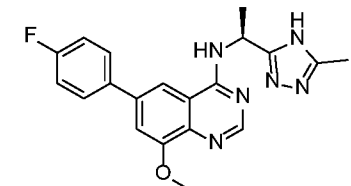
		1 H), 4.04 (s, 3 H), 3.17 (dd, J = 5.0, 16.1 Hz, 1 H), 2.94 (d, J = 15.9 Hz, 1 H). LCMS (Method 4): [MH ⁺] = 402 at 3.56 min.
Example 94	<p>3-[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]-1-methylpyrrolidin-2-one</p> 	¹ H NMR (400 MHz, DMSO): δ 9.10-9.10 (m, 1 H), 8.55 (s, 1 H), 8.19-8.14 (m, 1 H), 7.97-7.92 (m, 2 H), 7.65 (s, 1 H), 7.41 (dd, J = 8.8, 8.8 Hz, 2 H), 5.19 (q, J = 8.9 Hz, 1 H), 4.08 (s, 3 H), 3.47-3.41 (m, 2 H), 2.84 (s, 3 H), 2.50-2.44 (m, 1 H), 2.06 (ddd, J = 9.3, 12.2, 18.7 Hz, 1 H). LCMS (Method 4): [MH ⁺] = 367 at 2.85 min.
Example 95	<p>6-(4-Fluorophenyl)-8-methoxy-N-(1-tetrahydropyran-4-ylethyl)quinazolin-4-amine</p> 	¹ H NMR (400 MHz, DMSO): δ 8.41 (s, 1 H), 8.16-8.12 (m, 2 H), 7.94-7.90 (m, 3 H), 7.49 (d, J = 1.6 Hz, 1 H), 7.38 (dd, J = 8.8, 8.8 Hz, 2 H), 4.38 (dd, J = 8.0, 14.9 Hz, 1 H), 4.01 (s, 3 H), 3.90-3.82 (m, 2 H), 3.33-3.21 (m, 2 H), 1.88-1.78 (m, 1 H), 1.69 (dd, J = 13.0, 13.0 Hz, 2 H), 1.24 (d, J = 6.8 Hz, 5 H). LCMS (Method 4): [MH ⁺] = 382 at 3.32 min.
Example 96	<p>N-[[3-Chloro-5-(trifluoromethyl)-2-pyridyl]methyl]-6-(4-fluorophenyl)-8-methoxy-quinazolin-4-amine</p> 	¹ H NMR (400 MHz, DMSO): δ 8.94 (dd, J = 5.6, 5.6 Hz, 1 H), 8.87 (s, 1 H), 8.50 (d, J = 1.6 Hz, 1 H), 8.36 (s, 1 H), 8.20 (d, J = 1.6 Hz, 1 H), 7.94 (ddd, J = 3.2, 5.5, 12.1 Hz, 2 H), 7.55 (d, J = 1.6 Hz, 1 H), 7.39 (dd, J = 8.8, 8.8 Hz, 2 H), 5.07 (d, J = 5.5 Hz, 2 H), 4.03 (s, 3 H). LCMS (Method 4): [MH ⁺] = 463 at 3.91 min.
Example 97	<p>1-[4-[[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]methyl]-1-piperidyl]ethanone</p>	¹ H NMR (400 MHz, DMSO): δ 8.96 (s, 1 H), 8.54 (s, 1 H), 8.17 (d, J = 1.9 Hz, 1 H), 7.96-7.91 (m, 2 H), 7.63 (s, 1 H), 7.41 (dd, J = 8.9, 8.9 Hz, 2 H), 4.37 (d, J = 12.8 Hz, 1 H), 4.06 (s, 3 H), 3.84 (d, J = 13.7 Hz, 1 H), 3.56-3.47 (m, 2 H), 3.04-2.96 (m, 1 H), 2.09 (s, 1 H),

		1.99 (s, 4 H), 1.80-1.73 (m, 2 H), 1.26-1.02 (m, 2 H). LCMS (Method 3): [MH ⁺] = 409 at 4.01 min.
Example 98	<p>2,2-Difluoro-3-[[6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl]amino]propan-1-ol</p> 	¹ H NMR (400 MHz, DMSO) δ 8.56 (dd, J=6.0, 6.0 Hz, 1H), 8.49 (s, 1H), 8.20 (d, J=1.6 Hz, 1H), 7.97 - 7.93 (m, 2H), 7.55 (d, J=1.5 Hz, 1H), 7.39 (dd, J=8.9, 8.9 Hz, 2H), 5.66 - 5.65 (m, 1H), 4.23 - 4.11 (m, 2H), 4.03 (s, 3H), 3.70 (dd, J=13.7, 13.7 Hz, 2H). LCMS (Method 4): [MH ⁺] = 364 at 3.02 min.
Example 99	<p>6-(4-Fluorophenyl)-8-methoxy-N-(2-piperazin-1-ylethyl)quinazolin-4-amine</p> 	¹ H NMR (400 MHz, DMSO): δ 8.44 (s, 1 H), 8.32 (s, 1 H), 8.05 (d, J = 1.5 Hz, 1 H), 7.91 (ddd, J = 3.2, 5.3, 12.0 Hz, 2 H), 7.50 (d, J = 1.4 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 4.01 (s, 3 H), 3.73-3.66 (m, 2 H), 3.42-3.31 (m, 1 H), 2.90 (dd, J = 4.8, 4.8 Hz, 4 H), 2.67-2.60 (m, 2 H), 2.60-2.54 (m, 3 H). LCMS (Method 4): [MH ⁺] = 382 at 2.18 min.
Example 100	<p>6-(4-Fluorophenyl)-8-methoxy-N-(pyrrolidin-3-ylmethyl)quinazolin-4-amine</p> 	¹ H NMR (400 MHz, DMSO): δ 8.54 (dd, J = 5.4, 5.4 Hz, 1 H), 8.39 (s, 1 H), 8.10 (d, J = 1.4 Hz, 1 H), 7.95-7.90 (m, 2 H), 7.51 (d, J = 1.5 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 4.01 (s, 3 H), 3.69-3.54 (m, 2 H), 3.25-3.16 (m, 1 H), 3.12-3.04 (m, 1 H), 2.95 (dd, J = 7.0, 11.4 Hz, 1 H), 2.76-2.67 (m, 1 H), 2.06-1.93 (m, 1 H), 1.75-1.65 (m, 1 H). LCMS (Method 4): [MH ⁺] = 353 at 2.22 min.
Example 101	<p>6-(4-Fluorophenyl)-8-methoxy-N-(pyrrolidin-2-ylmethyl)quinazolin-4-amine</p> 	¹ H NMR (400 MHz, DMSO): δ 9.09 (s, 1 H), 8.46 (s, 1 H), 8.17 (d, J = 1.6 Hz, 1 H), 7.97-7.92 (m, 2 H), 7.52 (d, J = 1.4 Hz, 1 H), 7.37 (dd, J = 8.8, 8.8 Hz, 2 H), 4.02 (s, 3 H), 3.91-3.62 (m, 3 H), 3.18-3.01 (m, 2 H), 2.09-1.99 (m, 1 H), 1.95-1.78 (m, 2 H), 1.65 (ddd, J = 7.8, 12.5, 15.9 Hz, 1 H).

		LCMS (Method 4): [MH ⁺] = 353 at 2.22 min.
Example 102	6-(4-Fluorophenyl)-8-methoxy- <i>N</i> -(1-methyl-2-morpholino-ethyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.42 (s, 1 H), 8.09 (d, J = 1.6 Hz, 1 H), 7.49 (d, J = 1.6 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 4.78-4.67 (m, 1 H), 4.01 (s, 3 H), 3.54 (dd, J = 4.6, 4.6 Hz, 4 H), 2.60 (dd, J = 7.3, 12.3 Hz, 1 H), 2.49-2.38 (m, 5 H), 1.27 (d, J = 6.7 Hz, 3 H). LCMS (Method 4): [MH ⁺] = 397 at 2.3 min.
Example 103	(<i>S</i>)-6-(4-Fluorophenyl)-8-methoxy- <i>N</i> -((tetrahydrofuran-2-yl)methyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.45-8.42 (m, 2 H), 8.14 (d, J = 1.5 Hz, 1 H), 7.96-7.91 (m, 2 H), 7.51 (d, J = 1.5 Hz, 1 H), 7.38 (dd, J = 8.9, 8.9 Hz, 2 H), 4.20-4.12 (m, 1 H), 4.01 (s, 3 H), 3.86-3.79 (m, 1 H), 3.70-3.59 (m, 3 H), 2.02-1.79 (m, 3 H), 1.70-1.60 (m, 1 H). LCMS (Method 3): [MH ⁺] = 354 at 4.42 min.
Example 104	6-(4-Fluorophenyl)-8-methoxy- <i>N</i> -((1-methylpyrrolidin-3-yl)methyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.44 (s, 1 H), 8.24 (s, 1 H), 8.08 (d, J = 1.6 Hz, 1 H), 7.92 (ddd, J = 3.2, 5.4, 12.1 Hz, 2 H), 7.50 (d, J = 1.6 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 4.01 (s, 3 H), 3.61-3.46 (m, 2 H), 2.78-2.71 (m, 1 H), 2.70-2.64 (m, 2 H), 2.60-2.55 (m, 2 H), 2.37 (s, 3 H), 2.03-1.93 (m, 1 H), 1.64-1.54 (m, 1 H). LCMS (Method 4): [MH ⁺] = 367 at 2.24 min.
Example 105	<i>N</i> ¹ , <i>N</i> ¹ -Diethyl- <i>N</i> ³ -(6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)propane-1,3-diamine 	¹ H NMR (400 MHz, DMSO): δ 8.44 (s, 1 H), 8.39 (dd, J = 5.3, 5.3 Hz, 1 H), 8.02 (d, J = 1.6 Hz, 1 H), 7.93-7.88 (m, 2 H), 7.49 (d, J = 1.5 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 4.01 (s, 3 H), 3.58 (dd, J = 6.9, 12.4 Hz, 2 H), 2.62-2.54 (m, 6 H), 1.87-1.78 (m, 2 H), 0.99 (dd, J = 7.2, 7.2 Hz, 6 H). LCMS (Method 4): [MH ⁺] = 383 at 2.31 min.

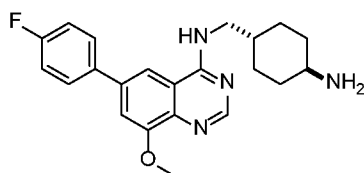
Example 106	<p>(<i>R</i>)-6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-(1-methylpiperidin-3-yl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.45 (s, 1 H), 8.11 (d, J = 1.8 Hz, 1 H), 7.95-7.90 (m, 3 H), 7.50 (d, J = 1.6 Hz, 1 H), 7.38 (dd, J = 8.9, 8.9 Hz, 2 H), 4.47-4.37 (m, 1 H), 4.01 (s, 3 H), 3.05 (dd, J = 3.6, 10.5 Hz, 1 H), 2.81 (d, J = 11.2 Hz, 1 H), 2.28 (s, 3 H), 2.04-1.92 (m, 3 H), 1.82-1.74 (m, 1 H), 1.68-1.57 (m, 1 H), 1.52-1.40 (m, 1 H). LCMS (Method 4): [MH⁺] = 367 at 2.28 min.</p>
Example 107	<p>6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-((1-methylpiperidin-2-yl)methyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.46 (s, 1 H), 8.29 (dd, J = 5.0, 5.0 Hz, 1 H), 8.17 (s, 1 H), 8.08 (d, J = 1.6 Hz, 1 H), 7.94-7.89 (m, 2 H), 7.51 (d, J = 1.4 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 4.02 (s, 3 H), 3.98-3.90 (m, 1 H), 3.59-3.53 (m, 1 H), 3.04-2.95 (m, 1 H), 2.69-2.68 (m, 1 H), 2.56 (d, J = 2.6 Hz, 3 H), 2.43-2.41 (m, 1 H), 1.83-1.79 (m, 1 H), 1.75-1.69 (m, 1 H), 1.62-1.52 (m, 2 H), 1.49-1.27 (m, 2 H). LCMS (Method 4): [MH⁺] = 381 at 2.32 min.</p>
Example 108	<p>6-(4-Fluorophenyl)-8-methoxy-<i>N</i>-(2-(1-methylazetidin-3-yl)ethyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.44 (s, 1 H), 8.32 (s, 1 H), 7.95 (d, J = 1.4 Hz, 1 H), 7.90-7.86 (m, 2 H), 7.49 (d, J = 1.4 Hz, 1 H), 7.35 (dd, J = 8.8, 8.8 Hz, 2 H), 4.08-3.95 (m, 6 H), 3.70 (dd, J = 7.3, 11.0 Hz, 1 H), 2.74-2.68 (m, 1 H), 2.39 (s, 3 H), 2.22-2.11 (m, 1 H), 1.82-1.72 (m, 1 H). LCMS (Method 3): [MH⁺] = 416 at 3.99 min.</p>
Example 109	<p>2-[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]-2-tetrahydropyran-4-yl-ethanol formate</p>	<p>¹H NMR (400 MHz, DMSO): δ 8.40 (s, 1 H), 8.21 (d, J = 1.6 Hz, 1 H), 8.16 (s, 1 H), 7.94 (ddd, J = 3.2, 5.4, 12.1 Hz, 2 H), 7.87 (d, J = 8.7 Hz, 1 H), 7.50 (d, J = 1.6 Hz, 1 H), 7.38 (dd, J = 8.9, 8.9 Hz, 2 H), 4.76 (s, 1 H), 4.40-4.31 (m, 1 H), 4.01 (s, 3 H), 3.92-3.82 (m, 2 H), 3.70-3.62 (m, 2 H), 3.35-3.24 (m, 2</p>

		H), 2.08-1.99 (m, 1 H), 1.71 (dd, J = 11.9, 28.0 Hz, 2 H), 1.39-1.23 (m, 2 H). LCMS (Method 3): [MH ⁺] = 398 at 3.88 min.
Example 110	6-(4-Fluorophenyl)-8-methoxy-N-[(1-methyl-4-piperidyl)methyl]quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.43 (s, 1 H), 8.34 (dd, J = 5.5, 5.5 Hz, 1 H), 8.10 (d, J = 1.6 Hz, 1 H), 7.94-7.89 (m, 2 H), 7.50 (d, J = 1.6 Hz, 1 H), 7.39 (dd, J = 8.8, 8.8 Hz, 2 H), 4.01 (s, 3 H), 3.46 (s, 2 H), 2.89 (d, J = 11.4 Hz, 2 H), 2.27 (s, 3 H), 2.09-2.03 (m, 2 H), 1.76 (dd, J = 10.2, 10.2 Hz, 3 H), 1.34-1.24 (m, 2 H). LCMS (Method 4): [MH ⁺] = 381 at 2.27 min.
Example 111	6-(4-Fluorophenyl)-8-methoxy-N-[(1-methylindazol-4-yl)methyl]quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 10.61 (s, 1 H), 8.78 (s, 1 H), 8.37 (s, 1 H), 8.23 (s, 1 H), 7.95 (dd, J = 5.6, 8.3 Hz, 2 H), 7.87 (s, 1 H), 7.60 (d, J = 8.4 Hz, 1 H), 7.45-7.36 (m, 3 H), 7.17 (d, J = 7.0 Hz, 1 H), 5.31 (s, 2 H), 4.17 (s, 3 H), 4.05 (s, 3 H). LCMS (Method 3): [MH ⁺] = 414 at 4.65 min.
Example 112	(R)-5-(1-((6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)amino)ethyl)-2-(trifluoromethyl)pyridine 1-oxide formate 	LCMS: 0.67 min, 459.1 [M+H] ⁺ , Method 5. ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 8.57 (s, 1 H) 8.51 (br d, J=6.58 Hz, 1 H) 8.37 - 8.44 (m, 1 H) 8.20 (s, 1 H) 8.17 (s, 1 H) 7.85 - 7.97 (m, 3 H) 7.55 (br d, J=8.33 Hz, 1 H) 7.32 - 7.43 (m, 2 H) 5.55 (br t, J=6.58 Hz, 1 H) 4.00 (s, 3 H) 1.64 (br d, J=7.02 Hz, 3 H).
Example 113	6-(4-fluorophenyl)-8-methoxy-N-(2-morpholinoethyl)quinazolin-4-amine 	LCMS: 0.85 min, 383.2 [M+H] ⁺ , Method 5. ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 8.39 (s, 1 H) 8.23 (br t, J=5.15 Hz, 1 H) 8.00 (d, J=1.10 Hz, 1 H) 7.78 - 7.94 (m, 2 H) 7.45 (d, J=1.10 Hz, 1 H) 7.34 (t, J=8.88 Hz, 2 H) 3.96 (s, 3 H) 3.61 - 3.70 (m, 2 H)

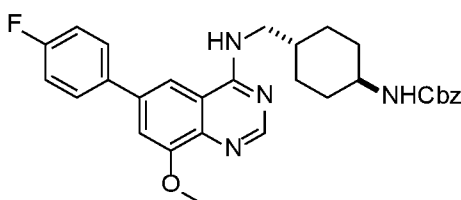
		3.50 - 3.57 (m, 4 H) 2.56 (br t, J=7.02 Hz, 2 H) 2.37 - 2.44 (m, 4 H).
Example 291	6-(4-Fluorophenyl)-8-methoxy- <i>N</i> -(1-(3-(pyridin-4-yl)-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.95 (d, J = 6.8 Hz, 1 H), 8.85-8.83 (m, 2 H), 8.49 (s, 1 H), 8.27 (d, J = 1.5 Hz, 1 H), 8.02-7.96 (m, 4 H), 7.62 (d, J = 1.5 Hz, 1 H), 7.44 (dd, J = 8.8, 8.8 Hz, 2 H), 5.98-5.93 (m, 1 H), 4.08 (s, 3 H), 1.88 (d, J = 7.1 Hz, 3 H). LCMS (Method 4): [MH ⁺] = 443 at 3.32 min.
Example 293	6-(4-fluorophenyl)-8-methoxy- <i>N</i> -(2-(3-methyl-1,2,4-oxadiazol-5-yl)propan-2-yl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.91 (d, J = 7.0 Hz, 1 H), 8.81-8.79 (m, 2 H), 8.45 (s, 1 H), 8.23 (d, J = 1.8 Hz, 1 H), 7.98-7.92 (m, 4 H), 7.58 (d, J = 1.6 Hz, 1 H), 7.40 (dd, J = 8.9, 8.9 Hz, 2 H), 5.94-5.89 (m, 1 H), 4.04 (s, 3 H), 1.84 (d, J = 7.2 Hz, 3 H). LCMS (Method 3): [MH ⁺] = 392 at 4.41 min.
Example 294	(<i>rac</i>)- <i>N</i> -(1-(4 <i>H</i> -1,2,4-triazol-3-yl)ethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 13.82-13.82 (m, 1 H), 8.62-8.54 (m, 1 H), 8.43-8.40 (m, 1 H), 8.24 (s, 1 H), 7.95-7.95 (m, 2 H), 7.54 (s, 1 H), 7.39-7.38 (m, 2 H), 5.79-5.79 (m, 1 H), 4.03 (s, 3 H), 1.67-1.67 (m, 3 H). 1 <i>NH</i> not observed. LCMS (Method 4): [MH ⁺] = 365 at 2.86 min.
Example 295	(<i>S</i>)-6-(4-fluorophenyl)-8-methoxy- <i>N</i> -(1-(5-methyl-4 <i>H</i> -1,2,4-triazol-3-yl)ethyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 13.37-13.37 (m, 1 H), 8.46-8.46 (m, 1 H), 8.42 (s, 1 H), 8.22 (s, 1 H), 7.95 (s, 2 H), 7.51 (s, 1 H), 7.37 (s, 2 H), 5.73-5.73 (m, 1 H), 4.01 (s, 3 H), 2.31 (s, 3 H), 1.63-1.62 (m, 3 H). LCMS (Method 4): [MH ⁺] = 379 at 2.91 min. Chiral analysis (Method 20) at 2.29 min.

Example 114

***N*-(((1*r*,4*r*)-4-Aminocyclohexyl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine**

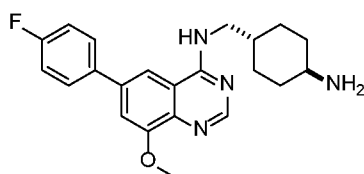


Step 1: Preparation of Benzyl ((1*r*,4*r*)-4-(((6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)amino)methyl)cyclohexyl)carbamate



To a solution of 6-(4-fluorophenyl)-8-methoxyquinazolin-4-ol (Intermediate 3) (80 mg, 0.30 mmol) in *N,N*-dimethylformamide (2 mL) was successively added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (169 mg, 0.32 mmol) and di-*isopropylethylamine* (0.32 mL, 1.85 mmol). The resulting mixture was heated to 40 °C and stirred for 20 min, benzyl ((1*r*,4*r*)-4-(aminomethyl)cyclohexyl)carbamate (93 mg, 0.36 mmol) was then added and the heating was maintained at 40 °C for 18 hours. After return to room temperature, the mixture was diluted with ethyl acetate (50 mL) and water (20 mL). The organic phase was washed with brine (2 × 20 mL), passed through a hydrophobic frit and the solvent was removed *in vacuo*. The residue was used directly in the next step without any further purification.

Step 2: Preparation of *N*-(((1*r*,4*r*)-4-aminocyclohexyl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine



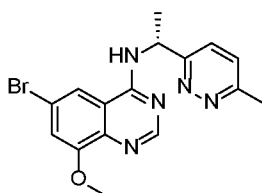
Nitrogen was bubbled for 5 min through a solution of benzyl ((1*r*,4*r*)-4-(((6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)amino)methyl)cyclohexyl)carbamate (152 mg, 0.30 mmol) in MeOH (3.0 mL) then Pd/C (10%) (31 mg, 0.03 mmol) was added followed by portion wise addition of sodium borohydride (88 mg, 2.36 mmol). The resulting mixture was stirred at room temperature for 2 hours. The reaction was filtered through Celite[®] and then loaded onto an SCX cartridge. The cartridge was washed with methanol and the filtrate was collected when eluting with a 7M solution of ammonia in methanol. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC to give the title compound (2.0 mg, 1.8%) as a brown solid.

¹H NMR (400 MHz, MeOD) δ 8.45 (s, 1 H), 8.31 (s, 1 H), 7.80 (d, J = 1.6 Hz, 1 H), 7.72-7.68 (m, 2 H), 7.38 (d, J = 1.6 Hz, 1 H), 7.13 (dd, J = 8.8, 8.8 Hz, 2 H), 3.98 (s, 3 H), 3.41 (d, J = 7.0 Hz, 2 H), 2.95-2.86 (m, 1 H), 1.97-1.87 (m, 4 H), 1.80-1.70 (m, 1 H), 1.32-1.03 (m, 4 H). LCMS (Method 4): [MH⁺] = 381 at 2.43 min.

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Intermediate 4

(*R*)-6-Bromo-8-methoxy-*N*-(1-(6-methylpyridazin-3-yl)ethyl)quinazolin-4-amine



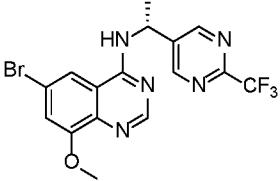
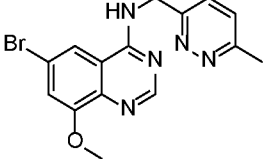
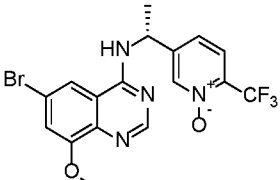
To a solution of 6-bromo-8-methoxyquinazolin-4-ol (Intermediate 2) (65 mg, 0.27 mmol) in *N,N*-dimethylformamide (1.5 mL) was successively added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (139 mg, 0.27 mmol) and di-

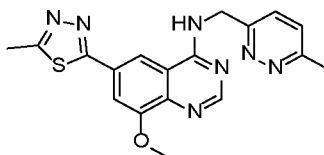
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isopropylethylamine (0.2 mL, 0.81 mmol). The resulting mixture was heated to 60 °C for one hour then (*R*)-1-(6-methylpyridazin-3-yl)ethan-1-amine (65 mg, 0.27 mmol) was added and the heating was maintained at 60 °C for 18 hours. After return to room temperature, the reaction mixture was directly concentrated onto silica gel and purified by chromatography on silica gel eluting with 0-100% (10% MeOH in ethyl acetate) in ethyl acetate to give the title compound as a beige solid (100 mg, quantitative yield).

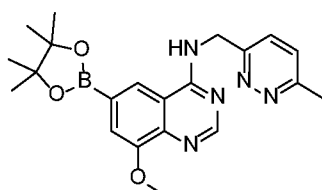
LCMS (Method 4): [MH⁺] = 374 at 2.42 min.

The following intermediates reported in the table below were synthesised following the same procedure described for the preparation of (*R*)-6-Bromo-8-methoxy-*N*-(1-(6-methylpyridazin-3-yl)ethyl)quinazolin-4-amine (Intermediate 4):

Intermediate No.	Chemical name Structure	Analytical data LC-MS
Intermediate 5	6-Bromo-8-methoxy- <i>N</i> -[(1 <i>R</i>)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl]quinazolin-4-amine 	LCMS (Method 4): [MH ⁺] = 428 at 3.19 min
Intermediate 6	6-Bromo-8-methoxy- <i>N</i> -((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine 	LCMS (Method 3): [MH ⁺] = 360 at 3.06 min.
Intermediate 7	(<i>R</i>)-5-(1-((6-Bromo-8-methoxyquinazolin-4-yl)amino)ethyl)-2-(trifluoromethyl)pyridine 1-oxide 	LCMS (Method 4): [MH ⁺] = 443 at 2.72 min.

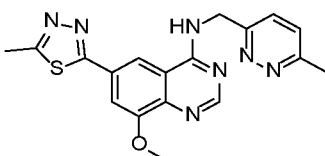
Example 115**8-Methoxy-6-(5-methyl-1,3,4-thiadiazol-2-yl)-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine**

- 5 Step 1: Preparation of 8-methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazolin-4-amine



- Nitrogen was bubbled for 5 min through a mixture of 6-bromo-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine (Intermediate 6) (250 mg, 0.69 mmol),
 10 *bis*-(pinacolato)diboron (194 mg, 0.76 mmol), [1,1'-*bis*-(diphenylphosphino)-ferrocene]dichloropalladium(II) (25 mg, 0.03 mmol) and potassium acetate (204 mg, 2.08 mmol) in 1,4-dioxane (15.0 mL). The mixture was heated at 90 °C for 18 hours. After return to room temperature, the reaction was filtered through Celite® and the solvent was removed *in vacuo*. The residue was taken on to the next step without further
 15 purification.

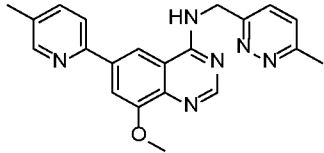
- Step 2: Preparation of 8-methoxy-6-(5-methyl-1,3,4-thiadiazol-2-yl)-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine

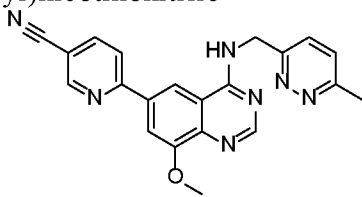
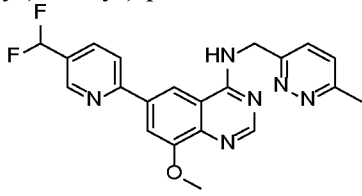
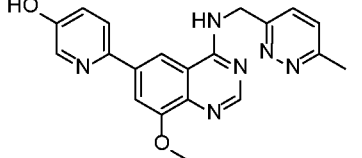
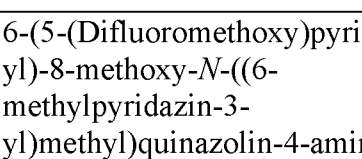


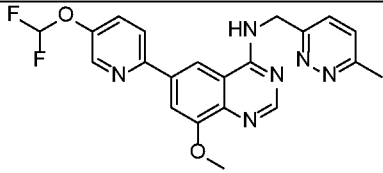
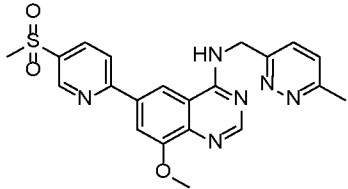
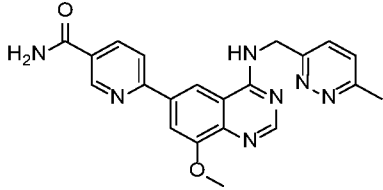
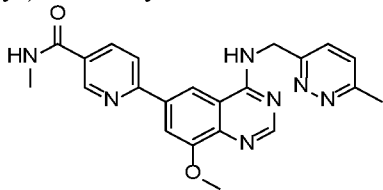
Nitrogen was bubbled for 5 min through a mixture of 2-bromo-5-methyl-1,3,4-thiadiazole (34 mg, 0.19 mmol), 8-methoxy-*N*-((6-methylpyridazin-3-yl)methyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazolin-4-amine (70 mg, 0.17 mmol), potassium carbonate (36 mg, 0.26 mmol) and water (0.5 mL) in 1,4-dioxane (4.0 mL), then tetrakis(triphenylphosphine)palladium(0) (20 mg, 0.02 mmol) was added. The resulting mixture was heated to 95 °C for 16 hours. After return to room temperature, the reaction was filtered through Celite®, rinsed with ethyl acetate (20 mL). The organic phases were combined, passed through a hydrophobic frit and the solvent was removed *in vacuo*. The residue was purified by preparative HPLC to give the title compound as an off-white solid (21.0 mg, 32%).

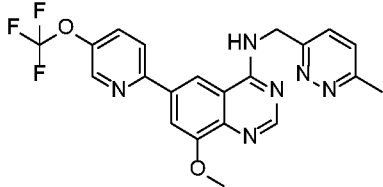
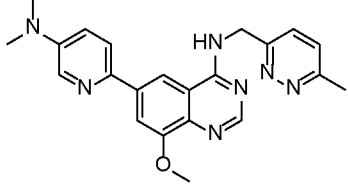
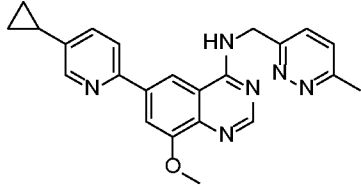
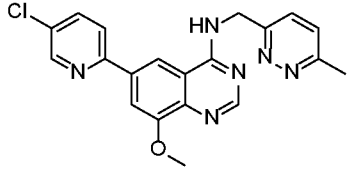
¹H NMR (400 MHz, DMSO): δ 9.31 (dd, J = 5.8, 5.8 Hz, 1 H), 8.47 (s, 1 H), 8.44 (d, J = 1.7 Hz, 1 H), 7.80 (d, J = 1.4 Hz, 1 H), 7.58 (d, J = 8.7 Hz, 1 H), 7.51 (d, J = 8.7 Hz, 1 H), 5.03 (d, J = 5.8 Hz, 2 H), 4.03 (s, 3 H), 2.84 (s, 3 H), 2.60 (s, 3 H). LCMS (Method 3): [MH⁺] = 380 at 2.13 min.

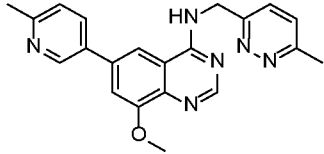
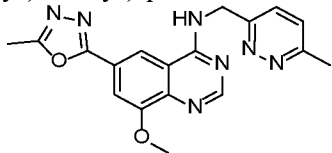
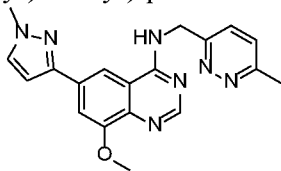
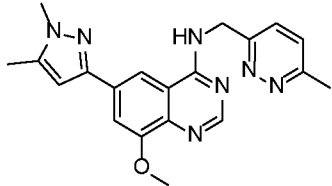
The following compounds reported in the table below were prepared according to the same procedure described for the preparation of 8-methoxy-6-(5-methyl-1,3,4-thiadiazol-2-yl)-*N*-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine:

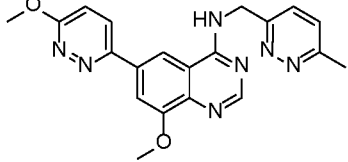
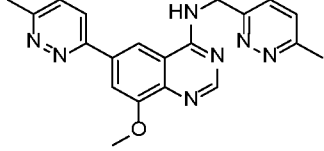
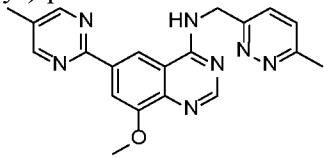
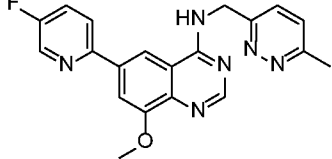
Example No.	Chemical Name Structure	Analytical data ¹ H NMR LC-MS
Example 116	8-Methoxy- <i>N</i> -((6-methylpyridazin-3-yl)methyl)-6-(5-methylpyridin-2-yl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 9.11 (dd, J = 5.9, 5.9 Hz, 1 H), 8.57 (dd, J = 1.7, 6.7 Hz, 2 H), 8.43 (s, 1 H), 8.12 (d, J = 8.2 Hz, 1 H), 8.04 (d, J = 1.4 Hz, 1 H), 7.81 (dd, J = 1.9, 8.2 Hz, 1 H), 7.57 (d, J = 8.5 Hz, 1 H), 7.50 (d, J = 8.8 Hz, 1 H), 5.04 (d, J = 5.8 Hz, 2 H), 4.02 (s, 3 H), 2.60 (s, 3 H), 2.39 (s, 3 H).

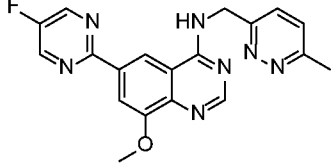
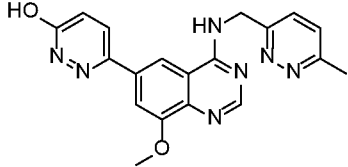
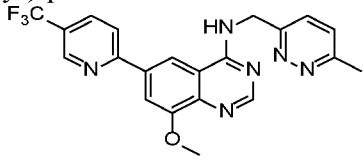
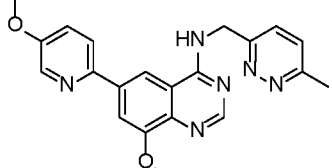
		LCMS (Method 4): [MH ⁺] = 373 at 2.46 min.
Example 117	6-(8-Methoxy-4-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-6-yl)nicotinonitrile 	¹ H NMR (400 MHz, DMSO): δ 9.22-9.16 (m, 2 H), 8.72 (d, J = 1.5 Hz, 1 H), 8.55-8.50 (m, 1 H), 8.46 (s, 1 H), 8.39 (d, J = 8.5 Hz, 1 H), 8.05 (d, J = 1.5 Hz, 1 H), 7.56 (d, J = 8.7 Hz, 1 H), 7.49 (d, J = 8.7 Hz, 1 H), 5.04 (d, J = 5.8 Hz, 2 H), 4.02 (s, 3 H), 2.59 (s, 3 H). LCMS (Method 3): [MH ⁺] = 384 at 3.09 min.
Example 118	6-(5-(Difluoromethyl)pyridin-2-yl)-8-methoxy-N-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 9.19 (dd, J = 5.8, 5.8 Hz, 1 H), 8.95 (s, 1 H), 8.68 (d, J = 1.5 Hz, 1 H), 8.46 (s, 1 H), 8.35 (d, J = 8.4 Hz, 1 H), 8.22 (d, J = 8.4 Hz, 1 H), 8.07 (d, J = 1.4 Hz, 1 H), 7.58 (d, J = 8.7 Hz, 1 H), 7.51 (d, J = 8.7 Hz, 1 H), 7.25 (t, J = 55.4 Hz, 1 H), 5.06 (d, J = 5.8 Hz, 2 H), 4.04 (s, 3 H), 2.61 (s, 3 H). LCMS (Method 3): [MH ⁺] = 409 at 3.33 min.
Example 119	6-(8-Methoxy-4-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-6-yl)pyridin-3-ol 	¹ H NMR (400 MHz, DMSO): δ 10.74-9.99 (m, 1 H), 9.03 (dd, J = 5.8, 5.8 Hz, 1 H), 8.42 (d, J = 1.4 Hz, 1 H), 8.39 (s, 1 H), 8.27 (d, J = 2.5 Hz, 1 H), 8.02 (d, J = 8.8 Hz, 1 H), 7.94 (d, J = 1.4 Hz, 1 H), 7.54 (d, J = 8.5 Hz, 1 H), 7.48 (d, J = 8.7 Hz, 1 H), 7.30 (dd, J = 2.8, 8.7 Hz, 1 H), 5.02 (d, J = 5.8 Hz, 2 H), 3.98 (s, 3 H), 2.59 (s, 3 H). LCMS (Method 4): [MH ⁺] = 375 at 2.14 min.
Example 120	6-(5-(Difluoromethoxy)pyridin-2-yl)-8-methoxy-N-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 9.13 (dd, J = 5.8, 5.8 Hz, 1 H), 8.64 (d, J = 2.9 Hz, 1 H), 8.58 (d, J = 1.5 Hz, 1 H), 8.45 (s, 1 H), 8.27 (d, J = 8.9 Hz, 1 H), 8.00 (d, J = 1.4 Hz, 1 H), 7.89 (dd, J = 2.9, 8.8 Hz, 1 H), 7.57 (d, J = 8.8 Hz, 1 H), 7.51 (d, J

		<p>= 8.7 Hz, 1 H), 7.42 (t, J = 73.4 Hz, 1 H), 5.05 (d, J = 5.8 Hz, 2 H), 4.02 (s, 3 H), 2.61 (s, 3 H). LCMS (Method 4): [MH⁺] = 425 at 2.78 min.</p>
Example 121	<p>8-Methoxy-<i>N</i>-(((6-methylpyridazin-3-yl)methyl)-6-(5-(methylsulfonyl)pyridin-2-yl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.26 (dd, J = 5.8, 5.8 Hz, 1 H), 9.20 (d, J = 2.0 Hz, 1 H), 8.75 (d, J = 1.5 Hz, 1 H), 8.53-8.42 (m, 3 H), 8.08 (d, J = 1.4 Hz, 1 H), 7.59 (d, J = 8.7 Hz, 1 H), 7.51 (d, J = 8.8 Hz, 1 H), 5.06 (d, J = 5.8 Hz, 2 H), 4.04 (s, 3 H), 3.40 (s, 3 H), 2.61 (s, 3 H). LCMS (Method 3): [MH⁺] = 437 at 3.08 min.</p>
Example 122	<p>6-(8-Methoxy-4-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-6-yl)nicotinamide</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.20-9.17 (m, 2 H), 8.69 (d, J = 1.4 Hz, 1 H), 8.46 (s, 1 H), 8.40 (dd, J = 2.3, 8.4 Hz, 1 H), 8.30 (d, J = 8.2 Hz, 1 H), 8.26 (s, 1 H), 8.08 (d, J = 1.4 Hz, 1 H), 7.69-7.67 (m, 1 H), 7.58 (d, J = 8.7 Hz, 1 H), 7.51 (d, J = 8.5 Hz, 1 H), 5.06 (d, J = 5.8 Hz, 2 H), 4.04 (s, 3 H), 2.61 (s, 3 H). LCMS (Method 3): [MH⁺] = 402 at 2.65 min.</p>
Example 123	<p>6-(8-Methoxy-4-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-6-yl)-<i>N</i>-methylnicotinamide</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.19 (t, J = 5.5 Hz, 1 H), 9.14 (d, J = 2.3 Hz, 1 H), 8.74-8.70 (m, 1 H), 8.68 (d, J = 1.4 Hz, 1 H), 8.46 (s, 1 H), 8.36 (dd, J = 2.3, 8.4 Hz, 1 H), 8.30 (d, J = 8.4 Hz, 1 H), 8.08 (d, J = 1.4 Hz, 1 H), 7.58 (d, J = 8.7 Hz, 1 H), 7.51 (d, J = 8.8 Hz, 1 H), 5.06 (d, J = 5.4 Hz, 2 H), 4.04 (s, 3 H), 2.87 (d, J = 4.6 Hz, 3 H), 2.61 (s, 3 H). LCMS (Method 4): [MH⁺] = 416 at 2.12 min.</p>

Example 124	<p>8-Methoxy-<i>N</i>-((6-methylpyridazin-3-yl)methyl)-6-(5-(trifluoromethoxy)pyridin-2-yl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.17 (dd, J = 5.9, 5.9 Hz, 1 H), 8.83 (d, J = 2.8 Hz, 1 H), 8.62 (d, J = 1.5 Hz, 1 H), 8.46 (s, 1 H), 8.34 (d, J = 8.9 Hz, 1 H), 8.14 (dd, J = 1.9, 8.7 Hz, 1 H), 8.01 (d, J = 1.5 Hz, 1 H), 7.58 (d, J = 8.7 Hz, 1 H), 7.51 (d, J = 8.7 Hz, 1 H), 5.05 (d, J = 5.8 Hz, 2 H), 4.03 (s, 3 H), 2.61 (s, 3 H). LCMS (Method 4): [MH⁺] = 443 at 3.10 min.</p>
Example 125	<p>6-[5-(Dimethylamino)-2-pyridyl]-8-methoxy-<i>N</i>-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.43-8.38 (m, 2 H), 8.26 (d, J = 2.9 Hz, 1 H), 8.08-8.01 (m, 2 H), 7.56 (d, J = 8.5 Hz, 1 H), 7.51 (d, J = 8.7 Hz, 1 H), 7.27 (dd, J = 3.1, 9.0 Hz, 1 H), 7.22-7.17 (m, 1 H), 5.04 (d, J = 5.8 Hz, 2 H), 4.00 (s, 3 H), 3.03 (s, 6 H), 2.98 (s, 3 H). LCMS (Method 4): [MH⁺] = 402 at 2.33 min.</p>
Example 126	<p>6-(5-Cyclopropylpyridin-2-yl)-8-methoxy-<i>N</i>-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.11 (dd, J = 5.8, 5.8 Hz, 1 H), 8.55 (dd, J = 1.7, 7.2 Hz, 2 H), 8.43 (s, 1 H), 8.09 (d, J = 8.3 Hz, 1 H), 8.03 (d, J = 1.3 Hz, 1 H), 7.61 (dd, J = 2.9, 8.6 Hz, 1 H), 7.57 (d, J = 9.2 Hz, 1 H), 7.50 (d, J = 8.7 Hz, 1 H), 5.04 (d, J = 5.6 Hz, 2 H), 4.01 (s, 3 H), 2.60 (s, 3 H), 2.09-2.02 (m, 1 H), 1.11-1.05 (m, 2 H), 0.87-0.82 (m, 2 H). LCMS (Method 3): [MH⁺] = 399 at 3.82 min.</p>
Example 127	<p>6-(5-Chloropyridin-2-yl)-8-methoxy-<i>N</i>-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.14 (dd, J = 5.8, 5.8 Hz, 1 H), 8.79 (d, J = 2.5 Hz, 1 H), 8.61 (d, J = 1.6 Hz, 1 H), 8.45 (s, 1 H), 8.25 (d, J = 8.7 Hz, 1 H), 8.16 (dd, J = 2.5, 8.7 Hz, 1 H), 8.01 (d, J = 1.4 Hz, 1 H), 7.57 (d, J = 8.7 Hz, 1 H), 7.51 (d, J = 8.7 Hz, 1 H), 5.05 (d, J = 5.8 Hz, 2 H), 4.02 (s, 3 H), 2.61 (s,</p>

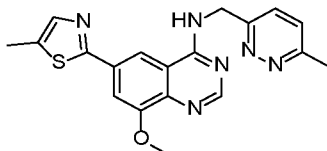
		3 H). LCMS (Method 3): [MH ⁺] = 393 at 3.51 min.
Example 128	8-Methoxy- <i>N</i> -((6-methylpyridazin-3-yl)methyl)-6-(6-methylpyridin-3-yl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 9.05 (t, J = 5.9 Hz, 1 H), 9.00 (d, J = 2.6 Hz, 1 H), 8.43 (s, 1 H), 8.25 (d, J = 1.6 Hz, 1 H), 8.21-8.17 (m, 1 H), 7.61-7.55 (m, 2 H), 7.50 (d, J = 8.7 Hz, 1 H), 7.43 (d, J = 8.2 Hz, 1 H), 5.04 (d, J = 5.8 Hz, 2 H), 4.03 (s, 3 H), 2.61 (s, 3 H), 2.56 (s, 3 H). LCMS (Method 3): [MH ⁺] = 373 at 2.93 min.
Example 129	8-Methoxy-6-(5-methyl-1,3,4-oxadiazol-2-yl)- <i>N</i> -((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 9.37 (s, 1 H), 8.58 (d, J = 1.5 Hz, 1 H), 8.49 (s, 1 H), 7.72 (d, J = 1.5 Hz, 1 H), 7.56 (d, J = 8.5 Hz, 1 H), 7.50 (d, J = 8.7 Hz, 1 H), 5.02 (d, J = 3.6 Hz, 2 H), 4.02 (s, 3 H), 2.65 (s, 3 H), 2.60 (s, 3 H). LCMS (Method 4): [MH ⁺] = 364 at 2.03 min.
Example 130	8-Methoxy-6-(1-methyl-1 <i>H</i> -pyrazol-3-yl)- <i>N</i> -((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.97 (dd, J = 5.8, 5.8 Hz, 1 H), 8.38 (s, 1 H), 8.25 (d, J = 1.4 Hz, 1 H), 7.82 (d, J = 2.3 Hz, 1 H), 7.69 (d, J = 1.3 Hz, 1 H), 7.55 (d, J = 8.7 Hz, 1 H), 7.50 (d, J = 8.7 Hz, 1 H), 6.85 (d, J = 2.3 Hz, 1 H), 5.02 (d, J = 5.6 Hz, 2 H), 3.98 (s, 3 H), 3.95 (s, 3 H), 2.60 (s, 3 H). LCMS (Method 3): [MH ⁺] = 362 at 2.74 min.
Example 131	6-(1,5-Dimethyl-1 <i>H</i> -pyrazol-3-yl)-8-methoxy- <i>N</i> -((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.95 (dd, J = 5.9, 5.9 Hz, 1 H), 8.37 (s, 1 H), 8.20 (d, J = 1.4 Hz, 1 H), 7.65 (d, J = 1.3 Hz, 1 H), 7.55 (d, J = 8.7 Hz, 1 H), 7.50 (d, J = 8.7 Hz, 1 H), 6.66 (s, 1 H), 5.02 (d, J = 5.8 Hz, 2 H), 3.97 (s, 3 H), 3.82 (s, 3 H), 2.60 (s, 3 H), 2.34 (s, 3 H). LCMS (Method 4): [MH ⁺] = 376 at 2.44 min.

Example 132	<p>8-Methoxy-6-(6-methoxypyridazin-3-yl)-<i>N</i>-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.07 (dd, J = 5.7, 5.7 Hz, 1 H), 8.46 (s, 1 H), 8.38 (d, J = 1.6 Hz, 1 H), 8.23 (d, J = 9.8 Hz, 1 H), 7.78 (d, J = 1.5 Hz, 1 H), 7.58 (d, J = 8.7 Hz, 1 H), 7.51 (d, J = 8.7 Hz, 1 H), 7.20 (d, J = 9.8 Hz, 1 H), 5.05 (d, J = 5.8 Hz, 2 H), 4.01 (s, 3 H), 3.82 (s, 3 H), 2.61 (s, 3 H). LCMS (Method 3): [MH⁺] = 390 at 2.84 min.</p>
Example 133	<p>8-Methoxy-6-(6-methylpyridazin-3-yl)-<i>N</i>-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.17 (dd, J = 5.6, 5.6 Hz, 1 H), 8.65 (d, J = 1.6 Hz, 1 H), 8.47 (s, 1 H), 8.32 (d, J = 8.8 Hz, 1 H), 8.10 (d, J = 1.5 Hz, 1 H), 7.78 (d, J = 8.8 Hz, 1 H), 7.58 (d, J = 8.7 Hz, 1 H), 7.51 (d, J = 8.7 Hz, 1 H), 5.05 (d, J = 5.5 Hz, 2 H), 4.05 (s, 3 H), 2.71 (s, 3 H), 2.60 (s, 3 H). LCMS (Method 3): [MH⁺] = 374 at 2.88 min.</p>
Example 134	<p>8-Methoxy-<i>N</i>-[(6-methylpyridazin-3-yl)methyl]-6-(5-methylpyrimidin-2-yl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.29 (dd, J = 5.7, 5.7 Hz, 1 H), 8.93 (d, J = 1.5 Hz, 1 H), 8.84 (s, 2 H), 8.44 (s, 1 H), 8.22 (d, J = 1.5 Hz, 1 H), 7.54 (d, J = 8.7 Hz, 1 H), 7.49 (d, J = 8.7 Hz, 1 H), 5.01 (d, J = 5.8 Hz, 2 H), 4.02 (s, 3 H), 2.60 (s, 3 H), 2.38 (s, 3 H). LCMS (Method 3): [MH⁺] = 374 at 3.25 min.</p>
Example 135	<p>6-(5-Fluoro-2-pyridyl)-8-methoxy-<i>N</i>-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.12 (dd, J = 5.9, 5.9 Hz, 1 H), 8.74 (d, J = 3.0 Hz, 1 H), 8.57 (d, J = 1.6 Hz, 1 H), 8.44 (s, 1 H), 8.27 (dd, J = 4.3, 8.9 Hz, 1 H), 8.00-7.94 (m, 2 H), 7.57 (d, J = 8.7 Hz, 1 H), 7.51 (d, J = 8.7 Hz, 1 H), 5.05 (d, J = 5.8 Hz, 2 H), 4.02 (s, 3 H), 2.61 (s, 3 H). LCMS (Method 3): [MH⁺] = 377 at 3.45 min.</p>

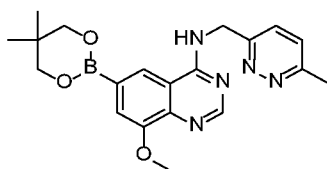
Example 136	<p>6-(5-Fluoropyrimidin-2-yl)-8-methoxy-<i>N</i>-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, CDCl₃): δ 8.76 (s, 1 H), 8.70 (s, 2 H), 8.61 (d, J = 1.5 Hz, 1 H), 8.21 (d, J = 1.4 Hz, 1 H), 7.57 (dd, J = 4.3, 4.3 Hz, 1 H), 7.51 (d, J = 8.5 Hz, 1 H), 7.37 (d, J = 8.7 Hz, 1 H), 5.13 (d, J = 4.6 Hz, 2 H), 4.17 (s, 3 H), 2.76 (s, 3 H). LCMS (Method 3): [MH⁺] = 378 at 3.3 min.</p>
Example 137	<p>6-[8-Methoxy-4-[(6-methylpyridazin-3-yl)methylamino]quinazolin-6-yl]pyridazin-3-ol</p> 	<p>¹H NMR (400 MHz, DMSO): δ 13.32 (s, 1 H), 9.05 (brs, 1 H), 8.44 (s, 1 H), 8.34 (d, J = 1.6 Hz, 1 H), 8.21 (d, J = 10.1 Hz, 1 H), 7.73 (d, J = 1.8 Hz, 1 H), 7.57 (d, J = 8.7 Hz, 1 H), 7.51 (d, J = 8.7 Hz, 1 H), 7.13 (d, J = 9.9 Hz, 1 H), 5.03 (s, 2 H), 3.98 (s, 3 H), 2.60 (s, 3 H). LCMS (Method 3): [MH⁺] = 376 at 2.33 min.</p>
Example 138	<p>8-Methoxy-<i>N</i>-((6-methylpyridazin-3-yl)methyl)-6-(5-(trifluoromethyl)pyridin-2-yl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.21 (dd, J = 5.7, 5.7 Hz, 1 H), 9.11 (s, 1 H), 8.72 (d, J = 1.5 Hz, 1 H), 8.48 (s, 1 H), 8.43 (s, 2 H), 8.08 (d, J = 1.4 Hz, 1 H), 7.58 (d, J = 8.7 Hz, 1 H), 7.51 (d, J = 8.7 Hz, 1 H), 5.06 (d, J = 5.6 Hz, 2 H), 4.04 (s, 3 H), 2.61 (s, 3 H). LCMS (Method 4): [MH⁺] = 427 at 3.06 min.</p>
Example 139	<p>8-Methoxy-6-(5-methoxypyridin-2-yl)-<i>N</i>-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.08 (dd, J = 5.8, 5.8 Hz, 1 H), 8.50 (d, J = 1.4 Hz, 1 H), 8.45 (d, J = 2.6 Hz, 1 H), 8.42 (s, 1 H), 8.17 (d, J = 2.8 Hz, 1 H), 8.00 (d, J = 1.4 Hz, 1 H), 7.60 (dd, J = 3.1, 8.9 Hz, 1 H), 7.57 (d, J = 8.8 Hz, 1 H), 7.51 (d, J = 8.5 Hz, 1 H), 5.04 (d, J = 5.6 Hz, 2 H), 4.01 (s, 3 H), 3.93 (s, 3 H), 2.60 (s, 3 H). LCMS (Method 3): [MH⁺] = 389 at 3.11 min.</p>

Example 140

8-Methoxy-*N*-((6-methylpyridazin-3-yl)methyl)-6-(5-methylthiazol-2-yl)quinazolin-4-amine

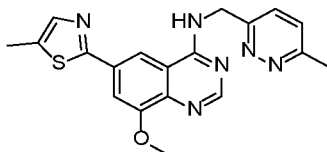


Step 1: Preparation of 6-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-8-methoxy-*N*-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine



Nitrogen was bubbled for 5 min through a mixture of 6-bromo-8-methoxy-*N*-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine (Intermediate 6) (100 mg, 0.28 mmol), *bis*(neopentyl glycolato)diboron (66 mg, 0.29 mmol), [1,1'-*bis*(diphenylphosphino)ferrocene]-dichloropalladium (II) complex with dichloromethane (10 mg, 0.02 mmol) and potassium acetate (54 mg, 0.55 mmol) in 1,4-dioxane (3.0 mL). The mixture was heated to 100 °C for 3 hours. After return to room temperature, the mixture was taken on to the next step as a 1,4-dioxane solution without further purification.

Step 2: Preparation of 8-methoxy-*N*-((6-methylpyridazin-3-yl)methyl)-6-(5-methylthiazol-2-yl)quinazolin-4-amine

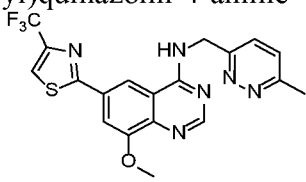
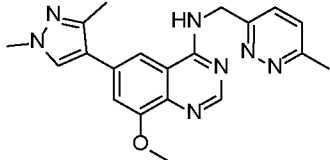


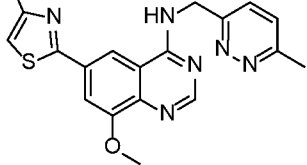
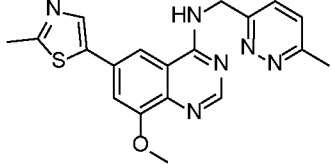
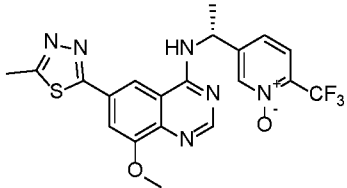
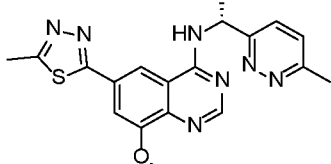
To the above solution of 6-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-8-methoxy-*N*-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine (100 mg, 0.28 mmol) was added aqueous caesium carbonate (181 mg, 0.56 mmol, 0.4 mL), 2-bromo-5-methylthiazole (64

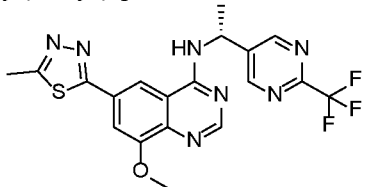
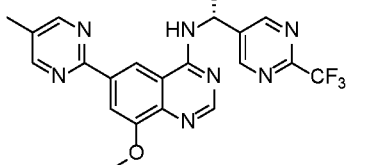
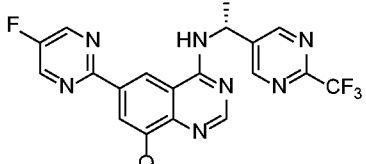
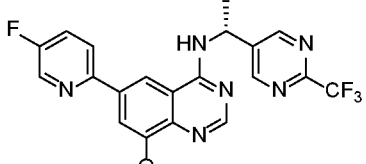
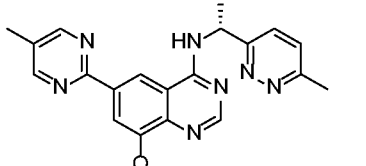
mg, 0.28 mmol) and tetrakis(triphenylphosphine)palladium(0) (20 mg, 0.02 mmol). The resulting mixture was heated to 95 °C for 16 hours. After return to room temperature, the mixture was filtered through Celite® and the filter cake rinsed with ethyl acetate (2 × 10 mL). The organic phases were washed with saturated aqueous ammonium chloride (10 mL), passed through a hydrophobic frit and the solvent was removed *in vacuo*. The residue was purified by preparative HPLC to give the title compound as an off-white solid (25 mg, 24%).

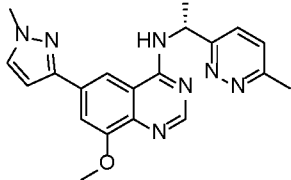
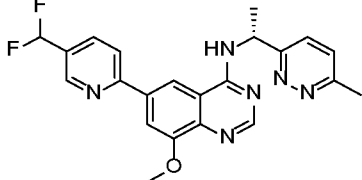
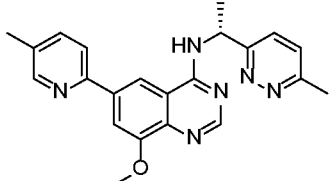
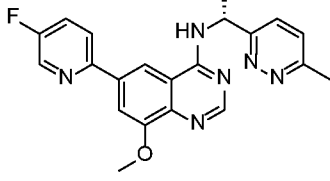
¹H NMR (400 MHz, DMSO): δ 9.24 (dd, J = 5.7, 5.7 Hz, 1 H), 8.43 (s, 1 H), 8.37 (d, J = 1.5 Hz, 1 H), 7.75 (d, J = 1.5 Hz, 1 H), 7.68 (d, J = 1.1 Hz, 1 H), 7.57 (d, J = 8.7 Hz, 1 H), 7.50 (d, J = 8.7 Hz, 1 H), 5.02 (d, J = 5.8 Hz, 2 H), 4.00 (s, 3 H), 2.60 (s, 3 H), 2.50 (s, 3 H). LCMS (Method 3): [MH⁺] = 379 at 3.20 min.

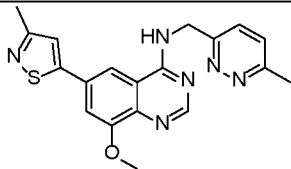
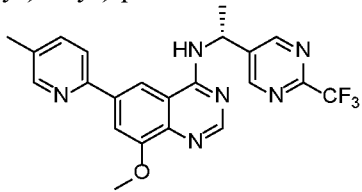
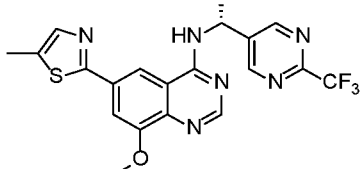
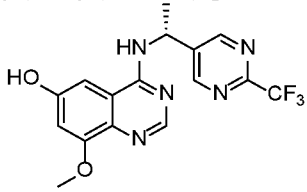
The following compounds reported in the table below were prepared according to the same procedure described for the preparation of 8-methoxy-*N*-((6-methylpyridazin-3-yl)methyl)-6-(5-methylthiazol-2-yl)quinazolin-4-amine:

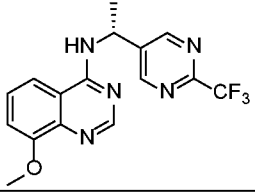
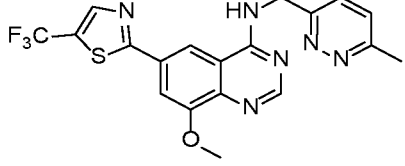
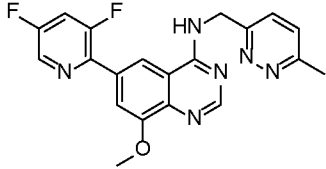
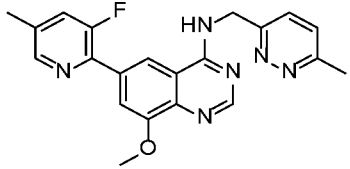
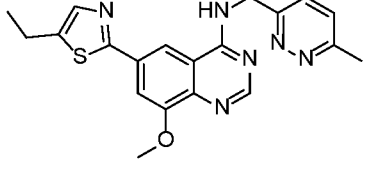
Example No.	Chemical Name Structure	Analytical data ¹ H NMR LC-MS
Example 141	8-Methoxy- <i>N</i> -((6-methylpyridazin-3-yl)methyl)-6-(4-(trifluoromethyl)thiazol-2-yl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 9.37 (dd, J = 5.7, 5.7 Hz, 1 H), 8.64 (s, 1 H), 8.53 (d, J = 1.6 Hz, 1 H), 8.47 (s, 1 H), 7.74 (d, J = 1.5 Hz, 1 H), 7.58 (d, J = 8.7 Hz, 1 H), 7.51 (d, J = 8.7 Hz, 1 H), 5.04 (d, J = 5.8 Hz, 2 H), 4.04 (s, 3 H), 2.60 (s, 3 H). LCMS (Method 3): [MH ⁺] = 433 at 2.95 min.
Example 142	6-(1,3-Dimethyl-1 <i>H</i> -pyrazol-4-yl)-8-methoxy- <i>N</i> -((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.96 (dd, J = 5.9, 5.9 Hz, 1 H), 8.39 (s, 1 H), 7.96 (d, J = 1.4 Hz, 1 H), 7.62 (s, 1 H), 7.50 (d, J = 5.6 Hz, 3 H), 5.01 (d, J = 5.9 Hz, 2 H), 3.96 (s, 3 H), 3.88 (s, 3 H), 2.60 (s, 3 H), 2.29 (s, 3 H). LCMS (Method 3): [MH ⁺] = 376 at 2.37 min.

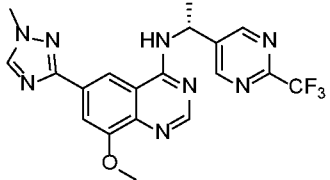
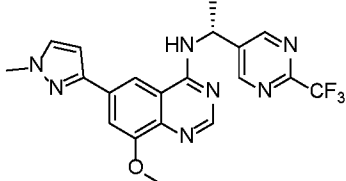
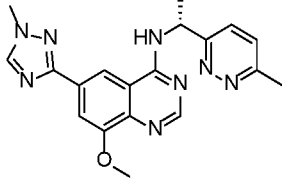
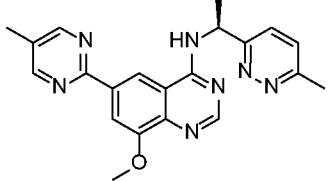
<p>Example 143</p>	<p>8-Methoxy-<i>N</i>-((6-methylpyridazin-3-yl)methyl)-6-(4-methylthiazol-2-yl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.26 (dd, J = 5.8, 5.8 Hz, 1 H), 8.44-8.41 (m, 2 H), 7.76 (d, J = 1.5 Hz, 1 H), 7.56 (d, J = 8.7 Hz, 1 H), 7.50 (d, J = 8.7 Hz, 1 H), 7.42 (s, 1 H), 5.03 (d, J = 5.9 Hz, 2 H), 4.01 (s, 3 H), 2.60 (s, 3 H), 2.49 (d, J = 0.7 Hz, 3 H). LCMS (Method 3): [MH⁺] = 379 at 3.39 min.</p>
<p>Example 144</p>	<p>8-Methoxy-<i>N</i>-((6-methylpyridazin-3-yl)methyl)-6-(2-methylthiazol-5-yl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.98 (dd, J = 5.8, 5.8 Hz, 1 H), 8.32 (s, 1 H), 8.15 (s, 1 H), 7.98 (d, J = 1.6 Hz, 1 H), 7.47 (d, J = 8.7 Hz, 1 H), 7.42 (d, J = 8.4 Hz, 2 H), 4.94 (d, J = 5.8 Hz, 2 H), 3.92 (s, 3 H), 2.65 (s, 3 H), 2.52 (s, 3 H). LCMS (Method 4): [MH⁺] = 379 at 2.33 min.</p>
<p>Example 145</p>	<p>(<i>R</i>)-5-(1-((8-Methoxy-6-(5-methyl-1,3,4-thiadiazol-2-yl)quinazolin-4-yl)amino)ethyl)-2-(trifluoromethyl)pyridine 1-oxide</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.72 (d, J = 7.2 Hz, 1 H), 8.52 (s, 1 H), 8.46 (d, J = 1.6 Hz, 1 H), 8.40 (s, 1 H), 7.84 (d, J = 8.4 Hz, 1 H), 7.67 (d, J = 1.5 Hz, 1 H), 7.50 (d, J = 8.3 Hz, 1 H), 5.52-5.46 (m, 1 H), 3.94 (s, 3 H), 2.77 (s, 3 H), 1.59 (d, J = 7.0 Hz, 3 H). LCMS (Method 4): [MH⁺] = 463 at 2.57 min.</p>
<p>Example 146</p>	<p>(<i>R</i>)-8-Methoxy-6-(5-methyl-1,3,4-thiadiazol-2-yl)-<i>N</i>-(1-(6-methylpyridazin-3-yl)ethyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.87 (d, J = 7.4 Hz, 1 H), 8.50 (d, J = 1.5 Hz, 1 H), 8.34 (s, 1 H), 7.69 (d, J = 1.5 Hz, 1 H), 7.55 (d, J = 8.7 Hz, 1 H), 7.42 (d, J = 8.7 Hz, 1 H), 5.71-5.65 (m, 1 H), 3.93 (s, 3 H), 2.76 (s, 3 H), 2.52 (s, 3 H), 1.64 (d, J = 7.2 Hz, 3 H). LCMS (Method 4): [MH⁺] = 394 at 2.30 min.</p>
<p>Example 147</p>	<p>(<i>R</i>)-8-Methoxy-6-(5-methyl-1,3,4-thiadiazol-2-yl)-<i>N</i>-(1-(2-(trifluoromethyl)pyrimidin-5-</p>	<p>¹H NMR (400 MHz, DMSO): δ 9.18 (s, 2 H), 8.88 (d, J = 6.9 Hz, 1 H), 8.52 (d, J = 1.6 Hz, 1 H), 8.48 (s, 1 H), 7.75 (d, J = 1.5 Hz, 1 H), 5.71-5.66 (m, 1 H), 4.02 (s, 3 H), 2.85 (s, 3 H), 1.75 (d, J = 7.2 Hz, 3</p>

	yl)ethyl)quinazolin-4-amine 	H). LCMS (Method 3): [MH ⁺] = 448 at 4.09 min.
Example 148	8-Methoxy-6-(5-methylpyrimidin-2-yl)-N-[(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl]quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 9.20 (s, 2 H), 8.98-8.94 (m, 2 H), 8.86 (s, 2 H), 8.46 (s, 1 H), 8.22 (d, J = 1.4 Hz, 1 H), 5.73-5.68 (m, 1 H), 4.01 (s, 3 H), 2.38 (s, 3 H), 1.76 (d, J = 7.0 Hz, 3 H). LCMS (Method 3): [MH ⁺] = 442 at 4.13 min.
Example 149	6-(5-Fluoropyrimidin-2-yl)-8-methoxy-N-[(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl]quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 9.20 (s, 2 H), 9.09 (s, 2 H), 9.00-8.94 (m, 2 H), 8.48 (s, 1 H), 8.17 (d, J = 1.4 Hz, 1 H), 5.73-5.68 (m, 1 H), 4.01 (s, 3 H), 1.76 (d, J = 7.2 Hz, 3 H). LCMS (Method 4): [MH ⁺] = 446 at 3.48 min.
Example 150	6-(5-Fluoro-2-pyridyl)-8-methoxy-N-[(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl]quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 9.19 (s, 2 H), 8.76-8.72 (m, 2 H), 8.59 (d, J = 1.5 Hz, 1 H), 8.44 (s, 1 H), 8.31 (dd, J = 4.3, 9.0 Hz, 1 H), 8.02-7.97 (m, 2 H), 5.72-5.67 (m, 1 H), 4.01 (s, 3 H), 1.76 (d, J = 7.2 Hz, 3 H). LCMS (Method 4): [MH ⁺] = 445 at 3.58 min.
Example 151	8-Methoxy-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-6-(5-methylpyrimidin-2-yl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 9.05 (d, J = 1.4 Hz, 1 H), 9.00 (d, J = 7.5 Hz, 1 H), 8.86 (s, 2 H), 8.40 (s, 1 H), 8.21 (d, J = 1.4 Hz, 1 H), 7.64 (d, J = 8.7 Hz, 1 H), 7.50 (d, J = 8.8 Hz, 1 H), 5.81-5.76 (m, 1 H), 4.01 (s, 3 H), 2.59 (s, 3 H), 2.39 (s, 3 H), 1.72 (d, J = 7.2 Hz, 3 H). LCMS (Method 3): [MH ⁺] = 388 at 3.64 min.
Example 152	8-Methoxy-6-(1-methylpyrazol-3-yl)-N-[(1R)-1-(6-	¹ H NMR (400 MHz, DMSO): δ 8.60 (d, J = 7.4 Hz, 1 H), 8.36-8.33

	<p>methylpyridazin-3-yl)ethyl]quinazolin-4-amine</p> 	<p>(m, 2 H), 7.83 (d, J = 2.1 Hz, 1 H), 7.69 (d, J = 1.3 Hz, 1 H), 7.62 (d, J = 8.7 Hz, 1 H), 7.50 (d, J = 8.7 Hz, 1 H), 6.92 (d, J = 2.4 Hz, 1 H), 5.78-5.73 (m, 1 H), 3.97 (s, 3 H), 3.96 (s, 3 H), 2.59 (s, 3 H), 1.72 (d, J = 7.2 Hz, 3 H). LCMS (Method 4): [MH⁺] = 376 at 2.44 min.</p>
Example 153	<p>6-[5-(Difluoromethyl)-2-pyridyl]-8-methoxy-<i>N</i>-[(1<i>R</i>)-1-(6-methylpyridazin-3-yl)ethyl]quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.96 (s, 1 H), 8.83 (d, J = 7.4 Hz, 1 H), 8.77 (d, J = 1.5 Hz, 1 H), 8.43-8.40 (m, 2 H), 8.23 (d, J = 8.4 Hz, 1 H), 8.07 (d, J = 1.4 Hz, 1 H), 7.64 (d, J = 8.7 Hz, 1 H), 7.51 (d, J = 8.7 Hz, 1 H), 7.26 (t, J = 53.8 Hz, 1 H), 5.82-5.76 (m, 1 H), 4.02 (s, 3 H), 2.60 (s, 3 H), 1.74 (d, J = 7.2 Hz, 3 H). LCMS (Method 4): [MH⁺] = 423 at 3.01 min.</p>
Example 154	<p>8-Methoxy-<i>N</i>-[(1<i>R</i>)-1-(6-methylpyridazin-3-yl)ethyl]-6-(5-methyl-2-pyridyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.78 (d, J = 6.8 Hz, 1 H), 8.67 (d, J = 1.4 Hz, 1 H), 8.60 (d, J = 1.9 Hz, 1 H), 8.39 (s, 1 H), 8.18 (d, J = 8.2 Hz, 1 H), 8.04 (d, J = 1.3 Hz, 1 H), 7.83 (dd, J = 1.9, 8.2 Hz, 1 H), 7.63 (d, J = 8.7 Hz, 1 H), 7.51 (d, J = 8.8 Hz, 1 H), 5.81-5.76 (m, 1 H), 4.01 (s, 3 H), 2.60 (s, 3 H), 2.40 (s, 3 H), 1.74 (d, J = 7.0 Hz, 3 H). LCMS (Method 4): [MH⁺] = 387 at 2.64 min.</p>
Example 155	<p>6-(5-Fluoro-2-pyridyl)-8-methoxy-<i>N</i>-[(1<i>R</i>)-1-(6-methylpyridazin-3-yl)ethyl]quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.72 (d, J = 2.8 Hz, 1 H), 8.62 (s, 1 H), 8.36 (s, 1 H), 8.29 (dd, J = 4.7, 8.9 Hz, 1 H), 7.95 (s, 1 H), 7.96-7.89 (m, 1 H), 7.62 (d, J = 8.7 Hz, 1 H), 7.50 (d, J = 8.7 Hz, 1 H), 5.73 (q, J = 7.0 Hz, 1 H), 3.99 (s, 3 H), 1.71 (d, J = 7.2 Hz, 3 H). LCMS (Method 3): [MH⁺] = 391 at 2.70 min.</p>
Example 156	<p>8-Methoxy-6-(3-methylisothiazol-5-yl)-<i>N</i>-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine</p>	<p>¹H NMR (400 MHz, DMSO): δ 9.14 (dd, J = 5.6, 5.6 Hz, 1 H), 8.44 (s, 1 H), 8.23 (s, 1 H), 8.19 (s, 1 H), 7.77 (s, 1 H), 7.57 (d, J = 8.7 Hz, 1 H), 7.51 (d, J = 8.8 Hz, 2 H), 5.03</p>

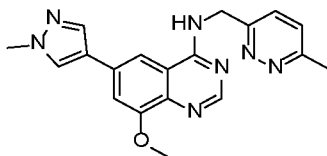
		(d, J = 5.5 Hz, 2 H), 2.60 (s, 3 H), 2.51 (s, 3 H). LCMS (Method 4): [MH ⁺] = 379 at 2.49 min.
Example 157	(<i>R</i>)-8-methoxy-6-(5-methylpyridin-2-yl)- <i>N</i> -(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine 	LCMS: Method 5 0.65 min, 441 [M+H] ⁺ , CSH 2 min. ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 9.17 (s, 2 H), 8.69 (d, J=6.6 Hz, 1 H), 8.53 - 8.60 (m, 2 H), 8.42 (s, 1 H), 8.12 (d, J=8.3 Hz, 1 H), 7.99 (d, J=1.3 Hz, 1 H), 7.81 (dd, J=8.3, 1.8 Hz, 1 H), 5.59 - 5.70 (m, 1 H), 4.00 (s, 3 H), 2.38 (s, 3 H), 1.75 (d, J=7.0 Hz, 3 H)
Example 158	(<i>R</i>)-8-methoxy-6-(5-methylthiazol-2-yl)- <i>N</i> -(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine 	LCMS: Method 5 0.73 min, 447 [M+H] ⁺ , CSH 2 min. ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 9.16 (s, 2 H), 8.79 (d, J=7.0 Hz, 1 H), 8.34 - 8.50 (m, 2 H), 7.69 (dd, J=5.9, 1.1 Hz, 2 H), 5.67 (t, J=7.0 Hz, 1 H), 3.98 (s, 3 H), 2.55 (s, 3 H), 1.74 (d, J=7.0 Hz, 3 H)
Example 159	(<i>R</i>)-8-methoxy-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazolin-6-ol 	Compound obtained as a side product in the preparation of Example 156B LCMS: 0.49 min, 366.1 [M+H] ⁺ , Method 5. ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 9.87 (s, 1 H), 9.12 (s, 2 H), 8.22 (s, 1 H), 8.13 (d, J=7.0 Hz, 1 H), 7.13 (d, J=2.2 Hz, 1 H), 6.83 (d, J=2.2 Hz, 1 H), 5.50 - 5.60 (m, 1 H), 3.85 (s, 3 H), 1.67 (d, J=7.5 Hz, 3 H)
Example 160	(<i>R</i>)-8-methoxy- <i>N</i> -(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine	Compound obtained as a side product in the preparation of Example 156B LCMS: 0.46 min, 350 [M+H] ⁺ , Method 5 ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 9.14 (s, 2 H), 8.44 - 8.53 (m, 1

		H), 8.40 (s, 1 H), 7.83 - 7.96 (m, 1 H), 7.44 - 7.55 (m, 1 H), 7.23 - 7.35 (m, 1 H), 5.54 - 5.72 (m, 1 H), 3.90 (s, 3 H), 1.69 (d, J=7.0 Hz, 3 H)
Example 161	8-Methoxy- <i>N</i> -((6-methylpyridazin-3-yl)methyl)-6-(5-(trifluoromethyl)thiazol-2-yl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 9.32 (dd, J = 5.9, 5.9 Hz, 1 H), 8.61 (dd, J = 1.4, 9.9 Hz, 2 H), 8.49 (s, 1 H), 7.81 (d, J = 1.6 Hz, 1 H), 7.59 (d, J = 8.7 Hz, 1 H), 7.51 (d, J = 8.7 Hz, 1 H), 5.04 (d, J = 5.8 Hz, 2 H), 4.03 (s, 3 H), 2.61 (s, 3 H). LCMS (Method 3): [MH ⁺] = 433 at 3.86 min.
Example 296	6-(3,5-Difluoropyridin-2-yl)-8-methoxy- <i>N</i> -((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.96 (dd, J = 5.8, 5.8 Hz, 1 H), 8.38 (s, 1 H), 7.86 (d, J = 1.3 Hz, 1 H), 7.55-7.48 (m, 2 H), 7.39 (d, J = 1.4 Hz, 1 H), 6.51 (s, 1 H), 5.01 (d, J = 5.9 Hz, 2 H), 4.32-4.30 (m, 2 H), 3.96 (s, 3 H), 3.90 (dd, J = 5.5, 5.5 Hz, 2 H), 2.65-2.59 (m, 5 H). LCMS (Method 3): [MH ⁺] = 395 at 2.48 min.
Example 297	6-(3-Fluoro-5-methyl-2-pyridyl)-8-methoxy- <i>N</i> -[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.77 (dd, J = 5.9, 5.9 Hz, 1 H), 8.32 (s, 1 H), 7.50-7.47 (m, 3 H), 7.07 (d, J = 1.5 Hz, 1 H), 4.98 (d, J = 5.9 Hz, 2 H), 3.92 (s, 3 H), 2.60 (s, 3 H), 2.10-2.02 (m, 1 H), 1.07-1.02 (m, 2 H), 0.89-0.84 (m, 2 H). LCMS (Method 4): [MH ⁺] = 392 at 2.57 min.
Example 298	6-(5-Ethylthiazol-2-yl)-8-methoxy- <i>N</i> -[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 9.25 (dd, J = 5.8, 5.8 Hz, 1 H), 8.43 (s, 1 H), 8.38 (d, J = 1.6 Hz, 1 H), 7.76 (d, J = 1.5 Hz, 1 H), 7.71 (s, 1 H), 7.56 (d, J = 8.7 Hz, 1 H), 7.50 (d, J = 8.7 Hz, 1 H), 5.02 (d, J = 5.8 Hz, 2 H), 4.00 (s, 3 H), 2.95 (q, J = 7.4 Hz, 2 H), 2.60 (s, 3 H), 1.33 (dd, J = 7.5, 7.5 Hz, 3 H). LCMS (Method 4): [MH ⁺] = 393 at 2.76 min.
Example 299	(<i>R</i>)-8-methoxy-6-(1-methyl-1 <i>H</i> -1,2,4-triazol-3-yl)- <i>N</i> -(1-(2-	¹ H NMR (400 MHz, DMSO): δ 9.18 (s, 2 H), 8.87 (d, J = 7.3 Hz, 1 H), 8.64 (s, 1 H), 8.58 (d, J = 1.4

	(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine 	Hz, 1 H), 8.43 (s, 1 H), 7.82 (d, J = 1.4 Hz, 1 H), 5.72-5.66 (m, 1 H), 3.99 (d, J = 4.9 Hz, 6 H), 1.74 (d, J = 7.2 Hz, 3 H). LCMS (Method 4): [MH ⁺] = 431 at 3.51 min.
Example 300	(<i>R</i>)-8-methoxy-6-(1-methyl-1H-pyrazol-3-yl)- <i>N</i> -(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 9.18 (s, 2 H), 8.59 (d, J = 7.0 Hz, 1 H), 8.39 (s, 1 H), 8.28 (d, J = 1.5 Hz, 1 H), 7.84 (d, J = 2.1 Hz, 1 H), 7.67 (d, J = 1.4 Hz, 1 H), 6.90 (d, J = 2.3 Hz, 1 H), 5.70-5.65 (m, 1 H), 3.98 (s, 3 H), 3.96 (s, 3 H), 1.75 (d, J = 7.2 Hz, 3 H). LCMS (Method 4): [MH ⁺] = 430 at 4.14 min.
Example 301	(<i>R</i>)-8-methoxy-6-(1-methyl-1H-1,2,4-triazol-3-yl)- <i>N</i> -(1-(6-methylpyridazin-3-yl)ethyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.92 (d, J = 7.4 Hz, 1 H), 8.67 (d, J = 1.6 Hz, 1 H), 8.64 (d, J = 0.5 Hz, 1 H), 8.37 (s, 1 H), 7.82 (d, J = 1.4 Hz, 1 H), 7.62 (d, J = 8.7 Hz, 1 H), 7.50 (d, J = 8.7 Hz, 1 H), 5.81-5.72 (m, 1 H), 4.00 (s, 3 H), 3.98 (s, 3 H), 2.59 (s, 3 H), 1.71 (d, J = 7.2 Hz, 3 H). LCMS (Method 4): [MH ⁺] = 377 at 2.93 min.
Example 326	8-Methoxy- <i>N</i> -[(1 <i>S</i>)-1-(6-methylpyridazin-3-yl)ethyl]-6-(5-methylpyrimidin-2-yl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 9.05 (d, J = 1.6 Hz, 1 H), 8.99 (d, J = 7.2 Hz, 1 H), 8.86 (s, 2 H), 8.40 (s, 1 H), 8.21 (d, J = 1.6 Hz, 1 H), 7.63 (d, J = 8.8 Hz, 1 H), 7.50 (d, J = 8.8 Hz, 1 H), 5.81-5.76 (m, 1 H), 4.01 (s, 3 H), 2.59 (s, 3 H), 2.38 (s, 3 H), 1.72 (d, J = 7.2 Hz, 3 H). LCMS (Method 3): [MH ⁺] = 388 at 3.64 min. Chiral analysis (Method 37) at 2.21 min.

Example 163

8-Methoxy-6-(1-methyl-1*H*-pyrazol-4-yl)-*N*-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine



To a solution of 6-bromo-8-methoxy-*N*-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine (Intermediate 6) (100 mg, 0.28 mmol) in 1,4-dioxane (2.0 mL) was added 1-methyl-4-(tributylstannyl)-*1H*-pyrazole (124 mg, 0.33 mmol) and

5 tetrakis(triphenylphosphine)palladium(0) (32 mg, 0.03 mmol). The resulting mixture was heated to 80 °C for 18 h. After return to room temperature, the reaction was filtered through Celite®. The Celite® cake was rinsed with ethyl acetate (2 × 20 mL). Combined organic phases were washed with 1 *N* aqueous potassium fluoride (10 mL), filtered through a hydrophobic frit and the solvent was removed *in vacuo*. The residue was

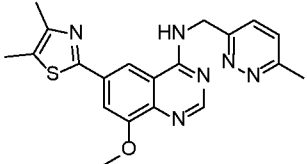
10 purified by preparative HPLC to give the title compound as an off-white solid (6.7 mg, 7%).

¹H NMR (400 MHz, DMSO): δ 8.83 (dd, *J* = 5.8, 5.8 Hz, 1 H), 8.36 (s, 1 H), 8.27 (s, 1 H), 8.09 (d, *J* = 1.5 Hz, 1 H), 8.02 (s, 1 H), 7.55 (d, *J* = 8.7 Hz, 1 H), 7.52-7.46 (m, 2 H), 5.03 (d, *J* = 5.8 Hz, 2 H), 3.98 (s, 3 H), 3.92 (s, 3 H), 2.60 (s, 3 H). LCMS

15 (Method 3): [MH⁺] = 362 at 2.64 min.

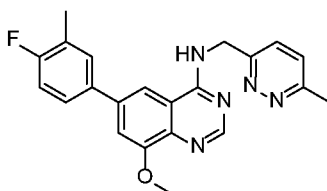
The following compound reported in the table below was prepared according to the same procedure described for the preparation of 8-Methoxy-6-(1-methyl-*1H*-pyrazol-4-yl)-*N*-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine:

Example No.	Chemical Name Structure	Analytical data ¹ H NMR LC-MS
Example 163a	6-(4,5-Dimethylthiazol-2-yl)-8-methoxy- <i>N</i> -((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine	¹ H NMR (400 MHz, DMSO): δ 9.24 (dd, <i>J</i> = 5.8, 5.8 Hz, 1 H), 8.42 (s, 1 H), 8.32 (d, <i>J</i> = 1.6 Hz, 1 H), 7.70 (d, <i>J</i> = 1.6 Hz, 1 H), 7.56 (d, <i>J</i> = 8.7 Hz, 1 H), 7.50 (d, <i>J</i> = 8.7 Hz, 1 H), 5.02 (d, <i>J</i> = 5.8 Hz, 2 H), 4.00 (s, 3 H), 2.60 (s, 3 H), 2.44 (s,

		3 H), 2.38 (s, 3 H). LCMS (Method 3): [MH ⁺] = 393 at 3.43 min.
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Example 164

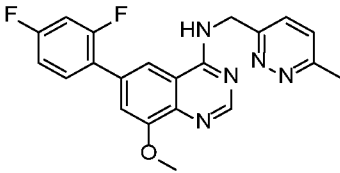
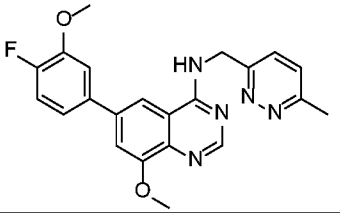
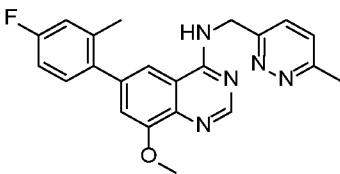
6-(4-Fluoro-3-methylphenyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine

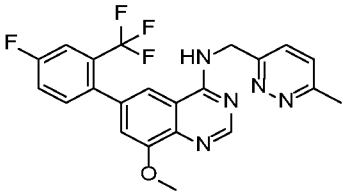
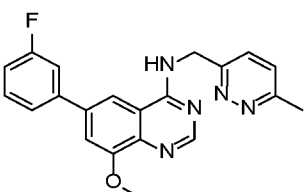
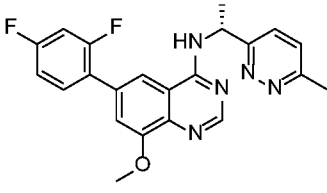
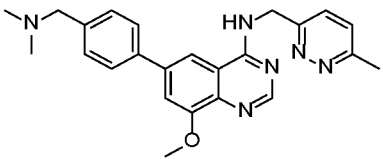
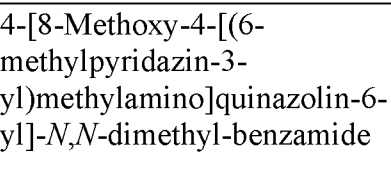


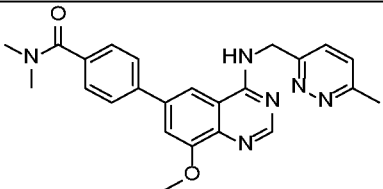
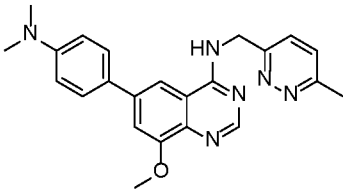
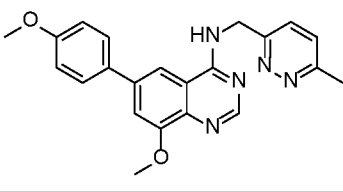
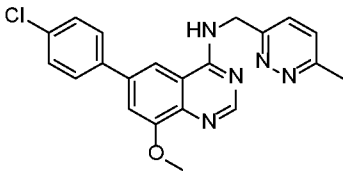
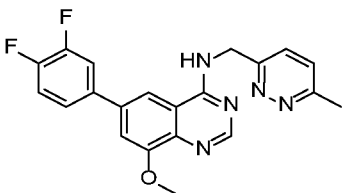
- 5 To a solution of 6-bromo-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine (Intermediate 6) (70 mg, 0.19 mmol) in 1,4-dioxane (4.0 mL) was added 4-fluoro-3-methylphenylboronic acid (33 mg, 0.21 mmol), tetrakis(triphenylphosphine)palladium(0) (20 mg, 0.02 mmol), potassium carbonate (36 mg, 0.26 mmol) and water (0.5 mL). The resulting mixture was heated to 95 °C for 18 h.
- 10 After return to room temperature, the reaction was filtered through Celite®. The Celite® cake was rinsed with ethyl acetate (2 × 20 mL). Combined organic phases were washed with brine (2 × 20 mL), filtered through a hydrophobic frit and the solvent was removed *in vacuo*. The residue was purified by preparative HPLC to give the title compound as an off-white solid (18 mg, 24%).
- 15 ¹H NMR (400 MHz, DMSO) d 9.03 (dd, J=5.8, 5.8 Hz, 1H), 8.41 (s, 1H), 8.15 (d, J=1.8 Hz, 1H), 7.82 (dd, J=2.0, 7.4 Hz, 1H), 7.77 - 7.72 (m, 1H), 7.57 - 7.49 (m, 3H), 7.31 (dd, J=9.1, 9.1 Hz, 1H), 5.03 (d, J=5.8 Hz, 2H), 4.03 (s, 3H), 2.60 (s, 3H), 2.37 (d, J=1.8 Hz, 3H).

LCMS (Method 4): [MH⁺] = 390 at 3.12 min.

The following compounds reported in the table below were prepared according to the same procedure described for the preparation of 6-(4-Fluoro-3-methylphenyl)-8-methoxy-*N*-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine:

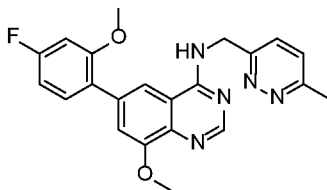
Example No.	Chemical Name Structure	Analytical data ¹ H NMR LC-MS
Example 165	6-(2,4-Difluorophenyl)-8-methoxy- <i>N</i> -((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 9.00 (dd, J = 5.8, 5.8 Hz, 1 H), 8.43 (s, 1 H), 8.02 (s, 1 H), 7.77-7.70 (m, 1 H), 7.50 (dd, J = 8.4, 19.7 Hz, 2 H), 7.45-7.41 (m, 1 H), 7.38 (s, 1 H), 7.30-7.25 (m, 1 H), 4.99 (d, J = 5.8 Hz, 2 H), 3.95 (s, 3 H), 2.58 (s, 3 H). LCMS (Method 3): [MH ⁺] = 394 at 3.68 min.
Example 166	6-(4-Fluoro-3-methoxyphenyl)-8-methoxy- <i>N</i> -((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 9.03 (dd, J = 5.8, 5.8 Hz, 1 H), 8.42 (s, 1 H), 8.14 (d, J = 1.5 Hz, 1 H), 7.60-7.49 (m, 3 H), 7.46-7.35 (m, 2 H), 5.04 (d, J = 5.8 Hz, 2 H), 4.04 (s, 3 H), 4.01 (s, 3 H), 2.60 (s, 3 H). LCMS (Method 4): [MH ⁺] = 406 at 2.97 min.
Example 167	6-(4-Fluoro-2-methylphenyl)-8-methoxy- <i>N</i> -((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.91 (dd, J = 5.8, 5.8 Hz, 1 H), 8.43 (s, 1 H), 7.82 (d, J = 1.3 Hz, 1 H), 7.51 (q, J = 8.7 Hz, 2 H), 7.40 (dd, J = 6.1, 8.5 Hz, 1 H), 7.27-7.23 (m, 2 H), 7.19-7.13 (m, 1 H), 4.98 (d, J = 5.8 Hz, 2 H), 3.95 (s, 3 H), 2.59 (s, 3 H), 2.34 (s, 3 H). LCMS (Method 4): [MH ⁺] = 390 at 3.04 min.
Example 168	6-(4-Fluoro-2-(trifluoromethyl)phenyl)-8-methoxy- <i>N</i> -((6-	¹ H NMR (400 MHz, DMSO): δ 8.91 (dd, J = 5.8, 5.8 Hz, 1 H), 8.46 (s, 1 H), 7.84-7.80 (m, 2 H), 7.73-7.62 (m, 2 H), 7.51

	<p>methylpyridazin-3-yl)methyl)quinazolin-4-amine</p> 	<p>(dd, $J = 8.7, 12.1$ Hz, 2 H), 7.22 (s, 1 H), 4.97 (d, $J = 5.8$ Hz, 2 H), 3.91 (s, 3 H), 2.59 (s, 3 H). LCMS (Method 3): $[MH^+] = 444$ at 4.23 min.</p>
Example 169	<p>6-(3-Fluorophenyl)-8-methoxy-<i>N</i>-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine</p> 	<p>1H NMR (400 MHz, DMSO): δ 9.06 (dd, $J = 5.9, 5.9$ Hz, 1 H), 8.43 (s, 1 H), 8.25 (d, $J = 1.6$ Hz, 1 H), 7.78 (d, $J = 7.8$ Hz, 2 H), 7.61-7.55 (m, 3 H), 7.51 (d, $J = 8.7$ Hz, 1 H), 7.30-7.24 (m, 1 H), 5.04 (d, $J = 5.8$ Hz, 2 H), 4.04 (s, 3 H), 2.60 (s, 3 H). LCMS (Method 3): $[MH^+] = 376$ at 3.68 min.</p>
Example 170	<p>6-(2,4-Difluorophenyl)-8-methoxy-<i>N</i>-[(1<i>R</i>)-1-(6-methylpyridazin-3-yl)ethyl]quinazolin-4-amine</p> 	<p>1H NMR (400 MHz, DMSO): δ 8.35 (s, 1 H), 8.14 (s, 1 H), 7.77-7.69 (m, 1 H), 7.59 (d, $J = 8.7$ Hz, 1 H), 7.49 (d, $J = 8.7$ Hz, 1 H), 7.43-7.35 (m, 2 H), 7.29-7.23 (m, 1 H), 5.69 (d, $J = 8.5$ Hz, 1 H), 3.93 (s, 3 H), 3.79 (s, 3 H), 1.66 (d, $J = 7.2$ Hz, 3 H). LCMS (Method 3): $[MH^+] = 408$ at 4.22 min.</p>
Example 171	<p>6-[4-[(Dimethylamino)methyl]phenyl]-8-methoxy-<i>N</i>-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine formate</p> 	<p>1H NMR (400 MHz, DMSO): δ 9.04 (brs, 1 H), 8.40 (s, 1 H), 8.21 (s, 1 H), 8.18 (d, $J = 1.1$ Hz, 1 H), 7.85 (d, $J = 8.2$ Hz, 2 H), 7.55 (dd, $J = 3.5, 5.1$ Hz, 2 H), 7.52-7.44 (m, 3 H), 5.02 (s, 2 H), 4.02 (s, 3 H), 3.52 (s, 2 H), 2.59 (s, 3 H), 2.22 (s, 6 H). LCMS (Method 3): $[MH^+] = 415$ at 3.24 min.</p>
Example 172	<p>4-[8-Methoxy-4-[(6-methylpyridazin-3-yl)methylamino]quinazolin-6-yl]-<i>N,N</i>-dimethyl-benzamide</p> 	<p>1H NMR (400 MHz, DMSO): δ 9.11 (dd, $J = 5.3, 5.3$ Hz, 1 H), 8.46 (s, 1 H), 8.28 (s, 1 H), 7.99 (d, $J = 8.3$ Hz, 2 H), 7.64-7.58 (m, 4 H), 7.54 (d, $J = 8.6$</p>

		^1H NMR (400 MHz, CDCl_3): δ 5.07 (d, $J = 5.8$ Hz, 2 H), 4.07 (s, 3 H), 3.04 (m, 6 H), 2.64 (s, 3 H). LCMS (Method 4): $[\text{MH}^+] = 429$ at 2.40 min.
Example 173	6-[4-(Dimethylamino)phenyl]-8-methoxy- <i>N</i> -[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine 	^1H NMR (400 MHz, CDCl_3): δ 8.67 (s, 1 H), 7.58-7.50 (m, 5 H), 7.38-7.32 (m, 2 H), 6.82 (d, $J = 8.9$ Hz, 2 H), 5.10 (d, $J = 4.1$ Hz, 2 H), 4.09 (s, 3 H), 3.03 (s, 6 H), 2.74 (s, 3 H). LCMS (Method 4): $[\text{MH}^+] = 401$ at 2.78 min.
Example 174	8-Methoxy-6-(4-methoxyphenyl)- <i>N</i> -[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine 	^1H NMR (400 MHz, DMSO): δ 9.01 (dd, $J = 5.9, 5.9$ Hz, 1 H), 8.39 (s, 1 H), 8.17 (s, 1 H), 8.14 (d, $J = 1.6$ Hz, 1 H), 7.86-7.83 (m, 2 H), 7.57-7.48 (m, 3 H), 7.10 (d, $J = 8.9$ Hz, 2 H), 5.03 (d, $J = 5.8$ Hz, 2 H), 4.02 (s, 3 H), 3.84 (s, 3 H), 2.60 (s, 3 H). LCMS (Method 4): $[\text{MH}^+] = 388$ at 2.83 min.
Example 175	6-(4-chlorophenyl)-8-methoxy- <i>N</i> -[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine 	^1H NMR (400 MHz, DMSO): δ 9.06 (dd, $J = 5.9, 5.9$ Hz, 1 H), 8.42 (s, 1 H), 8.23-8.19 (m, 1 H), 7.95-7.92 (m, 2 H), 7.61 (d, $J = 8.8$ Hz, 2 H), 7.58-7.55 (m, 2 H), 7.50 (d, $J = 8.7$ Hz, 1 H), 5.03 (d, $J = 5.8$ Hz, 2 H), 4.03 (s, 3 H), 2.60 (s, 3 H). LCMS (Method 4): $[\text{MH}^+] = 392$ at 3.18 min.
Example 176	6-(3,4-Difluorophenyl)-8-methoxy- <i>N</i> -[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine 	^1H NMR (400 MHz, DMSO): δ 9.04 (dd, $J = 5.9, 5.9$ Hz, 1 H), 8.41 (s, 1 H), 8.20 (d, $J = 1.6$ Hz, 1 H), 8.00 (ddd, $J = 2.3, 7.8, 12.5$ Hz, 1 H), 7.79-7.75 (m, 1 H), 7.65-7.59 (m, 1 H), 7.55 (d, $J = 8.8$ Hz, 2 H), 7.49 (d, $J = 8.7$ Hz, 1 H), 5.02 (d, $J = 5.8$ Hz, 2 H), 4.02 (s, 3 H), 2.59 (s, 3 H). LCMS (Method 3): $[\text{MH}^+] = 394$ at 3.79 min.

Example 176a

6-(4-Fluoro-2-methoxyphenyl)-8-methoxy-*N*-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine

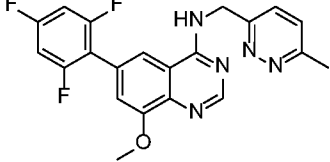
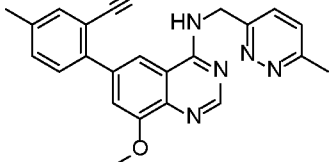
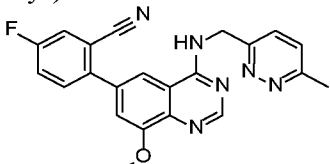
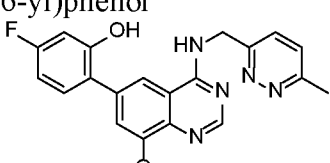
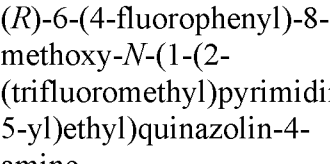


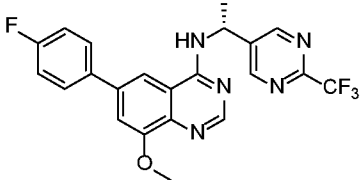
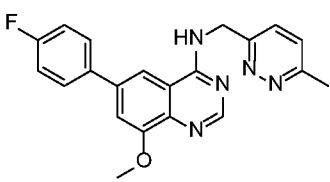
To a solution of 6-bromo-8-methoxy-*N*-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine (intermediate 6) (70 mg, 0.19 mmol) in 1,2-dimethoxyethane (3.0 mL) was added (4-fluoro-2-methoxyphenyl)boronic acid (41 mg, 0.24 mmol), [1,1'-*bis*(diphenylphosphino)ferrocene] dichloropalladium(II) complex with dichloromethane (8.2 mg, 0.01 mmol), caesium carbonate (130 mg, 0.40 mmol) and water (0.3 mL). The resulting mixture was heated to 95 °C for 18 h. After return to room temperature, the reaction was filtered through Celite®. The Celite® cake was rinsed with ethyl acetate (2 × 20 mL). Combined organic phases were washed with brine (2 × 20 mL), filtered through a hydrophobic frit and the solvent was removed *in vacuo*. The residue was purified by preparative HPLC to give the title compound as an off-white solid (35 mg, 45%).

¹H NMR (400 MHz, DMSO): δ 8.92 (dd, *J* = 5.8, 5.8 Hz, 1 H), 8.41 (s, 1 H), 7.91 (d, *J* = 1.5 Hz, 1 H), 7.54-7.46 (m, 3 H), 7.37 (d, *J* = 1.4 Hz, 1 H), 7.10 (dd, *J* = 2.4, 11.5 Hz, 1 H), 6.97-6.91 (m, 1 H), 4.99 (d, *J* = 5.6 Hz, 2 H), 3.93 (s, 3 H), 3.84 (s, 3 H), 2.59 (s, 3 H). LCMS (Method 3): [MH⁺] = 406 at 3.97 min.

The following compounds reported in the table below were prepared *via* adaptation of the above procedure starting from appropriate intermediate reported in table.

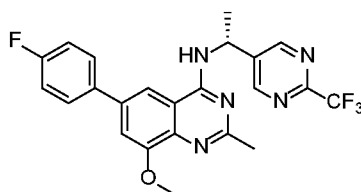
Example No.	Chemical Name Structure	Analytical data ¹ H NMR LC-MS	Starting Intermediate
Example 177	8-Methoxy- <i>N</i> -((6-methylpyridazin-3-yl)methyl)-6-(2,4,6-	¹ H NMR (400 MHz, DMSO): δ 9.00 (dd, <i>J</i> = 5.8, 5.8 Hz, 1 H), 8.47 (s,	Intermediate 6

	trifluorophenyl)quinazolin-4-amine 	1 H), 7.98 (s, 1 H), 7.54 (d, J = 8.5 Hz, 1 H), 7.49 (d, J = 8.7 Hz, 1 H), 7.43 (dd, J = 8.6, 8.6 Hz, 2 H), 7.33 (s, 1 H), 4.99 (d, J = 5.8 Hz, 2 H), 3.93 (s, 3 H), 2.59 (s, 3 H). LCMS (Method 3): [MH ⁺] = 412 at 3.66 min.	
Example 178	2-(8-Methoxy-4-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-6-yl)-5-methylbenzonitrile 	¹ H NMR (400 MHz, DMSO): δ 9.05 (dd, J = 5.7, 5.7 Hz, 1 H), 8.47 (s, 1 H), 8.08 (d, J = 1.8 Hz, 1 H), 7.86 (s, 1 H), 7.69 (s, 2 H), 7.54 (d, J = 8.7 Hz, 1 H), 7.50-7.47 (m, 2 H), 5.02 (d, J = 5.6 Hz, 2 H), 3.99 (s, 3 H), 2.60 (s, 3 H), 2.45 (s, 3 H). LCMS (Method 3): [MH ⁺] = 387 at 3.88 min	Intermediate 6
Example 179	5-Fluoro-2-(8-methoxy-4-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-6-yl)benzonitrile 	¹ H NMR (400 MHz, DMSO): δ 9.07 (dd, J = 5.8, 5.8 Hz, 1 H), 8.48 (s, 1 H), 8.10-8.05 (m, 2 H), 7.87-7.76 (m, 2 H), 7.55-7.48 (m, 3 H), 5.02 (d, J = 5.8 Hz, 2 H), 3.99 (s, 3 H), 2.60 (s, 3 H). LCMS (Method 4): [MH ⁺] = 401 at 2.71 min.	Intermediate 6
Example 180	5-Fluoro-2-(8-methoxy-4-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-6-yl)phenol 	¹ H NMR (400 MHz, DMSO): δ 10.21 (s, 1 H), 8.92 (dd, J = 5.6, 5.6 Hz, 1 H), 8.41 (s, 1 H), 7.94 (d, J = 1.3 Hz, 1 H), 7.54-7.44 (m, 4 H), 6.81-6.76 (m, 2 H), 4.99 (d, J = 5.6 Hz, 2 H), 3.93 (s, 3 H), 2.60 (s, 3 H). LCMS (Method 3): [MH ⁺] = 392 at 3.27 min.	Intermediate 6
Example 181	(R)-6-(4-fluorophenyl)-8-methoxy-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine 	LCMS (Method 5): 0.79 min, m/z 443.8 [M+2] ⁺ , ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 9.12 (s, 2 H), 8.55 (d, J=7.0 Hz, 1 H), 8.37 (s, 1 H), 8.14 (d,	Intermediate 5

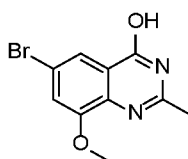
		$J=1.3$ Hz, 1 H), 7.83 - 7.96 (m, 2 H), 7.48 (d, $J=1.3$ Hz, 1 H), 7.35 (t, $J=8.8$ Hz, 2 H), 5.50 - 5.60 (m, 1 H), 3.97 (s, 3 H), 1.69 (d, $J=7.0$ Hz, 3 H).	
Example 182	6-(4-fluorophenyl)-8-methoxy- <i>N</i> -((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine 	LCMS (Method 6): 0.88 min, 375.9 m/z [M+H] ⁺ , ¹ H NMR (400 MHz, ACETONITRILE-d ₃) δ □ ppm 8.43 (s, 1 H), 7.66 - 7.84 (m, 3 H), 7.53 (d, $J=8.8$ Hz, 1 H), 7.44 (d, $J=1.3$ Hz, 1 H), 7.39 (d, $J=8.8$ Hz, 1 H), 7.20 - 7.30 (m, 2 H), 7.00 - 7.15 (m, 1 H), 5.06 (s, 2 H), 4.04 (s, 3 H), 2.62 (s, 3 H).	Intermediate 6

Example 183

(*R*)-6-(4-Fluorophenyl)-8-methoxy-2-methyl-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine



Step 1: Preparation of 6-bromo-8-methoxy-2-methylquinazolin-4-ol

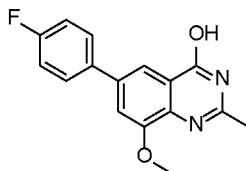


To a solution of 2-amino-5-bromo-3-methoxybenzoic acid hydrobromide (0.5 g, 1.53 mmol) (Intermediate 1) in *N,N*-dimethylformamide (5mL) was successively added

1-hydroxybenzotriazole hydrate (0.23 g, 1.68 mmol), *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.32 g, 1.68 mmol) and *N,N*-diisopropylethylamine (0.29 mL, 1.68 mmol). The resulting mixture was stirred at room temperature for 2 hours. The reaction was then cooled to 0 °C and 28% aqueous ammonium hydroxide solution
5 (1.5 mL) was added dropwise and the reaction was allowed to warm to room temperature overnight. The reaction was concentrated under reduced pressure and the residue was dissolved in triethyl orthoacetate (3.4 mL, 18.36 mmol), acetic acid (0.84 mL, 14.69 mmol) was added dropwise and the reaction was heated to 120 °C for 2 hours. The reaction was then cooled and concentrated. The crude residue was triturated with *iso*-
10 propanol and filtered to give the title compound as an off-white solid (0.10 g, 30%).

LCMS (Method 3): [MH⁺] = 268/270 at 3.28 min.

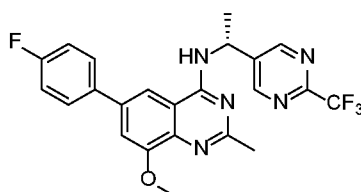
Step 2: Preparation of 6-(4-fluorophenyl)-8-methoxy-2-methylquinazolin-4-ol



Nitrogen was bubbled for 5 min through a mixture of 6-bromo-8-methoxy-2-methylquinazolin-4-ol (0.10 g, 0.37 mmol), 4-fluorophenylboronic acid (57 mg, 0.409 mmol), cesium carbonate (0.46 g, 1.41 mmol), water (0.5 mL) in 1,4-dioxane (2 mL), then [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (15 mg, 0.0186 mmol) was added. The reaction was heated to 120 °C for 4 hours. After return to room temperature, the reaction was diluted with water (10 mL) and ethyl acetate (10 mL), the reaction was then filtered and the collected solid was washed with water (10 mL) and diethyl ether (10 mL) to give the title compound as a grey solid (0.10 g, 94%).

LCMS (Method 3): [MH⁺] = 285 at 3.59 min.

Step 3: Preparation of (R)-6-(4-fluorophenyl)-8-methoxy-2-methyl-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine



15

To a solution of 6-(4-Fluorophenyl)-8-methoxy-2-methylquinazolin-4-ol (100 mg, 0.35 mmol) in *N,N*-dimethylformamide (2 mL) was successively added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (201 mg, 0.39 mmol) and diisopropylethylamine (0.31 mL, 1.76 mmol). The resulting mixture was heated to 40 °C and stirred for 20 min, (*R*)-1-(2-(trifluoromethyl)pyrimidin-5-yl)ethan-1-amine (88 mg, 0.387 mmol) was then added and the heating was maintained at 40 °C for 4 hours. After

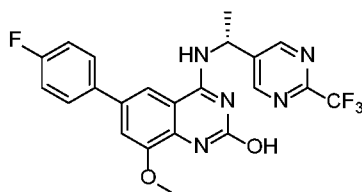
20

return to room temperature, the reaction was directly purified by preparative HPLC to give the title compound (15.1 mg, 9%).

¹H NMR (400 MHz, DMSO): δ 9.22 (s, 2 H), 8.55 (d, J = 6.8 Hz, 1 H), 8.18 (s, 1 H), 7.95 (dd, J = 5.6, 8.6 Hz, 2 H), 7.51 (s, 1 H), 7.42 (dd, J = 8.7, 8.7 Hz, 2 H), 5.73-5.66 (m, 1 H), 4.03 (s, 3 H), 2.46 (s, 3 H), 1.78 (d, J = 7.1 Hz, 3 H). LCMS (Method 4): [MH⁺] = 458 at 4.97 min.

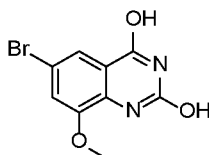
Example 184

(R)-6-(4-Fluorophenyl)-8-methoxy-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)-amino)-quinazolin-2-ol



10

Step 1: Preparation of 6-bromo-8-methoxyquinazoline-2,4-diol

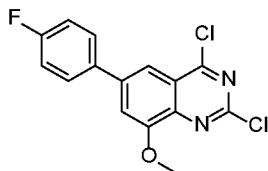


A mixture of 2-amino-5-bromo-3-methoxybenzoic acid hydrobromide (Intermediate 1) (1.0 g, 3.06 mmol) and urea (1.84 g, 30.58 mmol) was heated to 170 °C for 18 hours. After return to room temperature, the reaction was diluted with water (50 mL) and filtered. The collected solid was washed with water (20 mL) and diethyl ether (20 mL) to give the title compound as a light brown solid (0.7 g, 84%) which was taken on to the next step without further purification.

LCMS (Method 4): [MH⁺] = 271 at 3.17 min.

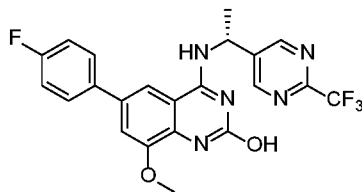
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Step 2: Preparation of 2,4-dichloro-6-(4-fluorophenyl)-8-methoxyquinazoline



Nitrogen was bubbled for 5 min through a mixture of 6-bromo-8-methoxyquinazoline-2,4-diol (0.5 g, 1.84 mmol), 4-fluorophenylboronic acid (284 mg, 2.03 mmol), cesium carbonate (2.28 g, 7.01 mmol) and water (2.5 mL) in 1,4-dioxane (10.0 mL), then [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (75 mg, 0.09 mmol) was added. The resulting mixture was heated to 120 °C for 4 hours. After return to room temperature, the solvent was removed *in vacuo*. The residue was dry loaded onto silica gel and purified by chromatography on silica gel, eluting with 0-5% methanol in dichloromethane to give 160 mg of a crude product. This product (68 mg) was suspended in phosphorus oxychloride (1 mL, 10.73 mmol) and *N,N*-diisopropylethylamine (0.026 mL, 0.147 mmol) was added dropwise followed by a drop of *N,N*-dimethylformamide. The solution was then heated to 130 °C for 18 hours. After return to room temperature, the solvent was removed *in vacuo*. The residue was taken up with H₂O (10 mL) and stirred for one hour at room temperature. The reaction was filtered to give the title compound as an off-white solid (44 mg, 65%).

LCMS (Method 4): [MH⁺] = 323 at 5.76 min.

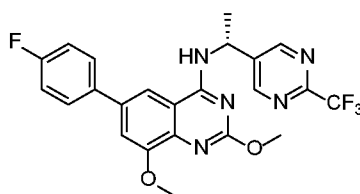
Step 3: Preparation of (*R*)-6-(4-fluorophenyl)-8-methoxy-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)-amino)-quinazolin-2-ol

A mixture of 2,4-dichloro-6-(4-fluorophenyl)-8-methoxyquinazoline (44 mg, 0.13 mmol), (*R*)-1-(2-(trifluoromethyl)pyrimidin-5-yl)ethan-1-amine (35 mg, 0.13 mmol) and *N,N*-diisopropylethylamine (0.046 mL, 0.27 mmol) in dichloromethane (2 mL) was stirred at room temperature for 2 hours. The reaction was then diluted with H₂O (10 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic phases were passed through a hydrophobic frit and concentrated *in vacuo*. The residue was dissolved in acetic acid (2 mL) and heated to 70 °C for 2 hours. After return to room temperature, the reaction was concentrated *in vacuo* and the residue was purified by preparative HPLC to give the title compound as an off-white solid (6.1 mg, 10%).

¹H NMR (400 MHz, DMSO): δ 10.04 (s, 1 H), 9.15 (s, 2 H), 8.68 (d, J = 7.2 Hz, 1 H), 8.04 (s, 1 H), 7.87-7.82 (m, 2 H), 7.48 (d, J = 1.4 Hz, 1 H), 7.36 (dd, J = 8.9, 8.9 Hz, 2 H), 5.66-5.60 (m, 1 H), 3.97 (s, 3 H), 1.71 (d, J = 7.2 Hz, 3 H). LCMS (Method 4): [MH⁺] = 460 at 4.5 min.

Example 185

(*R*)-6-(4-Fluorophenyl)-2,8-dimethoxy-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine



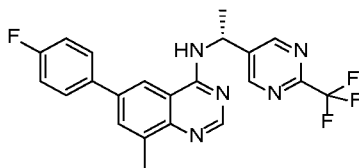
A mixture of 2,4-dichloro-6-(4-fluorophenyl)-8-methoxyquinazoline (143 mg, 0.44 mmol), (*R*)-1-(2-(trifluoromethyl)pyrimidin-5-yl)ethan-1-amine (117 mg, 0.44 mmol) and *N,N*-diisopropylethylamine (0.15 mL, 0.89 mmol) in dichloromethane (5 mL) was stirred at room temperature for 2 hours. The reaction was then diluted with H₂O (10 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic phases were passed through a hydrophobic frit and concentrated *in vacuo*. The residue was dissolved

in methanol (2 mL) and sodium methoxide (25% in methanol) (0.13 mL, 0.58 mmol) was added. The mixture was heated to 80 °C for 2 hours. After return to room temperature, the reaction was concentrated *in vacuo* and the residue was purified by preparative HPLC to give the title compound as a brown solid (3.5 mg, 3.2%).

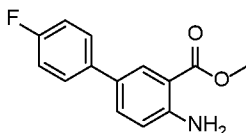
- 5 ¹H NMR (400 MHz, DMSO): δ 9.17 (s, 2 H), 8.68 (d, J = 6.9 Hz, 1 H), 8.15 (d, J = 1.8 Hz, 1 H), 7.93-7.88 (m, 2 H), 7.47 (d, J = 1.5 Hz, 1 H), 7.38 (dd, J = 8.9, 8.9 Hz, 2 H), 5.61 (dd, J = 6.8, 6.8 Hz, 1 H), 3.99 (s, 3 H), 3.83 (s, 3 H), 1.73 (d, J = 7.2 Hz, 3 H).
LCMS (Method 4): [MH⁺] = 474 at 3.87 min.

Example 186

- 10 **(R)-6-(4-Fluorophenyl)-8-iodo-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine**



Step 1: Preparation of methyl 4-amino-4'-fluoro-[1,1'-biphenyl]-3-carboxylate

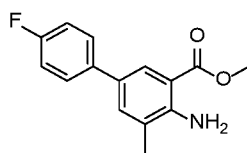


- 15 Nitrogen was bubbled for 5 min through a mixture of methyl 2-amino-5-bromobenzoate (2.00 g, 8.69 mmol), 4-fluorophenylboronic acid, pinacol ester (2.90 g, 12.04 mmol), potassium phosphate tribasic (3.69 g, 17.39 mmol), water (3.5 mL) in *N,N*-dimethylformamide (10.5 mL), then [1,1'-*bis*(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane
20 (710 mg, 0.87 mmol) was added. The resulting mixture was heated to 100 °C for 1.25 hours. After return to room temperature, the reaction was diluted with water (100 mL)

and diethyl ether (100 mL) and the organic phase was separated. The aqueous phase was extracted further with diethyl ether (100 mL) and then Ethyl acetate (100 mL). The organic phases were combined, washed with water (100 mL), dried over MgSO₄ and the solvent was removed *in vacuo*. The residue was purified by chromatography on silica gel eluting with 5–35% Ethyl acetate in cyclohexane to give the title compound as an off-white solid (2.08 g, 97%).

¹H NMR (400 MHz, CDCl₃): δ 8.06 (d, J = 2.3 Hz, 1 H), 7.50-7.44 (m, 3 H), 7.08 (dd, J = 8.7, 8.7 Hz, 2 H), 6.74 (d, J = 8.6 Hz, 1 H), 5.78 (s, 2 H), 3.90 (s, 3 H).

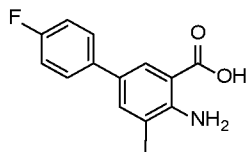
Step 2: Preparation of methyl 4-amino-4'-fluoro-5-iodo-[1,1'-biphenyl]-3-carboxylate



To a solution of methyl 4-amino-4'-fluoro-[1,1'-biphenyl]-3-carboxylate (2.08 g, 8.48 mmol) in dichloromethane (25 mL) was added *bis*(pyridine)iodonium tetrafluoroborate (4.73 g, 12.72 mmol) and TFA (2.1 mL, 27.42 mmol). The resulting mixture was stirred at room temperature for 2 days. HPLC analysis showed 70 % conversion and further *bis*(pyridine)iodonium tetrafluoroborate (1.25 g, 3.36 mmol) was added and the stirring was maintained for a further 2.5 hours. The reaction was diluted with dichloromethane (25 mL) and cautiously treated with a solution of NaHCO₃ (7 g, 83 mmol) in water (100 mL). The aqueous layer was collected and further extracted with dichloromethane (2 × 25 mL). The organic phases were combined, washed with an 8 % sodium thiosulphate aqueous solution (100 mL), filtered through a hydrophobic frit and the solvent was removed *in vacuo*. The residue was purified by chromatography on silica gel eluting with 0–25% Ethyl acetate in cyclohexane to give the title compound as an off-white solid (2.71 g, 86%).

^1H NMR (400 MHz, CDCl_3): δ 8.10-8.07 (m, 1 H), 8.04-8.00 (m, 1 H), 7.46-7.41 (m, 2 H), 7.09 (dd, $J = 8.6, 8.6$ Hz, 2 H), 6.48-6.37 (m, 2 H), 3.91 (s, 3 H).

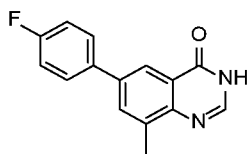
Step 3: Preparation of 4-amino-4'-fluoro-5-iodo-[1,1'-biphenyl]-3-carboxylic acid



5 To a solution of methyl 4-amino-4'-fluoro-5-iodo-[1,1'-biphenyl]-3-carboxylate (2.59 g, 6.98 mmol) in 1,4-dioxane (25 mL) and water (5 mL) was added lithium hydroxide monohydrate (1.75 g, 41.87 mmol). The mixture was stirred at room temperature for 18 hours. The reaction was diluted with water (100 mL) and diethyl ether (100 mL) and separated. The aqueous phase was acidified with 1N HCl (45 mL) to pH =
10 1 and extracted with dichloromethane (3×50 mL). The organic phases were combined, filtered through a hydrophobic frit and the solvent was removed *in vacuo* to give the title compound as an off-white solid (2.39 g, 96%).

^1H NMR (400 MHz, DMSO): δ 13.17 (s, 1 H), 8.18 (d, $J = 2.0$ Hz, 1 H), 8.09 (d, $J = 2.3$ Hz, 1 H), 7.65 (dd, $J = 5.4, 8.5$ Hz, 2 H), 7.27 (dd, $J = 8.8, 8.8$ Hz, 2 H), 6.84 (s, 2
15 H).

Step 4: Preparation of 6-(4-fluorophenyl)-8-iodoquinazolin-4(3*H*)-one

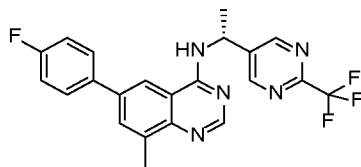


A solution of 4-amino-4'-fluoro-5-iodo-[1,1'-biphenyl]-3-carboxylic acid (2.39 g, 6.69 mmol) in formamide (4 mL) was heated to 130 °C for 16 hours. After return to room
20 temperature, the reaction was diluted with water (20 mL) and stirred for 20 minutes before

filtering. The solid was washed with water (3×5 mL) then 10% MeOH in diethyl ether (3×5 mL) to give the title compound as an off-white solid (2.14 g, 87%).

$^1\text{H NMR}$ (400 MHz, DMSO): δ 12.57 (s, 1 H), 8.66 (s, 1 H), 8.36 (s, 1 H), 8.28 (s, 1 H), 7.89 (dd, $J = 5.6, 7.8$ Hz, 2 H), 7.38 (dd, $J = 8.6, 8.6$ Hz, 2 H).

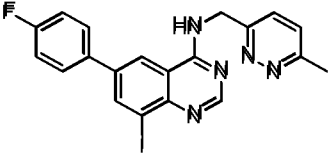
5 Step 5: Preparation of (*R*)-6-(4-fluorophenyl)-8-iodo-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine



To a solution of 6-(4-fluorophenyl)-8-iodoquinazolin-4-(3*H*)-one (1.14 g, 3.11 mmol) in *N,N*-dimethylformamide (10 mL) was successively added (benzotriazol-1-
 10 yloxy)tripyrrolidinophosphonium hexafluorophosphate (2.03 g, 1.25 mmol) and diisopropylethylamine (2.7 mL, 15.57 mmol). The resulting mixture was heated to 45 °C for one hour then (*R*)-1-(2-(trifluoromethyl)pyrimidin-5-yl)ethan-1-amine hydrochloride (0.96 g, 4.2 mmol) was added and the heating was maintained at 45 °C for 2 hours. After
 15 return to room temperature, the mixture was diluted with ethyl acetate (75 mL) and water (175 mL). The organic phase was washed with brine (2×20 mL), passed through a hydrophobic frit and the solvent was removed *in vacuo*. The residue was purified by chromatography on silica gel eluting with 0–15% ethyl acetate in dichloromethane to give the title compound as an off-white solid (1.27 g, 75%).

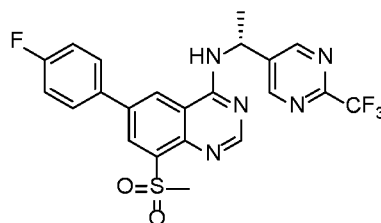
$^1\text{H NMR}$ (400 MHz, DMSO): δ 9.18 (s, 2 H), 8.88 (d, $J = 6.9$ Hz, 1 H), 8.71 (d, $J = 1.8$ Hz, 1 H), 8.67 (d, $J = 1.8$ Hz, 1 H), 8.51 (s, 1 H), 7.95-7.90 (m, 2 H), 7.40 (dd, $J = 8.9, 8.9$ Hz, 2 H), 5.73-5.67 (m, 1 H), 1.75 (d, $J = 7.2$ Hz, 3 H).

The following compound reported in the table below was prepared *via* adaptation of the above procedure using the appropriate amine.

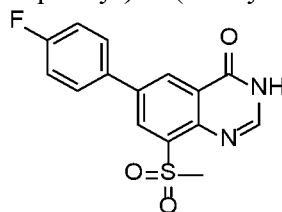
Example No.	Chemical name Structure	Analytical data ¹ H NMR LC-MS
Example 187	6-(4-fluorophenyl)-8-iodo-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine 	LCMS (Method 5): 0.96 min, m/z 472.0. ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 9.26 (br t, J = 5.62 Hz, 1 H), 8.64 (s, 2 H), 8.47 (s, 1 H), 7.88 (br dd, J = 8.60, 5.51 Hz, 2 H), 7.53 (d, J = 8.60 Hz, 1 H), 7.45 (d, J = 8.60 Hz, 1 H), 7.34 (br t, J = 8.71 Hz, 2 H), 5.02 (br d, J = 5.29 Hz, 2 H), 2.56 (s, 3 H).

Example 188

(R)-6-(4-fluorophenyl)-8-(methylsulfonyl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine



5 Step 1: Preparation of 6-(4-fluorophenyl)-8-(methylsulfonyl)quinazolin-4(3H)-one



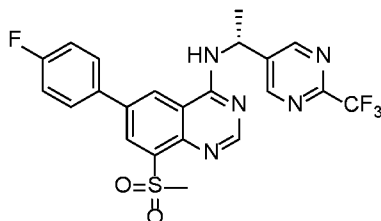
To a solution of 6-(4-fluorophenyl)-8-iodoquinazolin-4(3H)-one (200 mg, 0.546 mmol) in dry DMSO (1.5 mL), sodium methanesulfinate (67 mg, 0.655 mmol) was added followed by copper(I) iodide (10.40 mg, 0.055 mmol) and *L*-proline (13 mg, 0.109 mmol).

10 The reaction was heated to 110 °C and stirred for 18h. A second addition of all reagents led to complete consumption of the starting material. The reaction mixture was cooled to RT and loaded onto column. Purification by RP flash chromatography (Biotage Isolera, C8 40 g cartridge, gradient elution from 0 to 80% B in A; A: water/MeCN 95:5 + 0.1%

HCOOH, B: MeCN/water 95:5 + 0.1% HCOOH) yielded the titled compound (52 mg, 0.163 mmol, 30%) as white powder.

LCMS (Method 5): 0.81 min, 319 [M+H]⁺.

Step 2: Preparation of (*R*)-6-(4-fluorophenyl)-8-(methylsulfonyl)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine

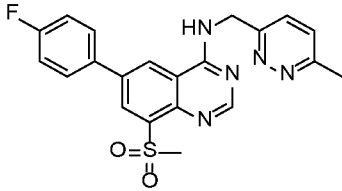


To a suspension of 6-(4-fluorophenyl)-8-(methylsulfonyl)quinazolin-4(3H)-one (52 mg, 0.163 mmol) in DMF (1 mL), (7-azabenzotriazol-1-yl)oxy)tripyrrolidinophosphonium hexafluorophosphate (94 mg, 0.180 mmol) and diisopropylethylamine (0.086 mL, 0.490 mmol) were added followed after 10 min by (*R*)-1-(2-(trifluoromethyl)pyrimidin-5-yl)ethan-1-amine HCl (56 mg, 0.245 mmol). The resulting mixture was stirred at RT for 16h. Purification by RP flash chromatography (Biotage Isolera, Ultra SNAP 30g cartridge, gradient elution from 0 to 90% of B in A; A: water/MeCN 95:5 + 0.1% HCOOH, B: MeCN/water 95:5 + 0.1% HCOOH) yielded impure titled compound. A second purification by flash chromatography (Biotage Isolera, KP-NH 28g cartridge, gradient elution from 5% to 100% EtOAc in heptane) yielded the titled compound (20 mg, 0.041 mmol, 25 % yield) as pale yellow powder.

LCMS (Method 5): 1.14 min, 492 [M+H]⁺.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.16 (s, 2 H), 9.04 (br d, J = 6.61 Hz, 1 H), 8.97 (s, 1 H), 8.58 (s, 1 H), 8.53 (d, J = 1.76 Hz, 1 H), 7.89 (dd, J = 8.60, 5.29 Hz, 2 H), 7.41 (t, J = 8.82 Hz, 2 H), 5.60 - 5.70 (m, 1 H), 3.53 (s, 3 H), 1.72 (d, J = 7.28 Hz, 3 H).

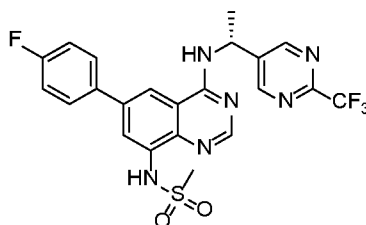
The following compound reported in the table below was prepared *via* adaptation of the above procedure using the appropriate amine.

Example No.	Chemical name Structure	Analytical data ¹ H NMR LC-MS
Example 189	6-(4-fluorophenyl)- <i>N</i> -((6-methylpyridazin-3-yl)methyl)-8-(methylsulfonyl)quinazolin-4-amine 	LCMS (Method 5): 0.82 min, m/z 424.0. ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 9.48 (br t, J = 5.18 Hz, 1 H), 8.92 - 9.01 (m, 1 H), 8.58 (s, 1 H), 8.55 (d, J = 1.54 Hz, 1 H), 7.88 (br dd, J = 8.49, 5.40 Hz, 2 H), 7.57 (d, J = 8.60 Hz, 1 H), 7.47 (d, J = 8.60 Hz, 1 H), 7.33 - 7.50 (m, 2 H), 5.04 (br d, J = 4.41 Hz, 2 H), 3.55 (s, 3 H), 2.56 (s, 3 H).

Example 190

(*R*)-*N*-(6-(4-fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-

5 yl)ethyl)amino)quinazolin-8-yl)methanesulfonamide



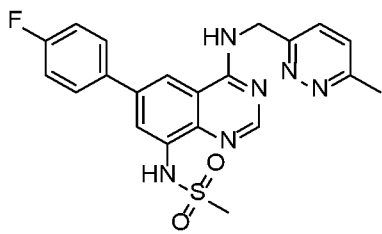
To a solution of (*R*)-6-(4-fluorophenyl)-8-iodo-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine (60 mg, 0.111 mmol) in 1,4-Dioxane (1.5 mL), methanesulfonamide (14 mg, 0.145 mmol), copper(I) iodide (2.119 mg, 0.011 mmol), *L*-proline (2.56 mg, 0.022 mmol) and potassium carbonate (46 mg, 0.334 mmol) were added. The resulting mixture was heated to 150 °C for 6h. The reaction was diluted with DCM and water was added. The two phases were separated, the aqueous layer was extracted with DCM (2 x 10 mL) and the combined organic phase was filtered through a PhaseSeparator tube. Volatiles were removed under reduced pressure.

Purification by RP flash chromatography (Biotage Isolera, Ultra SNAP 30g cartridge, gradient elution from 5% to 100% of B in A; A: water/MeCN 95:5 + 0.1% HCOOH, B: MeCN/water 95:5 + 0.1% HCOOH) yielded the titled compound (9 mg, 0.018 mmol, 16 % yield) as pale beige powder.

5 LCMS (Method 5): 1.17 min, 507 [M+H]⁺.

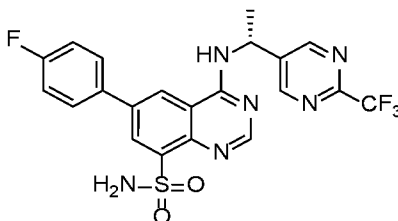
¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.14 (s, 3 H), 8.71 - 8.86 (m, 1 H), 8.47 (s, 1 H), 8.36 (br s, 1 H), 7.95 (s, 1 H), 7.81 (br dd, J = 8.16, 5.73 Hz, 2 H), 7.37 (br t, J = 8.71 Hz, 2 H), 5.66 (br s, 1 H), 3.12 (s, 3 H), 1.71 (br d, J = 7.06 Hz, 3 H).

The following compound reported in the table below was prepared *via* adaptation
10 of the above procedure.

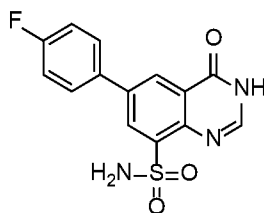
Example No.	Chemical name Structure	Analytical data ¹ H NMR LC-MS
Example 191	<i>N</i> -(6-(4-fluorophenyl)-4-oxo-3,4-dihydroquinazolin-8-yl)methanesulfonamide 	LCMS (Method 5): 0.79 min, m/z 439.0. ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 9.21 (br s, 1 H), 8.47 (s, 1 H), 8.33 (br s, 1 H), 7.97 (s, 1 H), 7.80 (br dd, J = 8.27, 5.62 Hz, 2 H), 7.53 (d, J = 8.60 Hz, 1 H), 7.46 (d, J = 8.60 Hz, 1 H), 7.36 (br t, J = 8.82 Hz, 2 H), 5.01 (br d, J = 5.07 Hz, 2 H), 3.14 (s, 3 H), 2.56 (s, 3 H).

Example 192

(R)-6-(4-fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazoline-8-sulfonamide

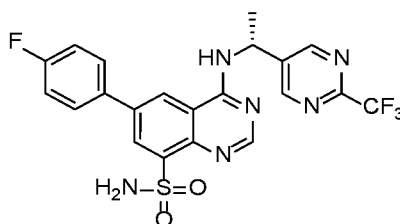


Step 1: Preparation of 6-(4-fluorophenyl)-4-oxo-3,4-dihydroquinazoline-8-sulfonamide



To a suspension of 6-(4-fluorophenyl)-8-(methylsulfonyl)quinazolin-4(3H)-one (167 mg, 0.525 mmol) in dry THF (2 mL), cooled to 0 °C, lithium diisopropylamide 2.0 M in THF heptane ethylbenzene (1.049 mL, 2.099 mmol) was added. The reaction was warmed to RT and stirred for 30 min until complete dissolution. To the resulting orange solution, tributylborane 1.0 M in THF (2.62 mL, 2.62 mmol) was added and the reaction was heated to 64 °C and stirred for 12h. A solution of (aminooxy)sulfonic acid (208 mg, 1.836 mmol) and potassium acetate (232 mg, 2.361 mmol) in water (2 mL) was added and the resulting mixture stirred at 65 °C for 6h. Volatiles were removed under reduced pressure. The crude was taken up with DMF and purified by RP flash chromatography (Biotage Isolera, Ultra SNAP C18 60g cartridge, gradient elution from 0 to 80% of B in A; A: water/MeCN 95:5 + 0.1% HCOOH, B: MeCN/water 95:5 + 0.1% HCOOH). An unseparable mixture of titled compound and starting material was isolated and used as such in the next step.

Step 2: Preparation of (*R*)-6-(4-fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazoline-8-sulfonamide



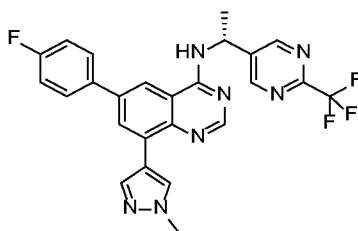
To a suspension of the crude 6-(4-fluorophenyl)-4-hydroxyquinazoline-8-sulfonamide (40 mg, 0.125 mmol) in DMF (1.5 mL), (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (78 mg, 0.150 mmol) and diisopropylethylamine (0.066 mL, 0.376 mmol) were added followed after 5 min by (*R*)-1-(2-(trifluoromethyl)pyrimidin-5-yl)ethan-1-amine (36 mg, 0.188 mmol). The resulting mixture was stirred at RT for 12h. The reaction was diluted with DCM and quenched with water. The two phases were separated and the aqueous layer was extracted once with DCM. Combined organic phase was filtered through a PhaseSeparator tube and volatiles removed under reduced pressure. Purification by flash chromatography (Biotage Isolera, Ultra SNAP 25g cartridge, gradient elution from 5% to 100% EtOAc in heptane) yielded impure titled compound. Second purification by flash chromatography (Biotage Isolera, SNAP NH 28g cartridge, gradient elution from 5% to 100% EtOAc in heptane) yielded the titled compound (4 mg, 8.12 μ mol, 6.48 % yield) as white powder.

LCMS (Method 5): 1.08 min, 493 [M+H]⁺.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.15 (s, 2 H), 9.01 (br s, 1 H), 8.88 (br d, J = 1.98 Hz, 1 H), 8.54 (s, 1 H), 8.42 - 8.49 (m, 1 H), 7.81 - 7.96 (m, 2 H), 7.40 (br t, J = 8.82 Hz, 2 H), 7.21 (br s, 2 H), 5.67 (br d, J = 6.84 Hz, 1 H), 1.72 (d, J = 7.06 Hz, 3 H).

Example 193

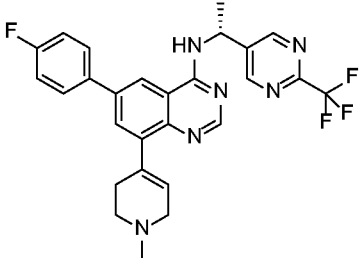
(*R*)-6-(4-fluorophenyl)-8-(1-methyl-1*H*-pyrazol-4-yl)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine

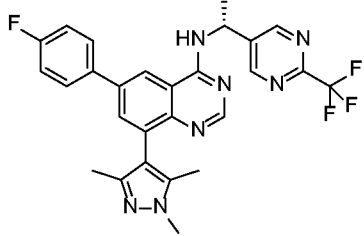
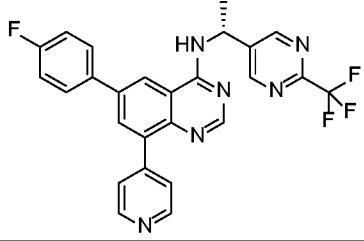
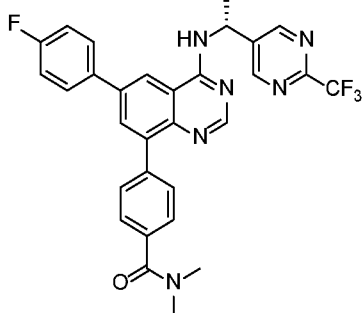


Nitrogen was bubbled for 15 min through a mixture of (*R*)-6-(4-Fluorophenyl)-8-iodo-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine (100 mg, 0.18 mmol), 1-methylpyrazole-4-boronic acid pinacol ester (52 mg, 0.25 mmol), cesium fluoride (85 mg, 0.56 mmol), water (0.5 mL) in *N,N*-dimethylformamide (2.0 mL), then tetrakis(triphenylphosphine)palladium(0) (21 mg, 0.02 mmol) was added. The resulting mixture was heated to 95 °C for 16 hours. After return to room temperature, the reaction was diluted with water (6 mL) and extracted with ethyl acetate (3 × 3 mL). The combined organic phases were filtered through a hydrophobic frit and the solvent was removed *in vacuo*. The residue was purified by preparative HPLC to give the title compound as an off-white solid (63 mg, 69%).

¹H NMR (400 MHz, DMSO): δ 9.24 (s, 2 H), 8.76 (d, J = 6.8 Hz, 1 H), 8.71 (s, 1 H), 8.59-8.54 (m, 2 H), 8.39 (d, J = 1.5 Hz, 1 H), 8.35 (s, 1 H), 8.03 (dd, J = 5.4, 8.7 Hz, 2 H), 7.45 (dd, J = 8.8, 8.8 Hz, 2 H), 5.80-5.71 (m, 1 H), 3.97 (s, 3 H), 1.80 (d, J = 7.1 Hz, 3 H). LCMS (Method 3): [MH⁺] = 494 at 5.1 min.

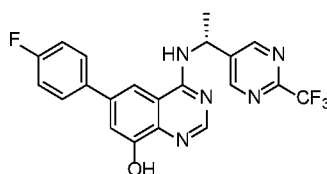
The following compounds reported in the table below were prepared according to the same procedure described for the preparation of (*R*)-6-(4-fluorophenyl)-8-(1-methyl-1*H*-pyrazol-4-yl)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine:

Example No.	Chemical name Structure	Analytical data ¹ H NMR LC-MS
Example 194	(<i>R</i>)-6-(4-Fluorophenyl)-8-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)- <i>N</i> -(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 9.22 (s, 2 H), 8.74 (d, J = 6.8 Hz, 1 H), 8.62 (d, J = 1.0 Hz, 1 H), 8.49 (s, 1 H), 7.96 (dd, J = 5.6, 8.6 Hz, 2 H), 7.91 (s, 1 H), 7.43 (dd, J = 8.8, 8.8 Hz, 2 H), 5.96 (s, 1 H), 5.77-5.68 (m, 1 H), 3.12-3.05 (m, 2 H), 2.81-2.74 (m, 2 H), 2.67-2.59 (m, 2 H), 2.35 (s, 3 H), 1.78 (d, J = 7.1 Hz, 3 H). LCMS (Method 4): [MH ⁺] = 509 at 3.17 min.

<p>Example 195</p>	<p>(<i>R</i>)-6-(4-Fluorophenyl)-<i>N</i>-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)-8-(1,3,5-trimethyl-1H-pyrazol-4-yl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.12 (s, 2 H), 8.67 (d, J = 6.8 Hz, 1 H), 8.56 (d, J = 1.3 Hz, 1 H), 8.32 (s, 1 H), 7.88-7.80 (m, 3 H), 7.31 (dd, J = 8.8, 8.8 Hz, 2 H), 5.65-5.57 (m, 1 H), 3.66 (s, 3 H), 1.99 (s, 3 H), 1.92 (s, 3 H), 1.67 (d, J = 7.1 Hz, 3 H). LCMS (Method 4): [MH⁺] = 522 at 3.77 min.</p>
<p>Example 196</p>	<p>(<i>R</i>)-6-(4-Fluorophenyl)-8-(pyridin-4-yl)-<i>N</i>-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.21 (s, 2 H), 8.87 (d, J = 6.9 Hz, 1 H), 8.78 (d, J = 2.0 Hz, 1 H), 8.67 (d, J = 6.0 Hz, 2 H), 8.48 (s, 1 H), 8.20 (d, J = 2.0 Hz, 1 H), 8.04-7.99 (m, 2 H), 7.78-7.75 (m, 2 H), 7.42 (dd, J = 8.9, 8.9 Hz, 2 H), 5.76-5.69 (m, 1 H), 1.78 (d, J = 7.2 Hz, 3 H). LCMS (Method 4): [MH⁺] = 491 at 3.9 min.</p>
<p>Example 197</p>	<p>(<i>R</i>)-4-(6-(4-Fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazolin-8-yl)-<i>N,N</i>-dimethylbenzamide</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.22-9.18 (m, 5 H), 8.91 (d, J = 6.9 Hz, 1 H), 8.80 (d, J = 2.0 Hz, 1 H), 8.49 (s, 1 H), 8.34 (d, J = 2.0 Hz, 1 H), 8.07-8.02 (m, 2 H), 7.43 (dd, J = 8.9, 8.9 Hz, 2 H), 5.75-5.69 (m, 1 H), 1.78 (d, J = 7.2 Hz, 3 H). LCMS (Method 3): [MH⁺] = 561 at 4.09 min.</p>

Example 198

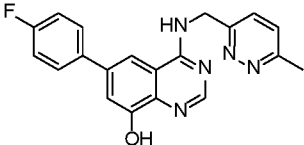
(*R*)-6-(4-fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)-quinazolin-8-ol



To a solution of 6-(4-fluorophenyl)-8-methoxy-*N*-[(1*R*)-1-[2-(trifluoromethyl)-pyrimidin-5-yl]ethyl]quinazolin-4-amine (490 mg, 1.11 mmol) in chloroform (8 mL) at 0 °C was added dropwise boron tribromide (0.32 mL, 3.32 mmol). The reaction was then allowed to warm to room temperature and was heated to 65 °C for 18 hours. After return
 5 to room temperature, the reaction was cooled down in an ice-bath and quenched with methanol (2 mL). The solvent was removed *in vacuo*. The residue was diluted with ethyl acetate (50 mL) and washed with saturated aqueous NaHCO₃ solution (50 mL). The aqueous layer was then extracted with ethyl acetate (2 × 20 mL). The organic phases were combined, passed through a hydrophobic frit and the solvent was removed *in vacuo* to
 10 give the title compound as a grey solid (416 mg, 88%).

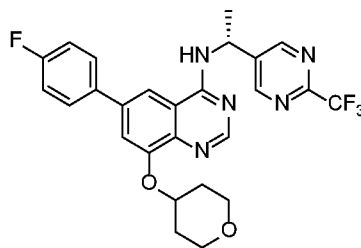
¹H NMR (400 MHz, DMSO): δ 9.18 (s, 2 H), 8.65 (d, J = 7.0 Hz, 1 H), 8.46 (s, 1 H), 8.09 (s, 1 H), 7.86 (dd, J = 5.5, 8.7 Hz, 2 H), 7.45 (d, J = 1.3 Hz, 1 H), 7.37 (dd, J = 8.8, 8.8 Hz, 2 H), 5.71-5.67 (m, 1 H), 1.75 (d, J = 7.0 Hz, 3 H). OH not observed.

The following compounds were prepared *via* adaptations of the above procedure
 15 starting from substrate reported in table.

Example No.	Structure	Analytical data LC-MS	Substrate
Example 199	6-(4-fluorophenyl)-4-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-8-ol 	LCMS: 0.51 min, 362.1 [M+H] ⁺ , Method 5method 2 min.	Example 182

Example 200

(*R*)-6-(4-Fluorophenyl)-8-((tetrahydro-2*H*-pyran-4-yl)oxy)-*N*-(1-(2-(trifluoromethyl) pyrimidin-5-yl)ethyl)quinazolin-4-amine

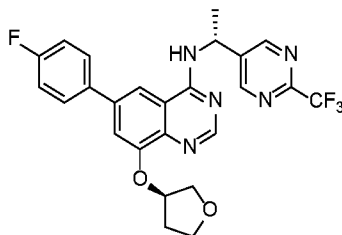


Nitrogen was bubbled for 5 min through a mixture of (R)-6-(4-fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazolin-8-ol (40 mg, 0.01 mmol), tetrahydro-4-pyranol (10 mg, 0.102 mmol) and cyanomethyltributylphosphorane (1 M in toluene, 0.14 mL, 0.14 mmol) in toluene (3.0 mL). The mixture was heated to 100 °C for 72 hours. After return to room temperature, the solvent was removed *in vacuo*. The residue was purified by preparative HPLC to give the title compound (17 mg, 38%) as an off white solid.

¹H NMR (400 MHz, DMSO): δ 9.18 (s, 2 H), 8.64 (d, J = 7.0 Hz, 1 H), 8.44 (s, 1 H), 8.23 (d, J = 1.6 Hz, 1 H), 7.94-7.89 (m, 2 H), 7.65 (d, J = 1.6 Hz, 1 H), 7.39 (dd, J = 8.8, 8.8 Hz, 2 H), 5.71-5.66 (m, 1 H) 5.02-4.94 (m, 1 H), 3.96-3.88 (m, 2 H), 3.51 (dd, J = 9.7, 9.7 Hz, 2 H), 2.07-2.00 (m, 2 H), 1.74 (d, J = 7.0 Hz, 5 H). LCMS (Method 3): [MH⁺] = 514 at 3.79 min.

Example 201

(R)-4-(2-(1,1-dioxidothiomorpholino)ethyl)-8-(4-fluorophenyl)-3-oxo-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide



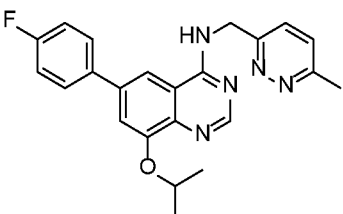
Potassium carbonate (47.7 mg, 0.345 mmol) was added to a mixture of (R)-6-(4-fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazolin-8-ol

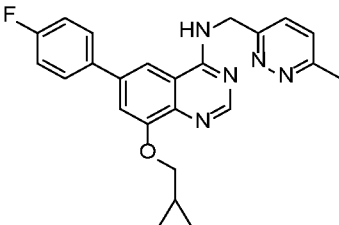
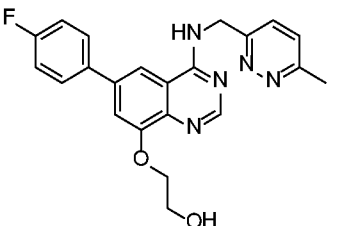
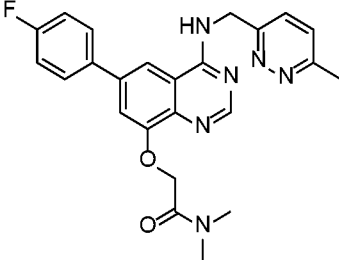
(64.4 mg, 0.150 mmol) and (S)-tetrahydrofuran-3-yl 4-methylbenzenesulfonate (41.8 mg, 0.172 mmol) in DMF (Volume: 3 ml). Stirring went on at 60 °C for 16 h. The reaction mixture was allowed to cool down to rt, then it was quenched by the addition of formic acid (0.017 ml, 0.450 mmol). Purification by RP chromatography (Biotage Isolera, 30 g C18 cartridge, gradient elution from 100:0 to 50:50 A/B, A: water/acetonitrile 95:5 + 0.1% HCOOH, B: acetonitrile:water 95:5 + 0.1% HCOOH) then DP chromatography (Biotage Isolera, 11 g NH cartridge, gradient elution from 0 to 40% ethyl acetate in dichloromethane) yielded 6-(4-fluorophenyl)-8-(((R)-tetrahydrofuran-3-yl)oxy)-N-((R)-1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine (8.3 mg, 0.017 mmol, 11.08 % yield) as a white powder.

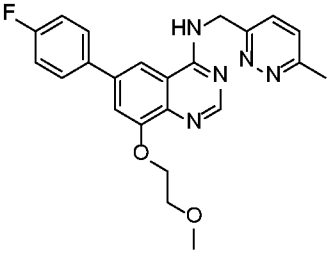
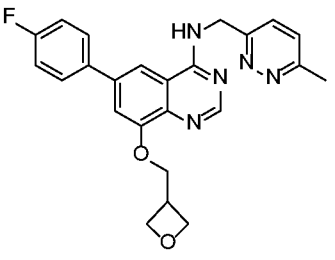
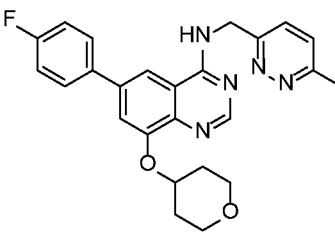
LCMS (Method 5): Method 5 0.74 min, 500.0 [M+H]⁺, CSH method 2 min.

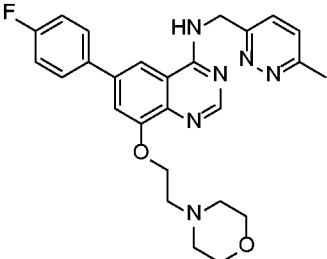
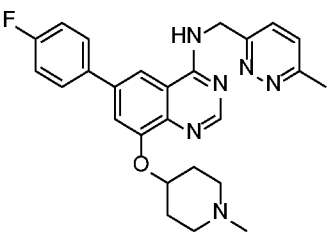
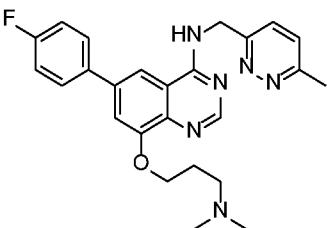
¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.16 (s, 2 H), 8.61 (d, J=6.6 Hz, 1 H), 8.42 (s, 1 H), 8.21 (d, J=1.3 Hz, 1 H), 7.84 - 8.01 (m, 2 H), 7.51 (d, J=1.3 Hz, 1 H), 7.38 (t, J=8.8 Hz, 2 H), 5.67 (t, J=7.0 Hz, 1 H), 5.35 - 5.50 (m, 1 H), 3.85 - 4.04 (m, 3 H), 3.79 (d, J=4.4 Hz, 1 H), 2.19 - 2.37 (m, 1 H), 2.03 - 2.17 (m, 1 H), 1.72 (d, J=7.0 Hz, 3 H).

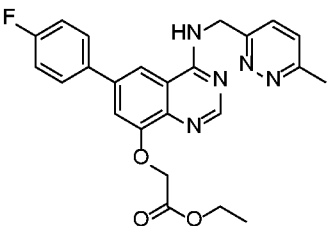
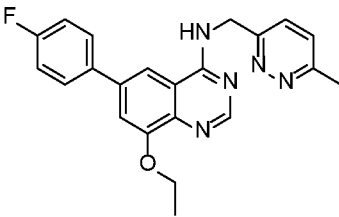
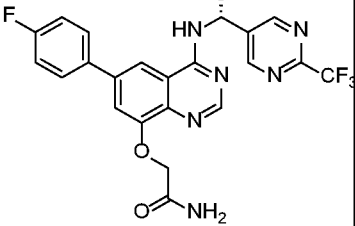
The following compounds were prepared via adaptations of the above procedures starting from substrate reported in table.

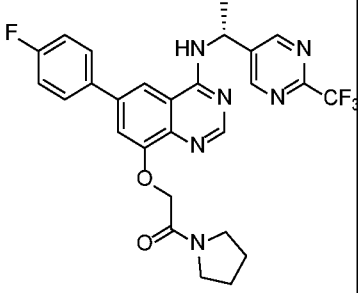
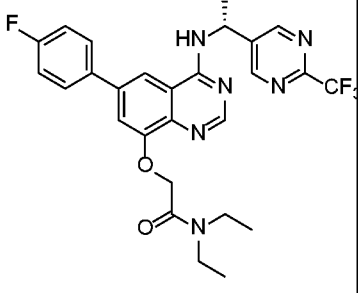
Example No.	Structure	Analytical data ¹ H NMR LC-MS	Reagents
Example 202	6-(4-fluorophenyl)-8-isopropoxy-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine 	LCMS (Method 7): 2.50 min, [M+H] ⁺ 404.5 ¹ H NMR (300 MHz, CHLOROFORM- <i>d</i>) δ ppm 8.78 (s, 1 H) 7.69 (br s, 1 H) 7.57 - 7.66 (m, 2 H) 7.50 - 7.57 (m, 2 H) 7.40 (d, J=8.62 Hz, 1 H) 7.32 (d, J=1.10 Hz, 1 H) 7.19 (t, J=8.71 Hz, 2 H) 5.11 (d, J=4.22 Hz, 2 H)	Example 199, isopropyl iodide, Cs ₂ CO ₃ , NaI

		4.91 (spt, $J=6.10$ Hz, 1 H) 2.77 (s, 3 H) 1.56 (d, $J=6.05$ Hz, 6 H)	
Example 203	<p>8-(cyclopropylmethoxy)-6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine</p> 	<p>LCMS (Method 7): 2.89 min, $[M+H]^+$ 416.4 1H NMR (300 MHz, CHLOROFORM-<i>d</i>) δ ppm 8.80 (s, 1 H) 7.70 (br s, 1 H) 7.59 - 7.67 (m, 2 H) 7.55 - 7.58 (m, 1 H) 7.52 (s, 1 H) 7.37 - 7.43 (m, 1 H) 7.29 - 7.31 (m, 1 H) 7.20 (t, $J=8.62$ Hz, 2 H) 5.12 (d, $J=4.22$ Hz, 2 H) 4.11 (d, $J=6.97$ Hz, 2 H) 2.77 (s, 3 H) 2.24 - 2.34 (m, 1 H) 1.47 - 1.55 (m, 1 H) 0.69 - 0.81 (m, 2 H) 0.41 - 0.53 (m, 2 H)</p>	Example 199, (Bromomethyl)cyclopropane, Cs_2CO_3 , NaI
Example 204	<p>2-[6-(4-fluorophenyl)-4-[(6-methylpyridazin-3-yl)methylamino]quinazolin-8-yl]oxyethanol</p> 	<p>LCMS (Method 7): 2.24 min, $[M+H]^+$ 406.4 1H NMR (300 MHz, CHLOROFORM-<i>d</i>) δ ppm 8.57 (s, 1 H) 8.00 - 8.22 (m, 1 H) 7.49 - 7.63 (m, 4 H) 7.36 - 7.47 (m, 2 H) 7.16 (t, $J=8.62$ Hz, 2 H) 5.10 (d, $J=4.58$ Hz, 2 H) 4.27 - 4.40 (m, 2 H) 4.00 - 4.13 (m, 2 H) 3.52 (br s, 1 H) 2.78 (s, 3 H)</p>	Example 199, 2-bromoethyl benzoate, Cs_2CO_3 , NaI
Example 205	<p>2-[6-(4-fluorophenyl)-4-[(6-methylpyridazin-3-yl)methylamino]quinazolin-8-yl]oxy-N,N-dimethylacetamide</p> 	<p>LCMS (Method 7): 3.22 min, $[M+H]^+$ 447.2 1H NMR (300 MHz, DMSO-<i>d</i>₆) δ ppm 8.99 - 9.14 (m, 1 H) 8.43 (s, 1 H) 8.19 (d, $J=1.47$ Hz, 1 H) 7.81 - 7.93 (m, 2 H) 7.45 - 7.60 (m, 3 H) 7.32 - 7.45 (m, 2 H) 5.77 (s, 1 H) 5.11 (s, 2 H) 5.03 (d, $J=5.69$ Hz, 2 H) 3.08 (s, 3 H) 2.87 (s, 4 H) 2.59 (s, 3 H)</p>	Example 199, 2-Cl-Dimethylacetamide, Cs_2CO_3

<p>Example 206</p>	<p>6-(4-fluorophenyl)-8-(2-methoxyethoxy)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine</p> 	<p>LCMS (Method 7): 2.42 min, [M+H]⁺ 420.1 ¹H NMR (300 MHz, CHLOROFORM-d) δ ppm 8.73 (s, 1 H), 7.71 - 7.86 (m, 1 H), 7.52 - 7.64 (m, 3 H), 7.50 - 7.54 (m, 1 H), 7.38 - 7.42 (m, 2 H), 7.11 - 7.27 (m, 2 H), 5.11 (d, J=3.12 Hz, 2 H), 4.44 (t, J=5.04 Hz, 2 H), 3.97 (t, J=5.04 Hz, 2 H), 3.50 (s, 3 H), 2.77 (s, 3 H)</p>	<p>Example 199, 2-MethoxyBromoethane Cs₂CO₃</p>
<p>Example 207</p>	<p>6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-(oxetan-3-ylmethoxy)quinazolin-4-amine</p> 	<p>LCMS (Method 7): 2.47 min, [M+H]⁺ 432.3 ¹H NMR (300 MHz, CHLOROFORM-d) δ ppm 8.75 (s, 1 H), 7.70 - 7.78 (m, 1 H), 7.56 - 7.67 (m, 3 H), 7.50 - 7.54 (m, 1 H), 7.38 - 7.43 (m, 1 H), 7.36 (d, J=1.28 Hz, 1 H), 7.15 - 7.27 (m, 2 H), 5.11 (d, J=4.40 Hz, 2 H), 5.02 (t, J=6.51 Hz, 2 H), 4.63 (t, J=5.96 Hz, 2 H), 4.56 (d, J=7.34 Hz, 2 H), 3.61 - 3.79 (m, 1 H), 2.77 (s, 3 H) 3.61 - 3.83 (m, 1 H) 2.77 (s, 3 H)</p>	<p>Example 199, 3-Iodomethyloxethane, Cs₂CO₃</p>
<p>Example 208</p>	<p>6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-tetrahydropyran-4-yloxy-quinazolin-4-amine</p> 	<p>LCMS (Method 7): 2.50 min, [M+H]⁺ 446.5 ¹H NMR (300 MHz, CHLOROFORM-d) δ ppm 8.79 (s, 1 H) 7.68 - 7.78 (m, 1 H) 7.57 - 7.66 (m, 3 H) 7.49 - 7.56 (m, 1 H) 7.33 - 7.46 (m, 2 H) 7.12 - 7.26 (m, 2 H) 5.12 (d, J=4.31 Hz, 2 H) 4.75 - 4.93 (m, 1 H) 4.05 - 4.21 (m, 2 H) 3.62 (ddd, J=11.85, 9.51, 2.66 Hz, 2 H) 2.77 (s, 3 H) 2.14 -</p>	<p>Example 199, 4-Mesyloxytetrahydropyrane, Cs₂CO₃</p>

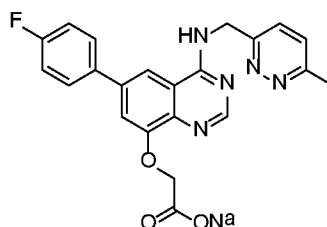
		2.27 (m, 2 H) 1.99 - 2.14 (m, 2 H)	
Example 209	<p>6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-(2-morpholinoethoxy)quinazolin-4-amine</p> 	<p>LCMS (Method 7): 2.25 min, [M+H]⁺ 475.1</p> <p>¹H NMR (300 MHz, CHLOROFORM-<i>d</i>) δ ppm 8.62 (s, 1 H) 8.11 (br s, 1 H) 7.45 - 7.61 (m, 4 H) 7.40 (d, <i>J</i>=8.62 Hz, 1 H) 7.25 - 7.28 (m, 1 H) 7.12 (t, <i>J</i>=8.71 Hz, 2 H) 5.08 (d, <i>J</i>=4.22 Hz, 2 H) 4.36 (t, <i>J</i>=6.05 Hz, 2 H) 3.72 - 3.83 (m, 4 H) 3.01 (t, <i>J</i>=6.05 Hz, 2 H) 2.73 (s, 3 H) 2.57 - 2.70 (m, 4 H)</p>	Example 199, N-(2-Chloroethyl)morpholine, Cs ₂ CO ₃
Example 210	<p>6-(4-fluorophenyl)-8-[(1-methyl-4-piperidyl)oxy]-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine</p> 	<p>LCMS (Method 7): 1.97 min, [M+H]⁺ 459.1</p> <p>¹H NMR (300 MHz, METHANOL-<i>d</i>₄) δ ppm 8.48 (s, 1 H), 8.37 (br s, 1 H), 8.04 (d, <i>J</i>=1.10 Hz, 1 H), 7.73 - 7.81 (m, 2 H), 7.66 - 7.73 (m, 1 H), 7.64 (d, <i>J</i>=1.28 Hz, 1 H), 7.55 - 7.61 (m, 1 H), 7.22 (t, <i>J</i>=8.71 Hz, 2 H), 5.05 - 5.17 (m, 3 H), 3.60 - 3.74 (m, 2 H), 3.34 - 3.39 (m, 2 H), 2.92 (s, 3 H), 2.66 (s, 3 H), 2.27 (br s, 4 H)</p>	Example 199, 4-Chloro-1-methylpiperidine, Cs ₂ CO ₃ , NaI
Example 211	<p>8-[3-(dimethylamino)propoxy]-6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine</p> 	<p>LCMS (Method 7): 2.30 min, [M+H]⁺ 447.1</p> <p>NMR (300 MHz, CHLOROFORM-<i>d</i>) δ ppm 8.71 (s, 1 H), 7.80 - 7.90 (m, 1 H), 7.51 - 7.62 (m, 4 H), 7.40 (d, <i>J</i>=8.62 Hz, 1 H), 7.34 (d, <i>J</i>=1.47 Hz, 1 H), 7.12 - 7.21 (m, 2 H), 5.10 (d, <i>J</i>=4.03 Hz, 2 H), 4.33 (t, <i>J</i>=6.88 Hz, 2 H), 2.75 (s, 3 H), 2.66</p>	Example 199, 3-Chloro-N,N-Dimethylaminopropane HCl, Cs ₂ CO ₃ , NaI

		(t, J=6.97 Hz, 2 H), 2.27 – 2.36 (m, 8 H)	
Example 212	ethyl 2-[6-(4-fluorophenyl)-4-[(6-methylpyridazin-3-yl)methylamino]quinazolin-8-yl]oxyacetate 	LCMS (Method 7): 2.69 min, [M+H] ⁺ 448.4 Se1 6min ¹ H NMR (300 MHz, CHLOROFORM-d) δ ppm 8.69 (s, 1 H), 7.85 (br s, 1 H), 7.50 - 7.61 (m, 4 H), 7.37 - 7.47 (m, 1 H), 7.24 (d, J=0.92 Hz, 1 H), 7.17 (t, J=8.62 Hz, 2 H), 5.10 (d, J=4.03 Hz, 2 H), 5.00 (s, 2 H), 4.30 (q, J=7.15 Hz, 2 H), 2.77 (s, 3 H), 1.29 (t, J=7.15 Hz, 3 H)	Example 199, Ethyl 2-Chloroacetate Cs ₂ CO ₃
Example 213	8-ethoxy-6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine 	LCMS (Method 7): 2.43 min, [M+H] ⁺ 390.5 ¹ H NMR (300 MHz, CHLOROFORM-d) δ ppm 8.75 (s, 1 H) 7.75 (br s, 1 H) 7.50 - 7.64 (m, 4 H) 7.38 - 7.44 (m, 1 H) 7.11 - 7.27 (m, 2 H) 5.11 (d, J=4.40 Hz, 2 H) 4.35 (q, J=6.97 Hz, 2 H) 2.77 (s, 3 H) 1.65 (t, J=4.30 Hz, 3 H)	Example 199, Ethyl iodide, Cs ₂ CO ₃
Example 310	R)-2-((6-(4-fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazolin-8-yl)oxy)acetamide 	¹ H NMR (400 MHz, DMSO): δ 9.21 (s, 2 H), 8.74 (d, J = 5.6 Hz, 1 H), 8.50 (s, 1 H), 8.33 (d, J = 1.5 Hz, 1 H), 7.98-7.93 (m, 2 H), 7.74 (s, 1 H), 7.70 (d, J = 1.5 Hz, 1 H), 7.54 (s, 1 H), 7.44 (dd, J = 8.8, 8.8 Hz, 2 H), 5.73 (dd, J = 6.4, 6.4 Hz, 1 H), 4.80 (s, 2 H), 1.78 (d, J = 7.1 Hz, 3 H). LCMS (Method 3): [MH] ⁺ = 487.4 at 4.54 min.	Example 198, Bromoacetamide, K ₂ CO ₃

Example 311	<p>(<i>R</i>)-2-((6-(4-fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazolin-8-yl)oxy)-1-(pyrrolidin-1-yl)ethan-1-one</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.18 (s, 2 H), 8.70 (d, J = 6.9 Hz, 1 H), 8.45 (s, 1 H), 8.23 (d, J = 1.5 Hz, 1 H), 7.91-7.86 (m, 2 H), 7.52 (d, J = 1.4 Hz, 1 H), 7.41 (dd, J = 8.8, 8.8 Hz, 2 H), 5.72-5.67 (m, 1 H), 5.03 (s, 2 H), 3.56 (dd, J = 6.8, 6.8 Hz, 2 H), 1.93-1.73 (m, 6 H). LCMS (Method 3): [MH⁺] = 541.5 at 4.8 min.</p>	<p>Example 198, 1-(chloroacetyl)pyrrolidine, K₂CO₃</p>
Example 312	<p>(<i>R</i>)-<i>N,N</i>-diethyl-2-((6-(4-fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazolin-8-yl)oxy)acetamide</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.18 (s, 2 H), 8.64 (d, J = 7.0 Hz, 1 H), 8.43 (s, 1 H), 8.22 (d, J = 1.6 Hz, 1 H), 7.89-7.85 (m, 2 H), 7.48 (d, J = 1.6 Hz, 1 H), 7.41 (dd, J = 8.9, 8.9 Hz, 2 H), 5.72-5.66 (m, 1 H), 5.08 (s, 2 H), 3.42 (q, J = 7.1 Hz, 2 H), 3.32-3.26 (m, 2 H), 1.74 (d, J = 7.0 Hz, 3 H), 1.17 (dd, J = 7.1, 7.1 Hz, 3 H), 1.04 (dd, J = 7.1, 7.1 Hz, 3 H). LCMS (Method 4): [MH⁺] = 543.5 at 4.8 min.</p>	<p>Example 198, 2-chloro-<i>N,N</i>-diethylacetamide, K₂CO₃</p>

Example 214

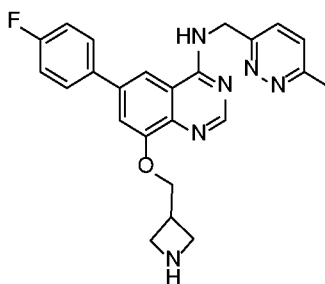
2-[6-(4-fluorophenyl)-4-[(6-methylpyridazin-3-yl)methylamino]quinazolin-8-yl]oxyacetic acid, sodium salt



NaOH (10.5 mg, 0.26 mmol) was added to ethyl 2-[6-(4-fluorophenyl)-4-[(6-methylpyridazin-3-yl)methylamino]quinazolin-8-yl]oxyacetate (117 mg, 0.26 mmol) (Example 211) in MeOH (2.2 mL). The mixture was stirred at rt for 3 days then diluted with diethyl ether and filtered to leave 2-[6-(4-fluorophenyl)-4-[(6-methylpyridazin-3-yl)methylamino]quinazolin-8-yl]oxyacetic acid sodium salt (87 mg, 75 % yield) as a white powder.

Example 215

8-(azetidin-3-ylmethoxy)-6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine



10

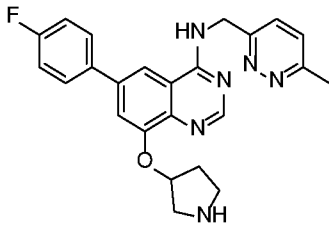
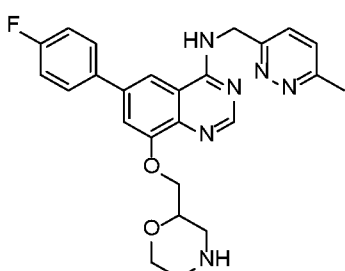
Cesium carbonate (360 mg, 1.1 mmol) was added to a mixture of Example 186A (200 mg, 0.55 mmol) and N-Boc-3-(Iodomethyl)azetidine (247 mg, 0.72 mmol) in DMF (Volume: 3 ml). Stirring went on at 25 °C for 48 h. The crude material was purified by . The intermediate Boc-protected amine (150 mg, 0.28 mmol) was treated with 8N HCl in MeOH at RT for 3 days to leave 8-(azetidin-3-ylmethoxy)-6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine (122 mg, 87 % yield) as a white powder.

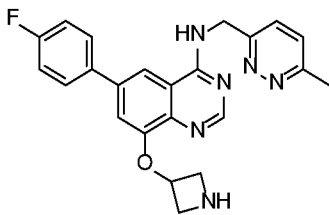
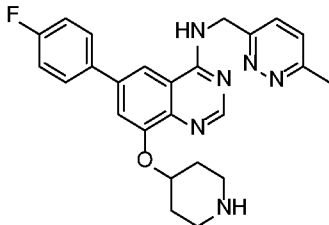
LCMS (Method 7):: 2.24 min, [M+H]⁺ 431.1Se1 6min

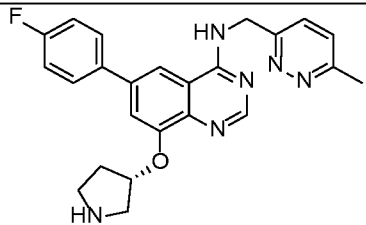
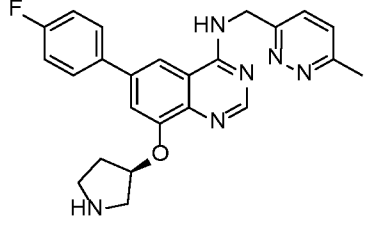
¹H NMR (300 MHz, METHANOL-d₄) δ ppm 8.80 (s, 1 H), 8.49 (d, J=8.80 Hz, 1 H), 8.37 (d, J=1.28 Hz, 1 H), 8.31 (br d, J=8.44 Hz, 1 H), 7.90 - 7.97 (m, 3 H), 7.33 (t, J=8.71 Hz, 2 H), 5.43 (s, 2 H), 4.60 (d, J=4.95 Hz, 2 H), 4.34 (dd, J=8.44, 3.48 Hz, 4 H), 2.89 (s, 3 H)

20

The following compounds were prepared via adaptations of the above procedures starting from substrate reported in table.

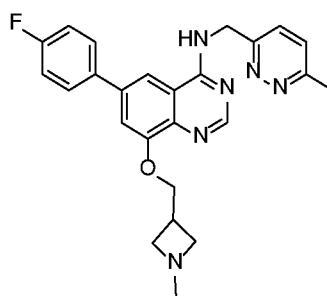
Example No.	Chemical Name Structure	Analytical data ¹ H NMR LC-MS	Reagents
Example 216	6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-pyrrolidin-3-yloxy-quinazolin-4-amine 	LCMS (Method 7): 2.17 min, [M+H] ⁺ 431.1 Se1 6min ¹ H NMR (300 MHz, DMSO-d ₆) δ ppm 11.19 - 11.27 (m, 1 H), 9.84 (br s, 1 H), 9.59 (br s, 1 H), 8.82 (s, 1 H), 8.62 (s, 1 H), 8.00 - 8.09 (m, 3 H), 7.80 (d, J=8.62 Hz, 1 H), 7.67 (d, J=8.62 Hz, 1 H), 7.45 (t, J=8.89 Hz, 2 H), 5.75 - 5.85 (m, 1 H), 5.26 (br d, J=4.58 Hz, 2 H), 3.33 - 3.45 (m, 4 H), 2.64 (s, 3 H), 2.23 - 2.32 (m, 2 H)	Example 199, tert-butyl 3- ((methylsulf onyl)oxy)pyr rolidine-1- carboxylate, Cs ₂ CO ₃
Example 217	6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-(morpholin-2-ylmethoxy)quinazolin-4-amine 	LCMS (Method 7): 2.23 min, [M+H] ⁺ 461.1 Se1 6min ¹ H NMR (300 MHz, DMSO-d ₆) δ ppm 10.96 - 11.49 (m, 1 H) 9.46 - 10.02 (m, 2 H) 8.81 (s, 1 H) 8.62 (s, 1 H) 8.03 (dd, J=8.71, 5.41 Hz, 2 H) 7.95 (s, 1 H) 7.82 (d, J=8.80 Hz, 1 H) 7.68 (d, J=8.80 Hz, 1 H) 7.44 (t, J=8.80 Hz, 2 H) 5.77 (s, 1 H) 5.25 (br d, J=5.50 Hz, 2 H) 4.45 - 4.62 (m, 2 H) 4.23 - 4.38 (m, 1 H) 3.99 - 4.11 (m, 1 H) 3.90 (br s, 2 H) 3.53	Example 199, tert-butyl 2- (((methylsulf onyl)oxy)me thyl)morphol ine-4- carboxylate, Cs ₂ CO ₃

		(br s, 2 H) 3.01 - 3.42 (m, 4 H) 2.64 (s, 3 H)	
Example 218	8-(azetidin-3-yloxy)-6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine 	LCMS (Method 7): 2.07 min, [M+H] ⁺ 417.1 ¹ H NMR (300 MHz, DMSO-d ₆) δ ppm 11.29 (br s, 1 H), 9.51 and 9.65 (br s, 2 H, 1 H each), 8.88 (s, 1 H), 8.67 (s, 1 H), 7.95 - 8.09 (m, 2 H), 7.65 - 7.84 (m, 3 H), 7.44 (t, J=8.89 Hz, 2 H), 5.50 - 5.64 (m, 1 H), 5.25 (br d, J=5.69 Hz, 2 H), 4.57 (br dd, J=11.46, 5.04 Hz, 2 H), 4.05 - 4.32 (m, 2 H), 2.64 (s, 3 H)	Example 199, tert-butyl 3-((methylsulfonyl)oxy)azetidine-1-carboxylate, Cs ₂ CO ₃
Example 219	6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-(4-piperidyloxy)quinazolin-4-amine 	LCMS (Method 7): 2.17 min, [M+H] ⁺ 445.1 Se1 6min ¹ H NMR (300 MHz, METHANOL-d ₄) δ ppm 8.77 (s, 1 H), 8.44 (d, J=8.80 Hz, 1 H), 8.35 (d, J=1.10 Hz, 1 H), 8.27 (d, J=8.80 Hz, 1 H), 8.00 (s, 1 H), 7.89 - 7.96 (m, 2 H), 7.33 (t, J=8.71 Hz, 2 H), 5.42 (s, 2 H), 5.26 - 5.33 (m, 1 H), 3.65 (ddd, J=12.65, 8.53, 4.13 Hz, 2 H), 3.35 - 3.39 (m, 2 H), 2.88 (s, 3 H), 2.21 - 2.46 (m, 4 H)	Example 199, tert-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate, Cs ₂ CO ₃
Example 313	6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-[(3S)-pyrrolidin-3-yl]oxyquinazolin-4-amine	¹ H NMR (400 MHz, DMSO): δ 8.42 (s, 1 H), 8.33 (s, 1 H), 8.24 (s, 1 H), 7.93-7.90 (m, 2 H), 7.62-7.65 (m, 1	Example 199, tert-butyl (R)-3-((methylsulfonyl)

		<p>H), 7.49-7.57 (m, 2 H), 7.36-7.49 (m, 2 H), 5.37 (brs, 1 H), 5.02 (s, 2 H), 3.18-3.37 (m, 4 H), 3.05-3.08 (m, 1 H), 2.59 (s, 3 H), 2.14-2.22 (m, 2 H). LCMS (Method 4): [MH⁺] = 431 at 2.23 min.</p>	<p>onyl)oxy)pyrrolidine-1-carboxylate, Cs₂CO₃</p>
Example 314	<p>6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-[(3R)-pyrrolidin-3-yl]oxyquinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.42 (s, 1 H), 8.33 (s, 1 H), 8.24 (s, 1 H), 7.93-7.90 (m, 2 H), 7.62-7.65 (m, 1 H), 7.49-7.57 (m, 2 H), 7.36-7.49 (m, 2 H), 5.26-5.28 (m, 1 H), 5.03 (s, 2 H), 3.05-3.33 (m, 4 H), 2.85-2.86 (m, 1 H), 2.60 (s, 3 H), 2.08-2.13 (m, 1 H), 1.90-1.93 (m, 1 H). LCMS (Method 4): [MH⁺] = 431 at 2.23 min.</p>	<p>Example 199, <i>tert</i>-butyl (<i>S</i>)-3-((methylsulfonyl)oxy)pyrrolidine-1-carboxylate, Cs₂CO₃</p>

Example 220

6-(4-fluorophenyl)-8-[(1-methylazetidin-3-yl)methoxy]-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine



- 5 8-(azetidin-3-ylmethoxy)-6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine (Example 215) (50 mg, 0.1 mmol) was reacted with Sodium carbonate (31.6 mg, 0.3 mmol) dimethylsulfate (247 mg, 0.72 mmol) in DMF (1.65 mL). Stirring went on at 25 °C for 18 h. The crude material was purified by

chromatography to leave 6-(4-fluorophenyl)-8-((1-methylazetididin-3-yl)methoxy)-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine (1.9 mg, 4 % yield) as a white powder

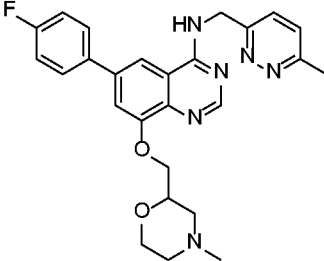
LCMS (Method 7): LCMS (Method 7): 2.09 min, [M+H]⁺ 445.1

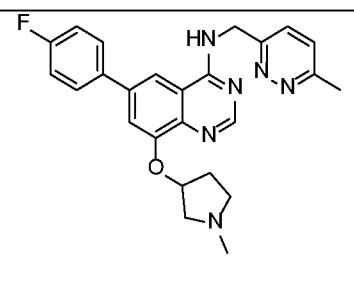
¹H NMR (300 MHz, DMSO-*d*₆) ¹H NMR (300 MHz, CHLOROFORM-*d*) δ ppm

5 8.71 (s, 1 H), 7.73 (br s, 1 H), 7.54 - 7.63 (m, 3 H), 7.51 (d, *J*=8.80 Hz, 1 H), 7.35 - 7.41 (m, 1 H), 7.33 (s, 1 H), 7.11 - 7.22 (m, 2 H), 5.09 (d, *J*=3.85 Hz, 2 H), 4.42 (d, *J*=6.24 Hz, 2 H), 3.63 - 3.70 (m, 2 H), 3.34 - 3.56 (m, 2 H), 3.06 - 3.30 (m, 1 H), 2.75 (s, 3 H), 2.53 (s, 3 H)

The following compounds were prepared via adaptations of the above procedures

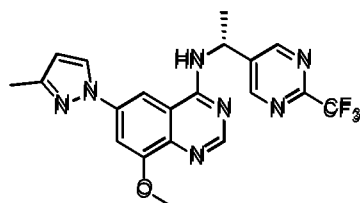
10 starting from substrate reported in table.

Example No.	Chemical Name Structure	Analytical data ¹ H NMR LC-MS	Reagents
Example 221	6-(4-fluorophenyl)-8-[(4-methylmorpholin-2-yl)methoxy]-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine 	LCMS(Method 7): 2.10 min, [M+H] ⁺ 475.1 SeI 6min ¹ H NMR (300 MHz, CHLOROFORM- <i>d</i>) δ ppm 8.58 (s, 1 H) 8.21 (br s, 1 H) 7.45 - 7.61 (m, 4 H) 7.41 (d, <i>J</i> =8.62 Hz, 1 H) 7.31 (d, <i>J</i> =1.47 Hz, 1 H) 7.11 (t, <i>J</i> =8.62 Hz, 2 H) 5.08 (d, <i>J</i> =4.58 Hz, 2 H) 4.28 - 4.39 (m, 1 H) 4.21 (br d, <i>J</i> =7.52 Hz, 2 H) 3.92 - 4.02 (m, 1 H) 3.81 (td, <i>J</i> =11.32, 2.29 Hz, 1 H) 3.50 (s, 1 H) 3.01 (br d, <i>J</i> =11.19 Hz, 1 H) 2.74 (s, 3 H) 2.70 (br s, 1 H) 2.36 (s, 3 H) 2.05 - 2.31 (m, 2 H) 1.27 (s, 2 H)	Example 217
Example 222	6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-(1-methylpyrrolidin-3-yl)oxy-quinazolin-4-amine	LCMS (Method 7): 2.02 min, [M+H] ⁺ 445.1 SeI 6min ¹ H NMR (300 MHz, METHANOL- <i>d</i> ₄) δ ppm 8.45 (s, 1 H), 8.04 (s, 1 H), 7.65 - 7.80 (m, 3 H), 7.58 (br d,	

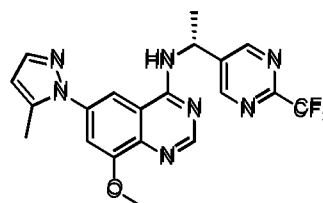
	<p>J=8.44 Hz, 2 H), 7.21 (t, J=8.44 Hz, 2 H), 5.58 (br s, 1 H), 5.10 (s, 2 H), 3.71 - 3.94 (m, 2 H), 3.61 (br d, J=11.19 Hz, 1 H), 3.39 (br d, J=4.03 Hz, 1 H), 3.08 (s, 3 H), 2.54 - 2.71 (m, 4 H), 2.29 - 2.45 (m, 1 H)</p>	
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Example 223 and Example 224

((R)-8-methoxy-6-(3-methyl-1H-pyrazol-1-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine (Ex. 223) and (R)-8-methoxy-6-(5-methyl-1H-pyrazol-1-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine (Ex. 224)



Example 223



Example 224

Nitrogen was bubbled for 5 min through a mixture of (*R*)-6-bromo-8-methoxy-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine (107 mg, 0.25 mmol), copper (*I*) iodide (2.4 mg, 0.01 mmol) and potassium carbonate (73 mg, 0.53 mmol). 5-Methyl-1*H*-pyrazole (20 mg, 0.25 mmol) and (*rac*)-(+)-*N,N'*-dimethyl-1,2-cyclohexanediamine (3.6 mg, 0.03 mmol) in toluene (0.5 mL) were added and the reaction mixture was heated to 115 °C for 72 hours. After return to room temperature, the reaction was filtered through Celite® and the filter cake rinsed with toluene (2 × 5 mL). The organic phases were filtered through a hydrophobic frit and the solvent was removed *in vacuo*. The residue was purified by preparative HPLC to give the title compounds. The structure of each regioisomer (Example 223 and Example 224) was confirmed by ¹H NMR studies.

Example 223: 33 mg, 30%, off-white solid

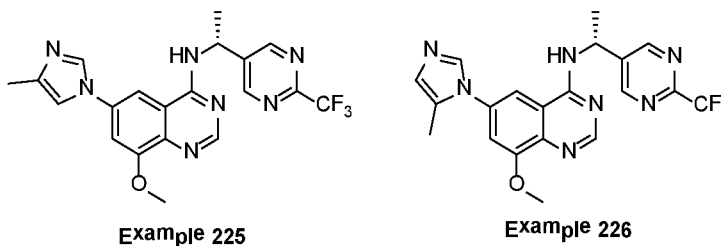
¹H NMR (400 MHz, DMSO): δ 9.18 (s, 2 H), 8.59 (d, J = 7.0 Hz, 1 H), 8.52 (d, J = 2.4 Hz, 1 H), 8.39 (s, 1 H), 8.23 (d, J = 2.1 Hz, 1 H), 7.69 (d, J = 2.0 Hz, 1 H), 6.46 (d, J = 2.3 Hz, 1 H), 5.69-5.63 (m, 1 H), 4.01 (s, 3 H), 2.35 (s, 3 H), 1.74 (d, J = 7.1 Hz, 3 H). LCMS (Method 3): [MH⁺] = 430 at 3.30 min.

5 **Example 224:** 6 mg, 6%, off-white solid

¹H NMR (400 MHz, DMSO): δ 9.16 (s, 2 H), 8.64 (d, J = 7.0 Hz, 1 H), 8.08 (d, J = 2.0 Hz, 1 H), 7.65 (d, J = 1.6 Hz, 1 H), 7.39 (d, J = 2.0 Hz, 1 H), 6.77 (s, 1 H), 6.37 (s, 1 H), 5.69-5.64 (m, 1 H), 3.97 (s, 3 H), 2.43 (s, 3 H), 1.70 (d, J = 7.1 Hz, 3 H). LCMS (Method 3): [MH⁺] = 430 at 3.18 min.

10 **Example 225 and Example 226**

(*R*)-8-Methoxy-6-(4-methyl-1*H*-imidazol-1-yl)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine (Ex. 225) and (*R*)-8-methoxy-6-(5-methyl-1*H*-imidazol-1-yl)-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine (Ex. 226)



15

Nitrogen was bubbled for 5 min through a mixture of (*R*)-6-bromo-8-methoxy-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine (214 mg, 0.50 mmol), copper (*I*) iodide (5.0 mg, 0.02 mmol) and caesium carbonate (145 mg, 1.05 mmol). 5-Methyl-1*H*-imidazole (50 mg, 0.60 mmol) and (*rac*)-(+)-*N,N'*-dimethyl-1,2-cyclohexanediamine (3.6 mg, 0.03 mmol) in *N,N*-dimethylformamide (0.3 mL) were added and the reaction mixture was heated to 115 °C for 72 hours. After return to room temperature, the reaction was filtered through Celite® and the filter cake rinsed with *N,N*-

20

dimethylformamide (2 × 3 mL). The organic phases were filtered through a hydrophobic frit and the solvent was removed *in vacuo*. The residue was purified by preparative HPLC to give the title compounds. The structure of each regioisomer **Example 225** and **Example 226** was confirmed by ¹H NMR.

5 **Example 225**: 18 mg, 8%, off-white solid

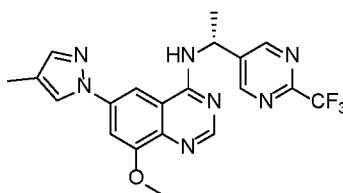
¹H NMR (400 MHz, DMSO): δ 9.17 (s, 2 H), 8.50 (d, J = 6.7 Hz, 1 H), 8.41 (s, 1 H), 8.32 (s, 1 H), 8.09 (d, J = 1.9 Hz, 1 H), 7.62 (s, 1 H), 7.53 (d, J = 2.1 Hz, 1 H), 5.69-5.63 (m, 1 H), 4.01 (s, 3 H), 2.23 (s, 3 H), 1.74 (d, J = 7.2 Hz, 3 H). LCMS (Method 4): [MH⁺] = 430 at 4.01 min.

10 **Example 226**: 14 mg, 7%, off-white solid

¹H NMR (400 MHz, DMSO): δ 9.40 (s, 1H), 9.33 (s, 1 H), 9.18 (s, 2 H), 8.70 (s, 1 H), 8.26 (s, 1 H), 7.74 (d, J = 1.5 Hz, 1 H), 7.65 (s, 1 H), 5.77 (q, J = 7.0 Hz, 1 H), 4.04 (s, 3 H), 2.31 (s, 3 H), 1.77-1.72 (m, 3 H). LCMS (Method 3): [MH⁺] = 430 at 2.23 min.

15 **Example 227**

(R)-8-Methoxy-6-(4-methyl-1H-pyrazol-1-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine



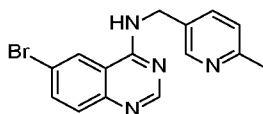
Nitrogen was bubbled for 5 min through a mixture of (*R*)-6-bromo-8-methoxy-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine (107 mg, 0.25 mmol),
20 copper (*I*) iodide (2.4 mg, 0.01 mmol), 4-methyl-1*H*-pyrazole (25 mg, 0.30 mmol) and potassium carbonate (73 mg, 0.53 mmol). (*rac*)-(+)-*N,N'*-dimethyl-1,2-

cyclohexanediamine (3.6 mg, 0.03 mmol) in toluene (0.5 mL) was added and the reaction mixture was heated to 115 °C for 72 hours. After return to room temperature, the reaction was filtered through Celite® and the filter cake was rinsed with toluene (2 × 5 mL). The organic phases were filtered through a hydrophobic frit and the solvent was removed *in vacuo*. The residue was purified by preparative HPLC to give the title compound (4 mg, 6%) as an off white solid.

¹H NMR (400 MHz, DMSO): δ 9.20 (s, 2 H), 8.67 (s, 1 H), 8.49 (s, 1 H), 8.45 (s, 1 H), 7.94 (d, J = 1.5 Hz, 1 H), 7.74 (s, 1 H), 5.83 (q, J = 6.9 Hz, 1 H), 4.13 (s, 3 H), 2.17 (s, 3 H), 1.80 (d, J = 7.2 Hz, 3 H). LCMS (Method 3): [MH⁺] = 430 at 4.42 min.

10 Intermediate 8

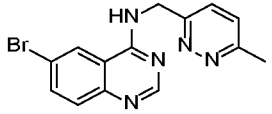
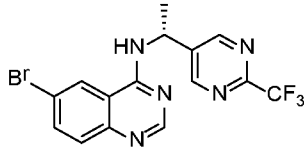
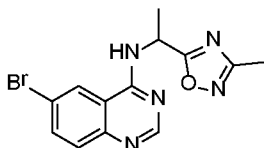
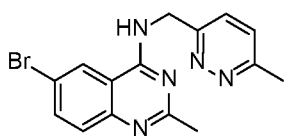
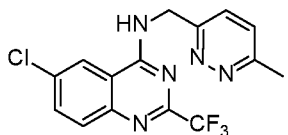
6-bromo-N-((6-methylpyridin-3-yl)methyl)quinazolin-4-amine

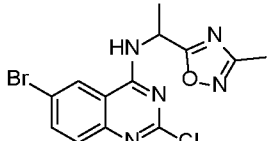


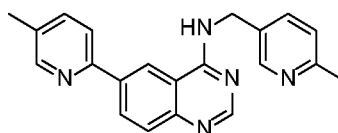
A mixture of 6-bromo-4-chloroquinazoline (1 g, 4.11 mmol), (6-methylpyridin-3-yl)methanamine (0.500 g, 4.09 mmol) and triethylamine (3 ml, 21.52 mmol) in 1,4-Dioxane/DMF 5:1 (Volume: 12 ml) was stirred at 100 °C for 16 h. The reaction mixture was concentrated under reduced pressure. Purification by column chromatography (Biotage Isolere, 55 g NH cartridge, gradient elution from 0 to 50% Acetone in heptane) yielded 6-bromo-N-((6-methylpyridin-3-yl)methyl)quinazolin-4-amine (1.35 g, 4.10 mmol, 100 % yield) as a pale yellow powder.

20 LCMS (Method 6) : 0.82 min, m/z 328.8 [M]⁺ and 330.8 [M+2]⁺,

The following intermediates were synthesised *via* adaptations of the same procedure by reacting suitable amines with substrate reported in the table.

Intermediate No.	Chemical Name Structure	Analytical data LC-MS	Substrate
Intermediate 9	6-bromo- <i>N</i> -((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine 	LCMS (Method 5): 0.38 min, m/z 330 [M] ⁺ and 332 [M+2] ⁺ .	6-bromo-4-chloroquinazoline
Intermediate 10	<i>(R)</i> -6-bromo- <i>N</i> -(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine 	LCMS (Method 5): 0.70 min, m/z 399 [M] ⁺ and 401 [M+2] ⁺ .	6-bromo-4-chloroquinazoline
Intermediate 11	6-bromo- <i>N</i> -(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine 	LCMS (Method 5): 0.54 min, m/z 334 [M] ⁺ and 336 [M+2] ⁺ .	6-bromo-4-chloroquinazoline
Intermediate 12	6-bromo-2-methyl- <i>N</i> -((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine 	LCMS (Method 5): : 0.36 min, m/z 343.8 [M] ⁺ and 345.8 [M+2] ⁺ ,	6-bromo-4-chloro-2-methylquinazoline
Intermediate 13	6-chloro- <i>N</i> -((6-methylpyridazin-3-yl)methyl)-2-(trifluoromethyl)quinazolin-4-amine 	LCMS (Method 6): : 0.95 min, m/z 354 [M+H] ⁺ ,	4,6-dichloro-2-(trifluoroethyl)quinazoline

Intermediate 14	6-bromo-2-chloro- <i>N</i> -(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine 	LCMS (Method 5): : 1.06 min, 367.8 [M] ⁺ , 369.7 [M+2] ⁺ , 371.6 [M+4] ⁺ ,	6-bromo-2,4-dichloroquinazolin-4-amine
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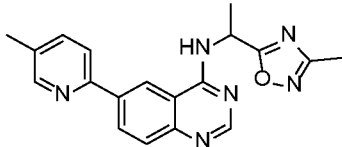
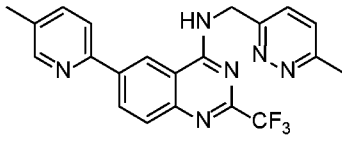
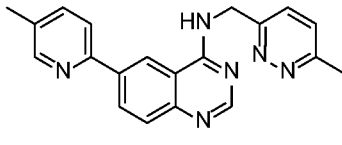
Example 228**6-(5-methylpyridin-2-yl)-*N*-((6-methylpyridin-3-yl)methyl)quinazolin-4-amine**

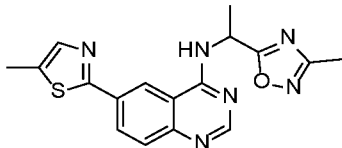
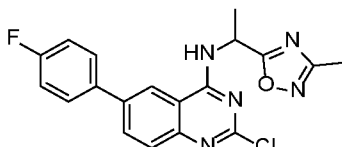
- 5 Tetrakis(triphenylphosphine)palladium(0) (70.2 mg, 0.061 mmol) was added to a mixture of 6-bromo-*N*-((6-methylpyridin-3-yl)methyl)quinazolin-4-amine (Intermediate 8) (100 mg, 0.304 mmol) and 5-methyl-2-(tributylstannyl)pyridine (0.315 ml, 0.911 mmol) in DMF (Volume: 2 ml). Stirring went on for 16 h at 80 °C. Purification by DP chromatography (Biotage Isolera, 28 g NH cartridge, gradient elution from 0 to 100%
10 EtOAc in dichloromethane in 20 CV) yielded 6-(5-methylpyridin-2-yl)-*N*-((6-methylpyridin-3-yl)methyl)quinazolin-4-amine (69.8 mg, 0.204 mmol, 67.3 % yield) as a white powder.

LCMS: 0.33 min, 341.9 m/z [M+H]⁺, CSH 2 min.

- ¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.02 (t, J=5.7 Hz, 1 H), 8.93 - 8.96 (m, 1
15 H), 8.55 - 8.58 (m, 1 H), 8.49 - 8.54 (m, 2 H), 8.48 (s, 1 H), 8.00 - 8.09 (m, 1 H), 7.73 - 7.82 (m, 2 H), 7.66 - 7.72 (m, 1 H), 7.16 - 7.22 (m, 1 H), 4.76 - 4.82 (m, 2 H), 2.43 (s, 3 H), 2.37 (s, 3 H).

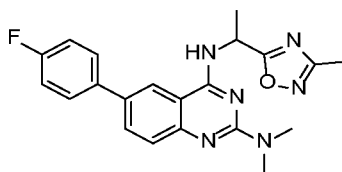
The following compounds were synthesised *via* adaptation of the above procedure using the appropriate stannane reagent and starting from substrate reported in table:

Example No.	Chemical Name Structure	Analytical data ¹ H NMR LC-MS	Starting Intermediate
Example 229	<i>N</i> -(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)-6-(5-methylpyridin-2-yl)quinazolin-4-amine 	LCMS (Method 5): 0.54 min, m/z 347.0 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 9.04 (d, J=1.54 Hz, 1 H), 9.01 (d, J=7.06 Hz, 1 H), 8.53 - 8.61 (m, 2 H), 8.47 (s, 1 H), 8.08 (d, J=7.94 Hz, 1 H), 7.78 - 7.85 (m, 2 H), 5.83 (quin, J=7.11 Hz, 1 H), 2.38 (s, 3 H), 2.32 (s, 3 H), 1.75 (d, J=7.06 Hz, 3 H).	Intermediate 11
Example 230	<i>N</i> -((6-methylpyridazin-3-yl)methyl)-6-(5-methylpyridin-2-yl)-2-(trifluoromethyl)quinazolin-4-amine 	LCMS (Method 2): [MH ⁺] = 411 at 4.36 min ¹ H NMR (400 MHz, CDCl ₃): δ 8.54 (d, J = 4.4 Hz, 2 H), 8.42-8.39 (m, 1 H), 8.02-7.99 (m, 2 H), 7.68 (d, J = 8.0 Hz, 1 H), 7.62-7.52 (m, 2 H), 7.39 (d, J = 8.4 Hz, 1 H), 5.15-5.08 (m, 2 H), 2.78 (s, 3 H), 2.74 (s, 3 H).	Intermediate 13
Example 231	<i>N</i> -((6-methylpyridazin-3-yl)methyl)-6-(5-methylpyridin-2-yl)quinazolin-4-amine 	LCMS (Method 6): 0.75 min, 342.9 m/z [M+H] ⁺ , ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 9.20 (t, J=5.9 Hz, 1 H), 9.00 (d, J=1.3 Hz, 1 H), 8.50 - 8.60 (s, 2 H), 8.44 (s,	Intermediate 9

		1 H), 8.06 (d, J=8.3 Hz, 1 H), 7.78 (d, J=8.8 Hz, 2 H), 7.45 - 7.60 (m, 2 H), 5.04 (d, J=6.1 Hz, 2 H), 2.59 (s, 3 H), 2.37 (s, 3 H).	
Example 232	<p><i>N</i>-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)-6-(5-methylthiazol-2-yl)quinazolin-4-amine</p> 	<p>LCMS (Method 2): [MH⁺] = 353 at 3.86 min.</p> <p>¹H NMR (400 MHz, CDCl₃): δ 9.22-9.20 (m, 1 H), 8.95 (s, 1 H), 8.54 (s, 1 H), 8.37-8.35 (m, 1 H), 7.68 (d, J = 8.0 Hz, 1 H), 7.67 (s, 1 H), 5.88-5.84 (m, 1 H), 2.60 (s, 3 H), 2.37 (s, 3 H), 1.79 (d, J = 8.0 Hz, 3 H).</p>	Intermediate 11
Example 233	<p>2-chloro-6-(4-fluorophenyl)-<i>N</i>-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine</p> 	<p>LCMS (Method 5): : 1.20 min, m/z 383.9 [M]⁺ and 385.7 [M+2]⁺,</p> <p>¹H NMR (400 MHz, DMSO-d₆) d ppm 9.33 (d, J=7.0 Hz, 1 H), 8.69 (d, J=1.8 Hz, 1 H), 8.19 (dd, J=8.6, 2.0 Hz, 1 H), 7.84 - 7.95 (m, 2 H), 7.76 (d, J=8.8 Hz, 1 H), 7.40 - 7.45 (m, 2 H), 5.75 - 5.80 (m, 1 H), 2.37 (br. s., 3 H), 1.77 (d, J=1.0 Hz, 3 H).</p>	Intermediate 14

Example 234

6-(4-fluorophenyl)-N₂,N₂-dimethyl-N₄-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazoline-2,4-diamine



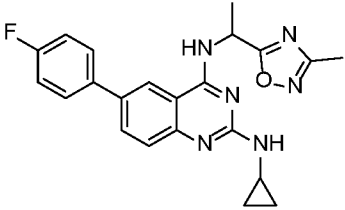
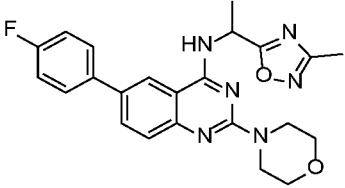
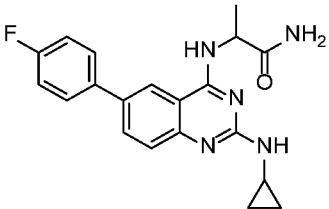
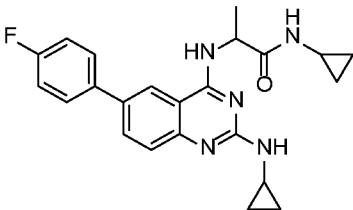
A solution of 2-chloro-6-(4-fluorophenyl)-*N*-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine (Example 223) (80 mg, 0.208 mmol) and dimethylamine 2.0 M in THF (0.625 ml, 1.251 mmol) in 1,4-dioxane (Volume: 3 ml) was stirred at 100 °C
 5 for 16 h. The reaction mixture was partitioned between saturated aqueous ammonium chloride and dichloromethane. The organic layer was concentrated under reduced pressure. Purification by DP chromatography (Biotage Isolera, 10 g KP-Sil cartridge, gradient elution from 0 to 70% [dichloromethane/MeOH 9:1] in dichloromethane in 15 CV) yielded 6-(4-fluorophenyl)-*N*₂,*N*₂-dimethyl-*N*₄-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazoline-2,4-diamine (73.5 mg, 0.187 mmol, 90 % yield) as a pale yellow
 10 powder.

LCMS: 0.71 min, *m/z* 393.0 [M+H]⁺, Method 5 acidic method.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.51 - 8.84 (m, 1 H), 8.45 (d, *J*=1.8 Hz, 1 H), 7.81 (dd, *J*=8.8, 5.7 Hz, 3 H), 7.32 (t, *J*=8.8 Hz, 3 H), 5.45 - 5.55 (m, 1 H), 3.02 (s, 6
 15 H), 2.30 (s, 3 H), 1.72 (d, *J*=7.0 Hz, 3 H).

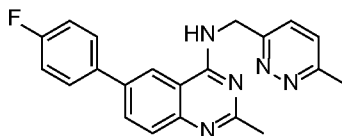
The following compounds were synthesised *via* adaptation of the above procedure. Example 237 was obtained using the same reaction conditions as Example 235, Example 238 was obtained using the same reaction conditions as Example 236

Example No.	Chemical Name Structure	Analytical data ¹ H NMR LC-MS
Example 235	<i>N</i> ₂ -cyclopropyl-6-(4-fluorophenyl)- <i>N</i> ₄ -(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazoline-2,4-diamine	LCMS (Method 5): 0.78 min, <i>m/z</i> 405.1 [M+H] ⁺ , ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.48 - 8.64 (m, 1 H), 8.42 (d, <i>J</i> =1.8 Hz, 1 H), 7.70 - 7.93 (m, 3 H), 7.25 - 7.35 (m, 3 H), 6.82 (s,

		1 H), 5.60 - 5.81 (m, 1 H), 2.58 - 2.77 (m, 1 H), 2.31 (s, 3 H), 1.71 (d, J=7.0 Hz, 3 H), 0.17 - 0.70 (m, 4 H).
Example 236	6-(4-fluorophenyl)-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)-2-morpholinoquinazolin-4-amine 	LCMS (Method 5): 0.67 min, m/z 435 [M+H] ⁺ , ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 8.69 (d, J=6.1 Hz, 1 H), 8.47 (d, J=1.8 Hz, 1 H), 7.90 (dd, J=8.8, 2.2 Hz, 1 H), 7.82 (dd, J=8.8, 5.3 Hz, 2 H), 7.27 - 7.43 (m, 3 H), 5.40 - 5.50 (s, 1 H), 3.46 - 3.80 (m, H), 2.31 (s, 3 H), 1.72 (d, J=7.5 Hz, 3 H).
Example 237	2-((2-(cyclopropylamino)-6-(4-fluorophenyl)quinazolin-4-yl)amino)propanamide 	LCMS (Method 5):: 0.72 min, m/z 406.1 [M+H] ⁺ , ¹ H NMR (400 MHz, DMSO-d ₆) d ppm 8.43 (s, 1 H), 7.92 - 8.07 (m, 1 H), 7.72 - 7.92 (m, 3 H), 7.21 - 7.43 (m, 3 H), 4.60 - 4.77 (m, 1 H), 2.85 - 2.70 (m, 1 H), 2.70 - 2.55 (m, 1 H), 1.41 (d, J=7.0 Hz, 3 H), 0.40 - 0.47 (m, 4 H), 0.32 - 0.50 (m, 4 H).
Example 238	N-cyclopropyl-2-((2-(cyclopropylamino)-6-(4-fluorophenyl)quinazolin-4-yl)amino)propanamide 	LCMS (Method 5):: 0.61 min, m/z 366.0 [M+H] ⁺ , ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 8.43 (s, 1 H), 8.11 (bs, 1 H), 7.69 - 7.91 (m, 3 H), 7.18 - 7.42 (m, 4 H), 6.96 (br s, 2 H), 4.73 (br t, J=7.23 Hz, 1 H), 2.75 - 2.94 (m, 1 H), 1.41 (d, J=7.23 Hz, 3 H), 0.55 - 0.71 (m, 2 H), 0.42 - 0.53 (m, 2 H).

Example 239

6-(4-fluorophenyl)-2-methyl-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine



Pd(dppf)Cl₂ · CH₂Cl₂ (11.86 mg, 0.015 mmol) was added to a mixture of 6-bromo-2-methyl-*N*-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine (Intermediate 9) (50 mg, 0.145 mmol), (4-fluorophenyl)boronic acid (30.5 mg, 0.218 mmol) and potassium phosphate (61.7 mg, 0.291 mmol) in DMF/water 2:1 (Volume: 3 ml). Stirring went on for 16 h at 80 °C. Purification by RP chromatography (Biotage Isolera, 30 g C18 cartridge, gradient elution from 0 to 65% B in A, A: water/acetonitrile 95:5 + 0.1% conc ammonia, B: acetonitrile:water 95:5 + 0.1% conc ammonia in 20 CV) then by RP chromatography (Biotage Isolera, 30 g C18 cartridge, gradient elution from 0 to 50% B in A, A: water/acetonitrile 95:5 + 0.1% HCOOH, B: acetonitrile:water 95:5 + 0.1% HCOOH in 15 CV) yielded 6-(4-fluorophenyl)-2-methyl-*N*-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine (35.9 mg, 0.100 mmol, 68.8 % yield) as an off-white powder.

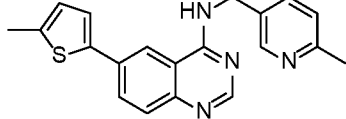
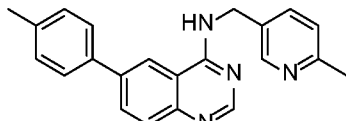
LCMS (Method 5): 0.53 min, m/z 360 [M+H]⁺.

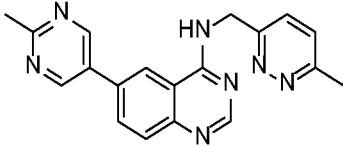
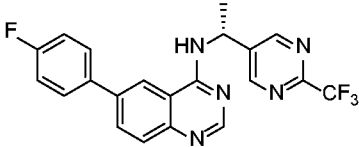
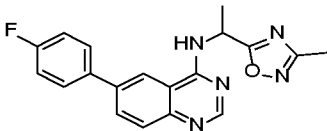
¹H NMR (400 MHz, DMSO-d₆) δ ppm 12.17 - 13.22 (bs, 1 H), 9.00 (br. s., 1 H), 8.60 (d, J=1.8 Hz, 1 H), 8.07 (dd, J=8.8, 1.8 Hz, 1 H), 7.87 (dd, J=8.8, 5.7 Hz, 2 H), 7.69 (d, J=8.3 Hz, 1 H), 7.46 - 7.61 (m, 2 H), 7.35 (t, J=8.8 Hz, 2 H), 5.03 (d, J=5.3 Hz, 2 H), 2.59 (s, 3 H), 2.43 (s, 3 H).

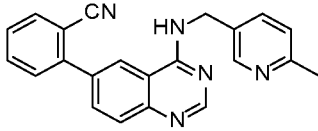
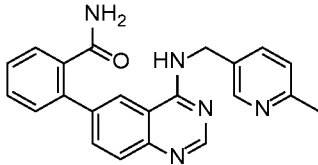
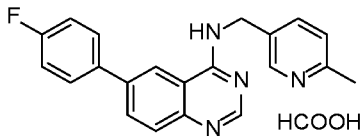
The following intermediates were synthesised *via* adaptations of the same procedure starting from suitable intermediates reported in table.

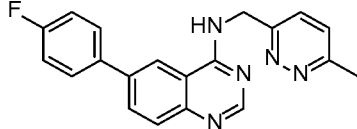
Example 246 was obtained with the same conditions used for Example 245.

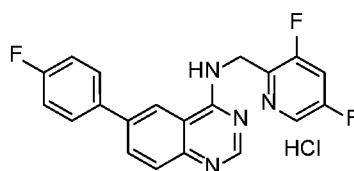
Example No.	Chemical Name Structure	Analytical data ¹ H NMR LC-MS	Starting Intermediate

Example 240	<p>N-((6-methylpyridin-3-yl)methyl)-6-(5-methylthiophen-2-yl)quinazolin-4-amine</p> 	<p>LCMS (Method 5): 0.42 min, m/z 346.9 [M+H]⁺.</p> <p>¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.91 (s, 1 H), 8.48 (dd, J=12.28, 1.75 Hz, 1 H), 8.45 (dd, J=12.28, 1.75 Hz, 1 H), 8.43 (s, 1 H), 7.99 (dd, J=8.55, 1.97 Hz, 1 H), 7.63 - 7.73 (m, 2 H), 7.44 (d, J=3.51 Hz, 1 H), 7.20 (d, J=7.89 Hz, 1 H), 6.88 (d, J=2.63 Hz, 1 H), 4.77 (br d, J=5.70 Hz, 2 H), 2.51 (s, 3 H), 2.43 (s, 3 H).</p>	Intermediate 8
Example 241	<p>N-((6-methylpyridin-3-yl)methyl)-6-(p-tolyl)quinazolin-4-amine</p> 	<p>LCMS (Method 5): 0.40 min, 341.0 m/z [M+H]⁺.</p> <p>¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.89 - 9.01 (m, 1 H), 8.59 (d, J=1.8 Hz, 1 H), 8.50 (d, J=1.8 Hz, 1 H), 8.46 (s, 1 H), 8.10 (s, 1 H), 7.75 (dd, J=8.6, 2.4 Hz, 3 H), 7.68 (dd, J=8.3, 2.2 Hz, 1 H), 7.33 (d, J=7.9 Hz, 2 H), 7.20 (d, J=7.9 Hz, 1 H), 4.78 (d, J=5.7 Hz, 2 H), 2.43 (s, 3 H), 2.37 (s, 3 H).</p>	Intermediate 8
Example 242	<p>N-((6-methylpyridazin-3-yl)methyl)-6-(2-methylpyrimidin-5-yl)quinazolin-4-amine</p>	<p>LCMS (Method 5): 0.35 min, m/z 344.0.</p> <p>¹H NMR (400 MHz, DMSO-d₆) δ ppm</p>	Intermediate 9

		<p>9.19 (s, 2 H), 9.06 - 9.16 (m, 1 H), 8.79 (d, J=2.2 Hz, 1 H), 8.48 (s, 1 H), 8.25 (d, J=1.8 Hz, 1 H), 7.83 (d, J=8.8 Hz, 1 H), 7.58 (d, J=8.4 Hz, 1 H), 7.50 (d, J=8.4 Hz, 1 H), 5.05 (d, J=5.7 Hz, 2 H), 2.70 (s, 3 H), 2.59 (s, 3 H).</p>	
Example 243	<p>(R)-6-(4-fluorophenyl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine</p> 	<p>LCMS (Method 5): 0.77 min, m/z 414.0.</p> <p>¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.17 (s, 2 H), 8.72 (d, J=7.1 Hz, 1 H), 8.67 (d, J=1.8 Hz, 1 H), 8.44 (s, 1 H), 8.12 (dd, J=8.6, 2.0 Hz, 1 H), 7.84 - 7.96 (m, 2 H), 7.78 (d, J=8.8 Hz, 1 H), 7.39 (t, J=8.8 Hz, 2 H), 5.69 (t, J=7.1 Hz, 1 H), 1.74 (d, J=7.1 Hz, 3 H).</p>	Intermediate 10
Example 244	<p>6-(4-fluorophenyl)-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine</p> 	<p>LCMS (Method 5): 0.72 min, m/z 350.0.</p> <p>¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.86 (d, J=7.0 Hz, 1 H), 8.65 (d, J=1.3 Hz, 1 H), 8.43 (s, 1 H), 8.12 (dd, J=8.6, 1.5 Hz, 1 H), 7.87 (dd, J=8.6, 5.5 Hz, 2 H), 7.78 (d, J=8.8 Hz, 1 H), 7.35 (t, J=8.8 Hz, 2 H), 5.77 (t, J=7.2 Hz, 1 H), 2.28 (s, 3 H), 1.70 (d, J=7.0 Hz, 3 H).</p>	Intermediate 11

Example 245	<p>2-(4-(((6-methylpyridin-3-yl)methyl)amino)quinazolin-6-yl)benzonitrile</p> 	<p>LCMS (Method 5): : 0.34 min, 351.9 m/z [M+H]⁺, ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.97 (t, J=5.5 Hz, 1 H), 8.53 (s, 2 H), 8.49 (d, J=1.3 Hz, 1 H), 7.95 - 8.05 (m, 2 H), 7.79 - 7.90 (m, 2 H), 7.75 (d, J=7.5 Hz, 1 H), 7.59 - 7.71 (m, 2 H), 7.19 (d, J=7.9 Hz, 1 H), 4.76 (d, J=5.7 Hz, 2 H), 2.42 (s, 3 H).</p>	Intermediate 8
Example 246	<p>2-(4-(((6-methylpyridin-3-yl)methyl)amino)quinazolin-6-yl)benzamide</p> 	<p>LCMS (Method 6): 0.68 min, 369.9 m/z [M+H]⁺, ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.88 (t, J=5.7 Hz, 1 H), 8.43 - 8.53 (m, 2 H), 8.33 (d, J=1.3 Hz, 1 H), 7.76 (d, J=1.8 Hz, 1 H), 7.60 - 7.70 (m, 3 H), 7.42 - 7.58 (m, 4 H), 7.33 (bs, 1 H), 7.19 (d, J=7.9 Hz, 1 H), 4.75 (d, J=5.7 Hz, 2 H), 2.42 (s, 3 H).</p>	Intermediate 8
Example 247	<p>6-(4-fluorophenyl)-N-(((6-methylpyridin-3-yl)methyl)amino)quinazolin-4-amine formate</p> 	<p>LCMS (Method 5): : 0.45 min, m/z 345.0 [M+H]⁺, ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.95 (t, 1 H), 8.59 (d, J=1.8 Hz, 1 H), 8.42 - 8.54 (m, 2 H), 8.02 - 8.19 (m, 2 H), 7.81 - 7.93 (m, 2 H), 7.77 (d, J=8.8 Hz, 1 H), 7.68 (dd, J=7.9, 2.2 Hz, 1 H), 7.36 (t,</p>	Intermediate 8

		J=8.8 Hz, 2 H), 7.20 (d, J=7.9 Hz, 1 H), 4.78 (d, J=5.7 Hz, 2 H), 2.43 (s, 3 H).	
Example 248	6-(4-fluorophenyl)-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine 	LCMS (Method 5): : 0.53 min, m/z 345.9 [M+H] ⁺ , ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 9.13 (t, J=5.9 Hz, 1 H), 8.65 (d, J=1.8 Hz, 1 H), 8.45 (s, 1 H), 8.13 (dd, J=8.8, 1.8 Hz, 1 H), 7.90 (dd, J=8.8, 5.3 Hz, 2 H), 7.78 (d, J=8.8 Hz, 1 H), 7.44 - 7.62 (m, 2 H), 7.37 (t, J=8.8 Hz, 2 H), 5.04 (d, J=5.7 Hz, 2 H), 2.59 (s, 3 H).	Intermediate 9

Example 249**N-((3,5-difluoropyridin-2-yl)methyl)-6-(4-fluorophenyl)quinazolin-4-amine hydrochloride**

- 5 DIPEA (0.15 mL, 0.861 mmol) was added to a mixture of 6-bromo-4-chloroquinazoline (100 mg, 0.411 mmol) and (3,5-difluoropyridin-2-yl)methanamine hydrochloride (74.2 mg, 0.411 mmol) in DMF (Volume: 2 ml). Stirring went on for 6 h at 80 °C. Upon completion of conversion of starting materials to 6-bromo-N-((3,5-difluoropyridin-2-yl)methyl)quinazolin-4-amine, water (1 mL) was added to the reaction
- 10 mixture followed by 4-fluorophenylboronic acid (86 mg, 0.614 mmol), potassium

phosphate (174 mg, 0.818 mmol) and Pd(dppf)Cl₂ · CH₂Cl₂ (33.5 mg, 0.041 mmol). Stirring went on for 16 h at 80 °C. The mixture was allowed to cool down to rt, then formic acid (150 μL, 3.98 mmol) was added. Purification by RP chromatography (Biotage Isolera, 30 g C18 cartridge, gradient elution from 100:0 to 65:35 A/B, A: water/acetonitrile 95:5 + 0.1% HCOOH, B: acetonitrile:water 95:5 + 0.1% HCOOH in 15 CV) yielded *N*-((3,5-difluoropyridin-2-yl)methyl)-6-(4-fluorophenyl)quinazolin-4-amine hydrochloride (98.4 mg, 0.244 mmol, 59.5 % yield) as an off-white powder.

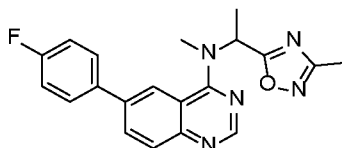
LCMS (Method 5): : 0.67 min, 366.9 m/z [M+H]⁺,

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.82 (br s, 1 H), 8.92 - 9.00 (m, 1 H), 8.84 - 8.91 (m, 1 H), 8.44 - 8.50 (m, 1 H), 8.34 - 8.44 (m, 1 H), 7.98 - 8.07 (m, 1 H), 7.87 - 7.97 (m, 3 H), 7.43 (t, J=8.88 Hz, 2 H), 5.13 (br d, J=5.26 Hz, 2 H).

Example 250

6-(4-fluorophenyl)-*N*-methyl-*N*-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine

quinazolin-4-amine



15

To a solution of 6-(4-fluorophenyl)-*N*-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine (30 g, 0.086 mmol) in DMF (1 mL), cooled to 0 °C, NaH (6.07 mg, 0.240 mmol) was added and the reaction stirred for 30 min before adding MeI (10.74 μL, 0.172 mmol). After 20h, the crude mixture was directly loaded onto column and purified by RP flash chromatography (Biotage Isolera, 12 g C18 cartridge, gradient elution from 0 to 80% B in A; A: water/MeCN 95:5 + 0.1% HCOOH, B: MeCN/water 95:5 + 0.1% HCOOH) yielded the titled compound (16 mg, 0.044 mmol, 51.3 % yield) as pale beige powder.

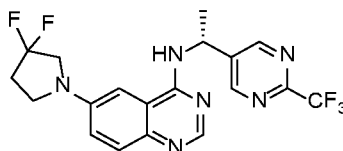
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LCMS (Method 5): 0.57 min, 364.0 [M+H]⁺.

¹H NMR (400 MHz, DMSO-d₆) δ □ppm 8.33 (d, J=2.2 Hz, 1 H), 8.08 (s, 1 H), 7.98 (dd, J=8.4, 2.2 Hz, 1 H), 7.69 - 7.77 (m, 2 H), 7.51 (d, J=8.8 Hz, 1 H), 7.32 (t, J=8.8 Hz, 2 H), 5.72 (d, J=6.6 Hz, 1 H), 3.63 (s, 3 H), 2.31 (s, 3 H), 1.53 (d, J=7.1 Hz, 3 H).

5 Example 251

(R)-6-(3,3-difluoropyrrolidin-1-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine

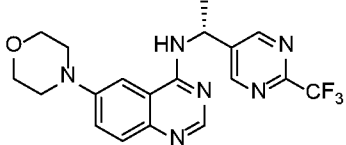
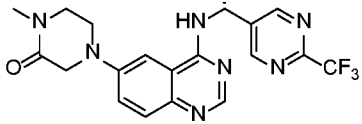
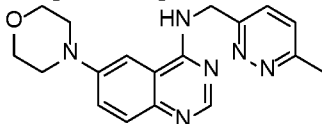


10 To a suspension of *(R)*-6-bromo-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine (40 mg, 0.100 mmol) in Toluene (1.5 mL), 3,3-difluoropyrrolidine hydrochloride (36 mg, 0.251 mmol) and cesium carbonate (82 mg, 0.251 mmol) were added, followed by *(R)*-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (13 mg, 0.020 mmol) and tris(dibenzylideneacetone)dipalladium (0) (9.20 mg, 15 10.05 μmol). The resulting mixture was heated to 100 °C and stirred for 7h. The mixture was cooled to RT and filtered. Volatiles were removed under reduced pressure. Purification by RP flash chromatography (Biotage Isolera, 30 g C18 cartridge, gradient elution from 0 to 90% B in A; A: water/MeCN 95:5 + 0.1% HCOOH, B: MeCN/water 95:5 + 0.1% HCOOH) yielded impure product. A second purification by flash 20 chromatography (Biotage Isolera, 11 g NH cartridge, gradient elution from 5% to 100% EtOAc in heptane) yielded the titled compound (21 mg, 4.95 μmol, 5 % yield) as white powder.

LCMS (Method 5): 0.68 min, 425.0 [M+H]⁺.

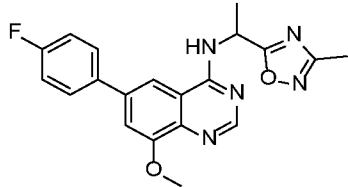
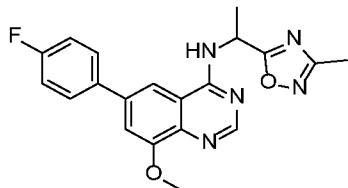
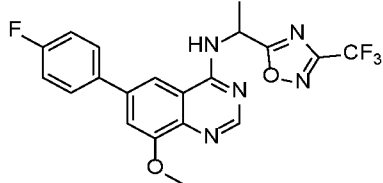
¹H NMR (400 MHz, DMSO-d₆) δ 9.13 (s, 2H), 8.31 (d, J=7.06 Hz, 1H), 8.27 (s, 1H), 7.55-7.62 (m, 3H), 5.66 (quin, J=6.89 Hz, 1H), 3.76 (t, J=13.89 Hz, 2H), 3.51 (t, J=7.06 Hz, 2H), 2.39-2.49 (m, 2H), 1.72 (d, J=7.06 Hz, 3H).

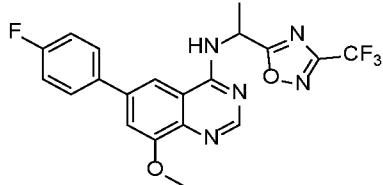
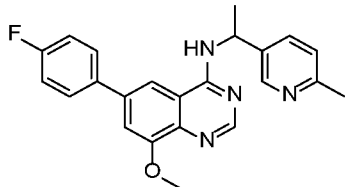
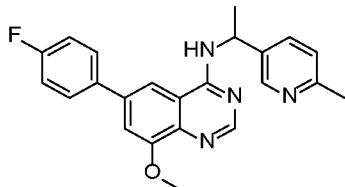
The following Examples were synthesised *via* adaptations of the above procedure.

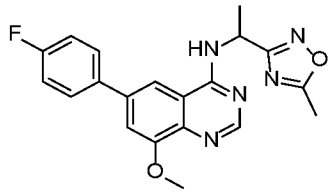
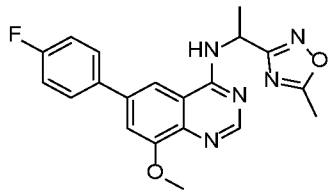
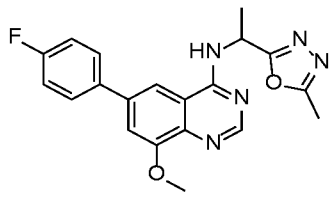
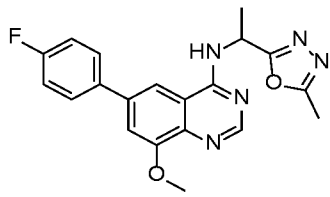
Example No.	Chemical Name Structure	Analytical data ¹ H NMR LC-MS
Example 252	(<i>R</i>)-6-morpholino- <i>N</i> -(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine 	LCMS (Method 5): 0.53 min, 405.0 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 9.13 (s, 2 H), 8.29 - 8.34 (m, 1 H), 8.27 (s, 1 H), 7.53 - 7.65 (m, 2 H), 7.35 - 7.47 (m, 1 H), 5.56 - 5.75 (m, 1 H), 3.75 - 3.94 (m, 4 H), 3.20 - 3.30 (m, 4 H), 1.71 (d, J=7.0 Hz, 3 H).
Example 253	(<i>R</i>)-1-methyl-4-(4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino) quinazolin-6-yl)piperazin-2-one 	LCMS (Method 5): 0.48 min, 432 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 9.13 (s, 2 H), 8.38 (d, J=6.6 Hz, 1 H), 8.26 (s, 1 H), 7.56 - 7.73 (m, 2 H), 7.53 (d, J=2.2 Hz, 1 H), 5.51 - 5.77 (m, 1 H), 3.95 (s, 2 H), 3.59 - 3.70 (m, 2 H), 3.45 - 3.57 (m, 2 H), 2.94 (s, 3 H), 1.73 (d, J=7.1 Hz, 3 H).
Example 254	<i>N</i> -((6-methylpyridazin-3-yl)methyl)-6-morpholinoquinazolin-4-amine 	LCMS (Method 5): 0.34 min, 337 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ □ ppm 8.68 - 8.77 (m, 1 H), 8.22 - 8.32 (m, 1 H), 7.37 - 7.64 (m, 5 H), 4.91 - 5.04 (m, 2 H), 3.72 - 3.87 (m, 4 H), 3.17 - 3.27 (m, 4 H), 2.58 (s, 3 H).

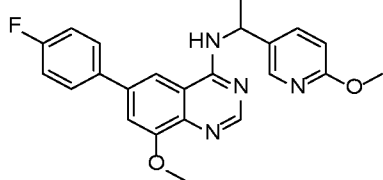
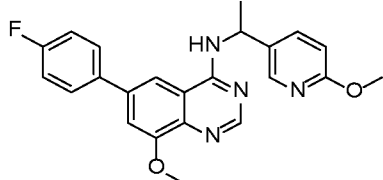
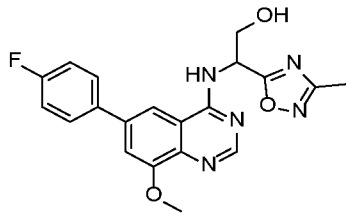
The following compounds reported in the table below were obtained as single isomers by chiral preparative SFC purification of the appropriate racemic mixture hereinabove described.

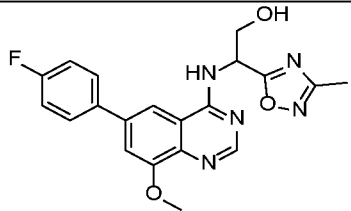
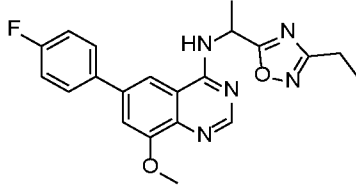
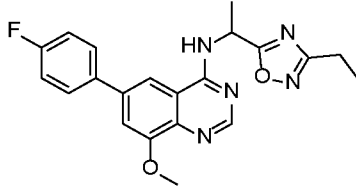
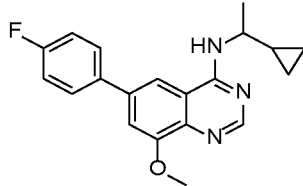
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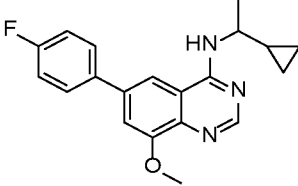
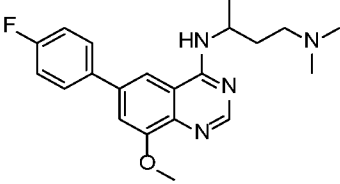
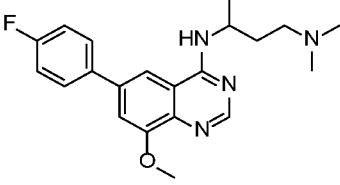
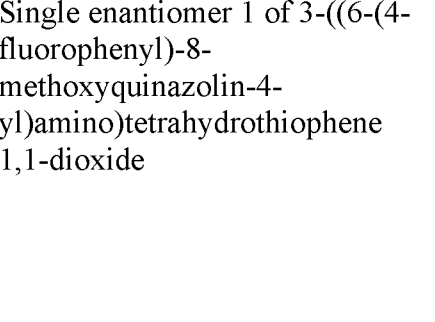
Example No.	Chemical Name Structure	Analytical data ¹ H NMR LC-MS
Example 255	Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy- <i>N</i> -(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.79 (d, J = 6.8 Hz, 1 H), 8.44 (s, 1 H), 8.20 (d, J = 1.5 Hz, 1 H), 7.97-7.93 (m, 2 H), 7.56 (d, J = 1.3 Hz, 1 H), 7.40 (dd, J = 8.9, 8.9 Hz, 2 H), 5.83-5.78 (m, 1 H), 4.03 (s, 3 H), 2.33 (s, 3 H), 1.74 (d, J = 7.2 Hz, 3 H). LCMS (Method 4): [MH ⁺] = 380 at 3.27 min. Chiral analysis (Method 9) at 2.7 min.
Example 256	Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy- <i>N</i> -(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.79 (d, J = 7.3 Hz, 1 H), 8.44 (s, 1 H), 8.21 (d, J = 1.6 Hz, 1 H), 7.97-7.93 (m, 2 H), 7.56 (d, J = 1.5 Hz, 1 H), 7.40 (dd, J = 8.9, 8.9 Hz, 2 H), 5.83-5.78 (m, 1 H), 4.03 (s, 3 H), 2.33 (s, 3 H), 1.74 (d, J = 7.2 Hz, 3 H). LCMS (Method 4): [MH ⁺] = 380 at 3.27 min. Chiral analysis (Method 9) at 3.27 min.
Example 257	Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy- <i>N</i> -(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.91 (d, J = 6.8 Hz, 1 H), 8.44 (s, 1 H), 8.17 (d, J = 1.6 Hz, 1 H), 7.97-7.92 (m, 2 H), 7.58 (d, J = 1.5 Hz, 1 H), 7.40 (dd, J = 8.9, 8.9 Hz, 2 H), 5.94-5.89 (m, 1 H), 4.04 (s, 3 H), 1.81 (d, J = 7.0 Hz, 3 H). LCMS (Method 3): [MH ⁺] = 434 at 4.96 min.

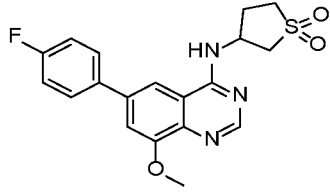
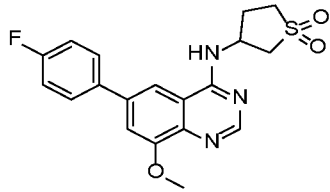
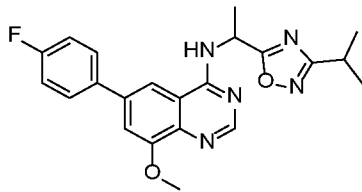
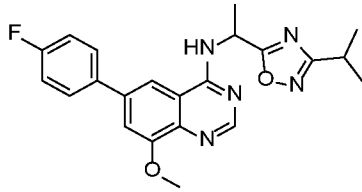
		Chiral analysis (Method 8) at 2.6 min.
Example 258	<p>Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-<i>N</i>-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine</p> 	¹ H NMR (400 MHz, DMSO): δ 8.91 (d, J = 7.4 Hz, 1 H), 8.44 (s, 1 H), 8.17 (d, J = 1.4 Hz, 1 H), 7.97-7.91 (m, 2 H), 7.58 (d, J = 1.5 Hz, 1 H), 7.43-7.38 (m, 2 H), 5.95-5.88 (m, 1 H), 4.04 (s, 4 H), 1.81 (d, J = 7.0 Hz, 3 H). LCMS (Method 3): [MH ⁺] = 434 at 4.95 min. Chiral analysis (Method 8) at 3.6 min.
Example 259	<p>Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-<i>N</i>-(1-(6-methylpyridin-3-yl)ethyl)quinazolin-4-amine</p> 	¹ H NMR (400 MHz, DMSO): δ 8.54 (d, J = 2.4 Hz, 1 H), 8.52-8.47 (m, 1 H), 8.40 (s, 1 H), 8.22 (d, J = 1.6 Hz, 1 H), 7.97-7.92 (m, 2 H), 7.73 (dd, J = 2.3, 8.1 Hz, 1 H), 7.51 (d, J = 1.5 Hz, 1 H), 7.40 (dd, J = 8.8, 8.8 Hz, 2 H), 7.21 (d, J = 8.0 Hz, 1 H), 5.63-5.58 (m, 1 H), 4.01 (s, 3 H), 2.43 (s, 3 H), 1.64 (d, J = 7.2 Hz, 3 H). LCMS (Method 4): [MH ⁺] = 389 at 2.55 min. Chiral analysis (Method 5) at 1.9 min.
Example 260	<p>Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-<i>N</i>-(1-(6-methylpyridin-3-yl)ethyl)quinazolin-4-amine</p> 	¹ H NMR (400 MHz, DMSO): δ 8.54 (d, J = 2.4 Hz, 1 H), 8.52-8.47 (m, 1 H), 8.40 (s, 1 H), 8.22 (d, J = 1.6 Hz, 1 H), 7.97-7.92 (m, 2 H), 7.73 (dd, J = 2.3, 8.1 Hz, 1 H), 7.51 (d, J = 1.5 Hz, 1 H), 7.40 (dd, J = 8.8, 8.8 Hz, 2 H), 7.21 (d, J = 8.0 Hz, 1 H), 5.63-5.58 (m, 1 H), 4.01 (s, 3 H), 2.43 (s, 3 H), 1.64 (d, J = 7.2 Hz, 3 H). LCMS (Method 4): [MH ⁺] = 389 at 2.55 min. Chiral analysis (Method 5) at 2.6 min.
Example 261	<p>Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-<i>N</i>-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine</p>	¹ H NMR (400 MHz, DMSO): δ 8.64 (d, J = 7.8 Hz, 1 H), 8.44 (s, 1 H), 8.23 (d, J = 1.6 Hz, 1 H), 7.97-7.93 (m, 2 H), 7.54 (d,

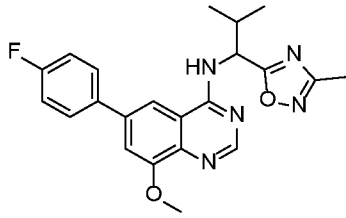
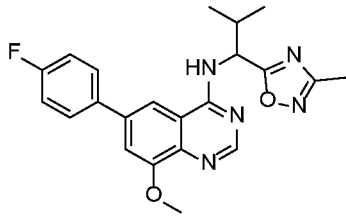
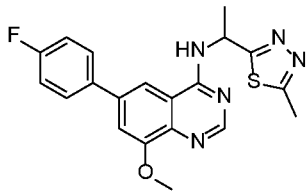
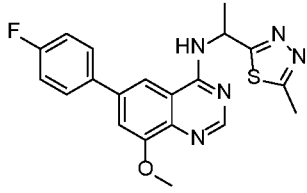
		$J = 1.5 \text{ Hz}$, 1 H), 7.39 (dd, $J = 8.9, 8.9 \text{ Hz}$, 2 H), 5.79-5.74 (m, 1 H), 4.03 (s, 3 H), 2.57 (s, 3 H), 1.68 (d, $J = 7.0 \text{ Hz}$, 3 H). LCMS (Method 3): $[\text{MH}^+] = 380$ at 4.14 min. Chiral analysis (Method 14) at 2.0 min.
Example 262 Single enantiomer 2	Single enantiomer of 6-(4-fluorophenyl)-8-methoxy- <i>N</i> -(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine 	$^1\text{H NMR}$ (400 MHz, DMSO): δ 8.64 (d, $J = 7.8 \text{ Hz}$, 1 H), 8.44 (s, 1 H), 8.23 (d, $J = 1.6 \text{ Hz}$, 1 H), 7.97-7.93 (m, 2 H), 7.54 (d, $J = 1.5 \text{ Hz}$, 1 H), 7.39 (dd, $J = 8.8, 8.8 \text{ Hz}$, 2 H), 5.79-5.74 (m, 1 H), 4.03 (s, 3 H), 2.58 (s, 3 H), 1.68 (d, $J = 7.0 \text{ Hz}$, 3 H). LCMS (Method 3): $[\text{MH}^+] = 380$ at 4.15 min. Chiral analysis (Method 14) at 3.1 min.
Example 263	Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy- <i>N</i> -(1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)quinazolin-4-amine 	$^1\text{H NMR}$ (400 MHz, DMSO): δ 8.73 (d, $J = 7.5 \text{ Hz}$, 1 H), 8.48 (s, 1 H), 8.17 (d, $J = 1.8 \text{ Hz}$, 1 H), 7.96-7.91 (m, 2 H), 7.56 (d, $J = 1.5 \text{ Hz}$, 1 H), 7.39 (dd, $J = 8.9, 8.9 \text{ Hz}$, 2 H), 5.90-5.85 (m, 1 H), 4.03 (s, 3 H), 2.48 (s, 3 H), 1.72 (d, $J = 7.0 \text{ Hz}$, 3 H). LCMS (Method 4): $[\text{MH}^+] = 380$ at 3.06 min. Chiral analysis (Method 19) at 2.63 min.
Example 264	Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy- <i>N</i> -(1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)quinazolin-4-amine 	$^1\text{H NMR}$ (400 MHz, DMSO): δ 8.80 (br s, 1 H), 8.50 (s, 1 H), 8.18 (d, $J = 1.5 \text{ Hz}$, 1 H), 7.96-7.92 (m, 2 H), 7.57 (s, 1 H), 7.39 (dd, $J = 8.9, 8.9 \text{ Hz}$, 2 H), 5.91-5.86 (m, 1 H), 4.04 (s, 3 H), 3.44-3.38 (m, 1 H), 2.48 (s, 3 H), 1.72 (d, $J = 7.0 \text{ Hz}$, 3 H). LCMS (Method 4): $[\text{MH}^+] = 380$ at 3.02 min. Chiral analysis (Method 19) at 3.57 min.
Example 265	Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy- <i>N</i> -(1-(6-methoxypyridin-3-yl)ethyl)quinazolin-4-amine	$^1\text{H NMR}$ (400 MHz, DMSO): δ 8.46 (d, $J = 7.7 \text{ Hz}$, 1 H), 8.42 (s, 1 H), 8.26 (d, $J = 2.5 \text{ Hz}$, 1 H), 8.20 (d, $J = 1.6 \text{ Hz}$, 1 H), 7.96-7.91 (m, 2 H), 7.80 (dd, J

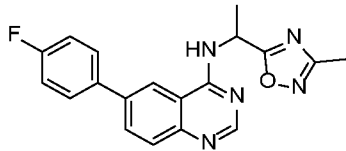
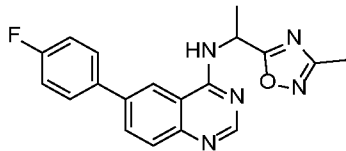
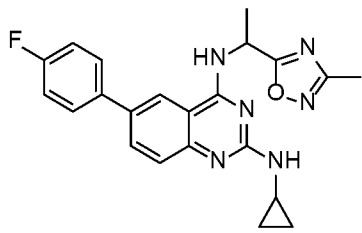
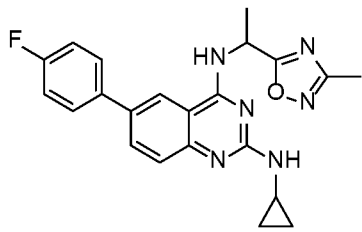
		<p>= 2.5, 8.7 Hz, 1 H), 7.51 (d, J = 1.5 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 6.80 (d, J = 8.7 Hz, 1 H), 5.63-5.58 (m, 1 H), 4.01 (s, 3 H), 3.82 (s, 3 H), 1.63 (d, J = 7.0 Hz, 3 H). LCMS (Method 4): [MH⁺] = 405 at 3.57 min. Chiral analysis (Method 20) at 1.68 min.</p>
Example 266	<p>Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-<i>N</i>-(1-(6-methoxypyridin-3-yl)ethyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.45 (d, J = 7.7 Hz, 1 H), 8.42 (s, 1 H), 8.26 (d, J = 2.5 Hz, 1 H), 8.20 (d, J = 1.6 Hz, 1 H), 7.96-7.91 (m, 2 H), 7.80 (dd, J = 2.6, 8.6 Hz, 1 H), 7.51 (d, J = 1.6 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 6.80 (d, J = 8.5 Hz, 1 H), 5.63-5.58 (m, 1 H), 4.01 (s, 3 H), 3.82 (s, 3 H), 1.63 (d, J = 7.2 Hz, 3 H). LCMS (Method 3): [MH⁺] = 405 at 3.58 min. Chiral analysis (Method 20) at 2.68 min.</p>
Example 267	<p>Single enantiomer 1 of 2-((6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)amino)-2-(3-methyl-1,2,4-oxadiazol-5-yl)ethan-1-ol</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.71 (d, J = 7.4 Hz, 1 H), 8.45 (s, 1 H), 8.25 (d, J = 1.6 Hz, 1 H), 7.99-7.94 (m, 2 H), 7.57 (d, J = 1.5 Hz, 1 H), 7.40 (dd, J = 8.9, 8.9 Hz, 2 H), 5.80-5.74 (m, 1 H), 5.38 (dd, J = 6.0, 6.0 Hz, 1 H), 4.03 (s, 6 H), 2.33 (s, 3 H). LCMS (Method 3): [MH⁺] = 389 at 2.55 min. Chiral analysis (Method 12) at 3.6 min.</p>
Example 268	<p>Single enantiomer 2 of 2-((6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)amino)-2-(3-methyl-1,2,4-oxadiazol-5-yl)ethan-1-ol</p>	<p>¹H NMR (400 MHz, DMSO): δ 8.71 (d, J = 7.4 Hz, 1 H), 8.45 (s, 1 H), 8.25 (d, J = 1.6 Hz, 1 H), 7.99-7.94 (m, 2 H), 7.57 (d, J = 1.6 Hz, 1 H), 7.40 (dd, J = 8.9, 8.9 Hz, 2 H), 5.80-5.74 (m, 1 H), 5.39 (dd, J = 6.0, 6.0 Hz, 1 H), 4.03 (s, 5 H), 3.44-3.38 (m, 1 H), 3.31 (s, 2 H), 2.33 (s, 3 H). LCMS (Method 4):</p>

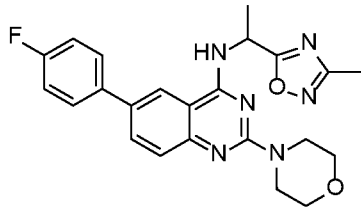
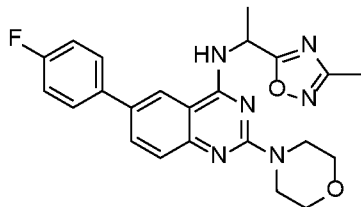
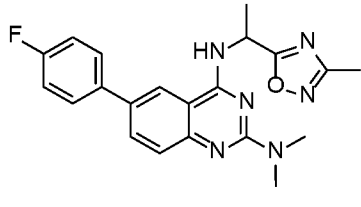
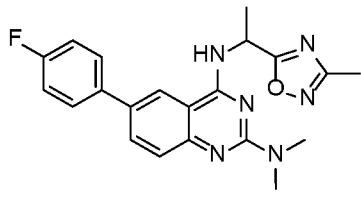
		<p>[MH⁺] = 396 at 2.97 min. Chiral analysis (Method 12) at 4.85 min.</p>
Example 269	<p>Single enantiomer 1 of <i>N</i>-(1-(3-ethyl-1,2,4-oxadiazol-5-yl)ethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.80 (d, J = 7.2 Hz, 1 H), 8.45 (s, 1 H), 8.21 (d, J = 1.5 Hz, 1 H), 7.97-7.92 (m, 2 H), 7.56 (d, J = 1.4 Hz, 1 H), 7.40 (dd, J = 8.9, 8.9 Hz, 2 H), 5.85-5.79 (m, 1 H), 4.03 (s, 3 H), 2.71 (q, J = 7.6 Hz, 2 H), 1.74 (d, J = 7.2 Hz, 3 H), 1.22 (dd, J = 7.6, 7.6 Hz, 3 H). LCMS (Method 4): [MH⁺] = 394 at 3.47 min. Chiral analysis (Method 9) at 2.61 min.</p>
Example 270	<p>Single enantiomer 2 of <i>N</i>-(1-(3-ethyl-1,2,4-oxadiazol-5-yl)ethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.80 (d, J = 7.3 Hz, 1 H), 8.45 (s, 1 H), 8.21 (d, J = 1.6 Hz, 1 H), 7.97-7.93 (m, 2 H), 7.57 (d, J = 1.6 Hz, 1 H), 7.40 (dd, J = 8.8, 8.8 Hz, 2 H), 5.85-5.80 (m, 1 H), 4.03 (s, 3 H), 2.71 (q, J = 7.5 Hz, 2 H), 1.74 (d, J = 7.2 Hz, 3 H), 1.22 (dd, J = 7.5, 7.5 Hz, 3 H). LCMS (Method 3): [MH⁺] = 394 at 4.68 min. Chiral analysis (Method 9) at 3.46 min.</p>
Example 271	<p>Single enantiomer 1 of <i>N</i>-(1-cyclopropylethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.36 (s, 1 H), 8.13-8.08 (m, 2 H), 7.94-7.89 (m, 2 H), 7.47 (d, J = 1.5 Hz, 1 H), 7.37 (dd, J = 8.9, 8.9 Hz, 2 H), 3.99 (s, 3 H), 3.94 (dd, J = 8.2, 14.9 Hz, 1 H), 1.32 (d, J = 6.7 Hz, 3 H), 1.17-1.08 (m, 1 H), 0.55-0.22 (m, 1 H). LCMS (Method 4): [MH⁺] = 338 at 3.67 min. Chiral analysis (Method 14) at 6.55 min.</p>

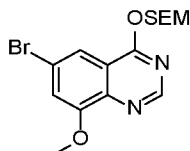
Example 272	Single enantiomer 2 of <i>N</i> -(1-cyclopropylethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.36 (s, 1 H), 8.13-8.08 (m, 2 H), 7.94-7.89 (m, 2 H), 7.47 (d, J = 1.5 Hz, 1 H), 7.37 (dd, J = 8.9, 8.9 Hz, 2 H), 3.99 (s, 3 H), 3.94 (dd, J = 8.3, 14.9 Hz, 1 H), 1.32 (d, J = 6.5 Hz, 3 H), 1.16-1.08 (m, 1 H), 0.55-0.23 (m, 1 H). LCMS (Method 3): [MH ⁺] = 338 at 3.68 min. Chiral analysis (Method 14) at 7.91 min.
Example 273	Single enantiomer 1 of <i>N</i> ³ -(6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)- <i>N</i> ¹ , <i>N</i> ¹ -dimethylbutane-1,3-diamine 	¹ H NMR (400 MHz, DMSO): δ 8.42 (s, 1 H), 8.09-8.04 (m, 2 H), 7.94-7.89 (m, 2 H), 7.48 (d, J = 1.5 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 4.56-4.48 (m, 1 H), 4.01 (s, 3 H), 2.35-2.28 (m, 2 H), 2.14 (s, 6 H), 1.89-1.67 (m, 1 H), 1.27 (d, J = 6.7 Hz, 3 H). LCMS (Method 4): [MH ⁺] = 369 at 2.37 min. Chiral analysis (Method 7) at 1.62 min.
Example 274	Single enantiomer 2 of <i>N</i> ³ -(6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)- <i>N</i> ¹ , <i>N</i> ¹ -dimethylbutane-1,3-diamine 	¹ H NMR (400 MHz, DMSO): δ 8.42 (s, 1 H), 8.09-8.04 (m, 2 H), 7.94-7.89 (m, 2 H), 7.48 (d, J = 1.5 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 4.56-4.48 (m, 1 H), 4.01 (s, 3 H), 2.35-2.28 (m, 2 H), 2.14 (s, 6 H), 1.88-1.68 (m, 1 H), 1.27 (d, J = 6.5 Hz, 3 H). LCMS (Method 4): [MH ⁺] = 369 at 2.37 min. Chiral analysis (Method 7) at 2.4 min.
Example 275	Single enantiomer 1 of 3-((6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)amino)tetrahydrothiophene 1,1-dioxide 	¹ H NMR (400 MHz, DMSO): δ 8.57 (s, 1 H), 8.43-8.38 (m, 1 H), 8.13 (d, J = 1.6 Hz, 1 H), 7.98-7.94 (m, 2 H), 7.58 (d, J = 1.6 Hz, 1 H), 7.45 (dd, J = 8.9, 8.9 Hz, 2 H), 5.14 (dd, J = 7.2, 15.8 Hz, 1 H), 4.07 (s, 3 H), 3.73 (dd, J = 8.2, 13.3 Hz, 1 H), 3.53-3.46 (m, 1 H), 3.35-3.28

		(m, 1 H), 3.19 (dd, J = 8.0, 13.2 Hz, 1 H), 2.67-2.61 (m, 1 H), 2.45-2.36 (m, 1 H). LCMS (Method 4): [MH ⁺] = 388 at 2.97 min. Chiral analysis (Method 15) at 4.5 min.
Example 276	<p>Single enantiomer 2 of 3-((6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)amino)tetrahydrothiophene 1,1-dioxide</p> 	¹ H NMR (400 MHz, DMSO): δ 8.64 (d, J = 7.8 Hz, 1 H), 8.44 (s, 1 H), 8.23 (d, J = 1.6 Hz, 1 H), 7.97-7.93 (m, 2 H), 7.54 (d, J = 1.5 Hz, 1 H), 7.39 (dd, J = 8.8, 8.8 Hz, 2 H), 5.79-5.74 (m, 1 H), 4.03 (s, 3 H), 2.58 (s, 3 H), 1.68 (d, J = 7.0 Hz, 3 H). LCMS (Method 4): [MH ⁺] = 388 at 2.98 min. Chiral analysis (Method 15) at 6.86 min.
Example 277	<p>Single enantiomer 1 of 6-(4-fluorophenyl)-N-[1-(3-isopropyl-1,2,4-oxadiazol-5-yl)ethyl]-8-methoxy-quinazolin-4-amine</p> 	¹ H NMR (400 MHz, DMSO): δ 8.79 (d, J = 7.3 Hz, 1 H), 8.45 (s, 1 H), 8.20 (d, J = 1.8 Hz, 1 H), 7.97-7.93 (m, 2 H), 7.56 (d, J = 1.6 Hz, 1 H), 7.40 (dd, J = 8.9, 8.9 Hz, 2 H), 5.86-5.81 (m, 1 H), 4.03 (s, 3 H), 3.09-3.01 (m, 1 H), 1.74 (d, J = 7.2 Hz, 3 H), 1.25 (dd, J = 1.3, 7.0 Hz, 6 H). LCMS (Method 4): [MH ⁺] = 408 at 3.66 min. Chiral analysis (Method 11) at 2.52 min.
Example 278	<p>Single enantiomer 2 of 6-(4-fluorophenyl)-N-[1-(3-isopropyl-1,2,4-oxadiazol-5-yl)ethyl]-8-methoxy-quinazolin-4-amine</p> 	¹ H NMR (400 MHz, DMSO): δ 8.79 (d, J = 7.3 Hz, 1 H), 8.45 (s, 1 H), 8.20 (d, J = 1.8 Hz, 1 H), 7.97-7.93 (m, 2 H), 7.56 (d, J = 1.6 Hz, 1 H), 7.40 (dd, J = 8.9, 8.9 Hz, 2 H), 5.86-5.81 (m, 1 H), 4.03 (s, 3 H), 3.09-3.01 (m, 1 H), 1.74 (d, J = 7.2 Hz, 3 H), 1.25 (dd, J = 1.3, 7.0 Hz, 6 H). LCMS (Method 4): [MH ⁺] = 408 at 3.73 min. Chiral analysis (Method 11) at 3.23 min.
Example 279	<p>Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-N-[2-methyl-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl]quinazolin-4-amine</p>	¹ H NMR (400 MHz, DMSO): δ 8.68 (d, J = 7.8 Hz, 1 H), 8.44 (s, 1 H), 8.31 (d, J = 1.6 Hz, 1 H), 7.96 (ddd, J = 3.2, 5.4, 12.1 Hz, 2 H), 7.56 (d, J = 1.5 Hz, 1

		<p>H), 7.41 (dd, J = 8.9, 8.9 Hz, 2 H), 5.53 (dd, J = 8.5, 8.5 Hz, 1 H), 4.02 (s, 3 H), 2.34 (s, 3 H), 1.13 (d, J = 6.7 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 3 H). LCMS (Method 4): [MH⁺] = 408 at 3.67 min.</p> <p>Chiral analysis (Method 13) at 3.68 min.</p>
Example 280	<p>Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-N-[2-methyl-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl]quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.68 (d, J = 7.8 Hz, 1 H), 8.44 (s, 1 H), 8.31 (d, J = 1.6 Hz, 1 H), 7.99-7.94 (m, 2 H), 7.56 (d, J = 1.5 Hz, 1 H), 7.41 (dd, J = 8.8, 8.8 Hz, 2 H), 5.53 (dd, J = 8.4, 8.4 Hz, 1 H), 4.02 (s, 3 H), 2.34 (s, 3 H), 1.13 (d, J = 6.7 Hz, 3 H), 0.95 (d, J = 6.7 Hz, 3 H). LCMS (Method 4): [MH⁺] = 408 at 3.68 min. Chiral analysis (Method 13) at 1.62 min.</p>
Example 281	<p>Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,3,4-thiadiazol-2-yl)ethyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.82 (d, J = 7.5 Hz, 1 H), 8.50 (s, 1 H), 8.20 (d, J = 1.6 Hz, 1 H), 7.96-7.92 (m, 2 H), 7.56 (d, J = 1.5 Hz, 1 H), 7.39 (dd, J = 8.8, 8.8 Hz, 2 H), 6.00-5.94 (m, 1 H), 4.03 (s, 3 H), 2.66 (s, 3 H), 1.81 (d, J = 7.0 Hz, 3 H). LCMS (Method 4): [MH⁺] = 396 at 3.12 min. Chiral analysis (Method 6) at 1.8 min.</p>
Example 282	<p>Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,3,4-thiadiazol-2-yl)ethyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.83 (d, J = 7.5 Hz, 1 H), 8.50 (s, 1 H), 8.20 (d, J = 1.8 Hz, 1 H), 7.96-7.92 (m, 2 H), 7.56 (d, J = 1.6 Hz, 1 H), 7.39 (dd, J = 8.9, 8.9 Hz, 2 H), 5.99-5.94 (m, 1 H), 4.03 (s, 3 H), 2.66 (s, 3 H), 1.80 (d, J = 7.0 Hz, 3 H). LCMS (Method 4): [MH⁺] = 396 at 3.11 min. Chiral analysis (Method 6) at 3.03 min.</p>
Example 283	<p>Single enantiomer 1 of 6-(4-fluorophenyl)-N-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]quinazolin-4-amine</p>	<p>¹H NMR (400 MHz, DMSO): δ 8.95 (d, J = 7.1 Hz, 1 H), 8.74 (d, J = 1.3 Hz, 1 H), 8.52 (s, 1 H), 8.21 (dd, J = 1.6, 8.7 Hz, 1</p>

		<p>H), 7.96 (dd, J = 5.6, 8.6 Hz, 2 H), 7.87 (d, J = 8.6 Hz, 1 H), 7.45 (dd, J = 8.8, 8.8 Hz, 2 H), 5.89-5.83 (m, 1 H), 2.37 (s, 3 H), 1.79 (d, J = 7.3 Hz, 3 H). LCMS (Method 3): [MH⁺] = 350 at 4.31 min. Chiral analysis (Method 8) at 1.92 min.</p>
Example 284	<p>Single enantiomer 2 of 6-(4-fluorophenyl)-<i>N</i>-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.83 (d, J = 7.1 Hz, 1 H), 8.61 (s, 1 H), 8.40 (s, 1 H), 8.09 (dd, J = 1.5, 8.6 Hz, 1 H), 7.83 (dd, J = 5.6, 8.6 Hz, 2 H), 7.74 (d, J = 8.6 Hz, 1 H), 7.32 (dd, J = 8.8, 8.8 Hz, 2 H), 5.77-5.71 (m, 1 H), 2.25 (s, 3 H), 1.67 (d, J = 7.1 Hz, 3 H). LCMS (Method 8): [MH⁺] = 350 at 2.45 min.</p>
Example 285	<p>Single enantiomer 1 of <i>N</i>²-cyclopropyl-6-(4-fluorophenyl)-<i>N</i>⁴-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]quinazoline-2,4-diamine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.47-8.47 (m, 1 H), 8.36 (s, 1 H), 7.80 (dd, J = 1.5, 8.6 Hz, 1 H), 7.74 (dd, J = 5.6, 8.6 Hz, 2 H), 7.31-7.22 (m, 3 H), 6.76 (d, J = 1.3 Hz, 1 H), 5.63-5.62 (m, 1 H), 2.69-2.54 (m, 1 H), 2.24 (s, 3 H), 1.65 (d, J = 7.1 Hz, 3 H), 0.55-0.52 (m, 2 H), 0.41-0.37 (m, 1 H), 0.26-0.26 (m, 1 H). LCMS (Method 4): [MH⁺] = 405 at 3.61 min. Chiral analysis (Method 16) at 1.86 min.</p>
Example 286	<p>Single enantiomer 2 of <i>N</i>²-cyclopropyl-6-(4-fluorophenyl)-<i>N</i>⁴-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]quinazoline-2,4-diamine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.41-8.38 (m, 1 H), 7.88 (dd, J = 1.8, 8.8 Hz, 1 H), 7.79 (dd, J = 5.5, 8.5 Hz, 2 H), 7.45-7.38 (m, 1 H), 7.30 (dd, J = 8.8, 8.8 Hz, 2 H), 5.71-5.60 (m, 1 H), 2.72-2.59 (m, 1 H), 2.29 (s, 3 H), 1.70 (d, J = 7.2 Hz, 3 H), 0.64-0.58 (m, 2 H), 0.45-0.42 (m, 1 H), 0.37-0.28 (m, 1 H). NH not observed. LCMS (Method 3): [MH⁺] = 405 at 4.77 min. Chiral analysis (Method 16) at 2.41 min.</p>

<p>Example 287</p>	<p>Single enantiomer 1 of 6-(4-fluorophenyl)-<i>N</i>-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]-2-morpholino-quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.76 (d, J = 5.8 Hz, 1 H), 8.53 (s, 1 H), 7.97 (d, J = 8.8 Hz, 1 H), 7.88 (dd, J = 5.4, 8.5 Hz, 2 H), 7.46-7.35 (m, 3 H), 5.59-5.51 (m, 1 H), 3.69-3.59 (m, 8 H), 2.36 (s, 3 H), 1.77 (d, J = 7.1 Hz, 3 H). LCMS (Method 3): [MH⁺] = 435 at 4.95 min. Chiral analysis (Method 17) at 1.17 min.</p>
<p>Example 288</p>	<p>Single enantiomer 2 of 6-(4-fluorophenyl)-<i>N</i>-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]-2-morpholino-quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 7.22 (d, J = 1.5 Hz, 1 H), 6.69 (dd, J = 2.0, 8.8 Hz, 1 H), 6.59 (dd, J = 5.6, 8.6 Hz, 2 H), 6.20 (d, J = 8.6 Hz, 1 H), 6.10 (dd, J = 8.8, 8.8 Hz, 2 H), 4.22 (q, J = 7.1 Hz, 1 H), 2.44-2.30 (m, 8 H), 1.08 (s, 3 H), 0.50 (d, J = 7.1 Hz, 3 H). NH not observed. LCMS (Method 3): [MH⁺] = 435 at 4.94 min. Chiral analysis (Method 17) at 1.89 min.</p>
<p>Example 289</p>	<p>Single enantiomer 1 of 6-(4-fluorophenyl)-<i>N</i>²,<i>N</i>²-dimethyl-<i>N</i>⁴-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]quinazoline-2,4-diamine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.40-8.37 (m, 1 H), 7.85 (d, J = 8.8 Hz, 1 H), 7.77 (dd, J = 5.7, 8.2 Hz, 2 H), 7.38 (d, J = 8.8 Hz, 1 H), 7.28 (dd, J = 8.7, 8.7 Hz, 2 H), 5.44 (q, J = 7.0 Hz, 1 H), 2.97 (s, 6 H), 2.27 (s, 3 H), 1.69 (d, J = 7.1 Hz, 3 H). NH not observed. LCMS (Method 3): [MH⁺] = 393 at 5.11 min. Chiral analysis (Method 18) at 3.65 min.</p>
<p>Example 290</p>	<p>Single enantiomer 2 of 6-(4-fluorophenyl)-<i>N</i>²,<i>N</i>²-dimethyl-<i>N</i>⁴-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]quinazoline-2,4-diamine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.65 (d, J = 5.6 Hz, 1 H), 8.49 (d, J = 1.3 Hz, 1 H), 7.92 (dd, J = 1.6, 8.7 Hz, 1 H), 7.86 (dd, J = 5.6, 8.6 Hz, 2 H), 7.43-7.34 (m, 3 H), 5.60-5.51 (m, 1 H), 3.07 (s, 6 H), 2.35 (s, 3 H), 1.77 (d, J = 7.1 Hz, 3 H). LCMS (Method 3): [MH⁺] = 393 at 5.12 min. Chiral analysis (Method 18) at 5.26 min.</p>

Intermediate 15**6-bromo-8-methoxy-4-((2-(trimethylsilyl)ethoxy)methoxy)quinazoline**

5

6-Bromo-8-methoxyquinazolin-4-ol (200 mg, 0.78 mmol) (intermediate 2) was dissolved in N,N-dimethylformamide (10 mL) and the reaction mixture cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil, 38 mg, 0.94 mmol) was added portion-wise and the reaction mixture stirred for 30 min. (2-Chloromethoxyethyl)trimethylsilane
10 (0.21 ml, 1.18 mmol) was then added dropwise. The reaction was then stirred at 0 °C for 1 hour and then allowed to warm to room temperature. The reaction mixture was quenched with water (5 mL) and partitioned with ethyl acetate (15 mL). The phases were separated and the aqueous layer washed with ethyl acetate (2 × 10 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated in vacuo. The crude
15 product was purified by column chromatography on silica gel, eluting with 0 – 40% ethyl acetate in cyclohexane to give the title compound (181 mg, 60%) as a colourless solid.

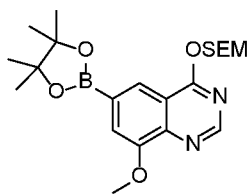
¹H NMR (400 MHz, CDCl₃): δ 8.17 (s, 1 H), 8.04 (d, J = 2.0 Hz, 1 H), 7.3 (d, J = 2.0 Hz, 1 H), 5.43 (s, 2 H), 4.02 (s, 3 H), 3.66 (m, J = 4.1 Hz, 2 H), 0.95 (m, J = 4.1 Hz, 2 H), 0.02 (s, 9 H). LCMS (Method 3): [MH⁺] = 385 at 5.24 min.

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Intermediate 16

8-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-((2-(trimethylsilyl)ethoxy)methoxy)quinazoline

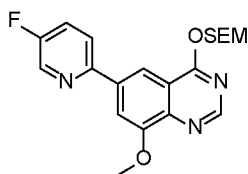
228



Nitrogen was bubbled for 10 minutes through a mixture of 6-bromo-8-methoxy-4-((2-(trimethylsilyl)ethoxy)methoxy)quinazoline (190 mg, 0.49 mmol), bis(pinacolato)diboron (150 mg, 0.59 mmol) and potassium acetate (97 mg, 0.99 mmol) in 1,4-dioxane (5 mL), then [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (36 mg, 0.05 mmol) was added. The reaction mixture was then heated at 95 °C for 2 hours. After this time the reaction was cooled to room temperature and filtered through Celite®. The title compound was used directly as a solution in 1,4-dioxane, assuming a quantitative yield.

10 Intermediate 17

6-(5-Fluoropyridin-2-yl)-8-methoxy-4-((2-(trimethylsilyl)ethoxy)methoxy)quinazoline

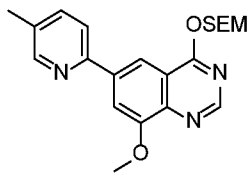
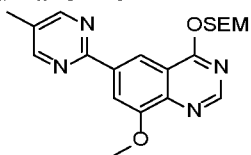


To 8-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-((2-(trimethylsilyl)ethoxy)methoxy)quinazoline (330 mg, 0.78 mmol) was added 2-bromo-5-fluoropyridine (137 mg, 0.78 mmol), cesium carbonate (508 mg, 1.56 mmol), 1,4-dioxane (8 mL) and water (1 mL). Nitrogen was bubbled through the reaction mixture for 10 minutes before tetrakis(triphenylphosphine)palladium(0) (90 mg, 0.078 mmol) was added. The reaction was then heated at 90 °C for 16 hours. After this time the reaction mixture was cooled to room temperature, filtered through Celite® and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 0

– 60% ethyl acetate in cyclohexane to give the title compound (226 mg, 72%) as a pale yellow solid.

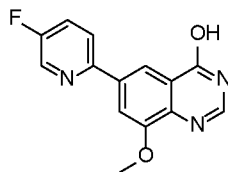
¹H NMR (400 MHz, DMSO): δ 8.76 (d, J = 2.4 Hz, 1 H), 8.46 (s, 1 H), 8.42 (d, J = 1.7 Hz, 1 H), 8.30 (dd, J = 9.1 Hz, 4.4 Hz, 1 H), 8.06 (d, J = 1.7 Hz, 1 H), 7.91 (dt, J = 2.4, 9.1 Hz, 1 H), 5.44 (s, 2 H), 4.06 (s, 3 H), 3.64 (t, J = 8.1 Hz, 2 H), 0.97 (t, J = 8.1 Hz, 2 H), 0.01 (s, 9 H). LCMS (Method 3): [MH⁺] = 402 at 5.43 min.

The following intermediates reported in the table below were synthesised following the same procedure described for the preparation of 6-(5-Fluoropyridin-2-yl)-8-methoxy-4-((2-(trimethylsilyl)ethoxy)-methoxy)-quinazoline (Intermediate 17):

Intermediate No.	Chemical Name Structure	Analytical Data ¹ H NMR LC-MS
Intermediate 21	6-(5-methylpyridin-2-yl)-8-methoxy-4-((2-(trimethylsilyl)ethoxy)methoxy)quinazoline 	¹ H NMR (400 MHz, DMSO): δ 8.60-8.59 (m, 1 H), 8.43 (d, J = 2.0 Hz, 2 H), 8.10-8.08 (m, 2 H), 7.80-7.78 (m, 1 H), 5.44 (s, 2 H), 4.05 (s, 3 H), 3.70-3.64 (m, 2 H), 3.36 (s, 3 H), 0.94-0.90 (m, 2 H), 0.01 (s, 9 H). LCMS (Method 4): [MH ⁺] = 398 at 5.12 min.
Intermediate 22	6-(5-Methylpyrimidin-2-yl)-8-methoxy-4-((2-(trimethylsilyl)ethoxy)methoxy)quinazoline 	¹ H NMR (400 MHz, CDCl ₃): δ 9.00 (d, J = 2.0 Hz, 1 H), 8.68 (s, 2 H), 8.33 (d, J = 1.6 Hz, 1 H), 8.22 (s, 1 H), 5.48 (s, 2 H), 4.17 (s, 3 H), 3.71-3.67 (m, 2 H), 2.38 (s, 3 H), 0.99-0.97 (m, 2 H), 0.01 (s, 9 H). LCMS (Method 4): [MH ⁺] = 399 at 5.18 min.

10

Intermediate 23**6-(5-fluoropyridin-2-yl)-8-methoxyquinazolin-4-ol**



6-(5-Fluoropyridin-2-yl)-8-methoxy-4-((2-(trimethylsilyl)ethoxy)methoxy)quinazoline (225 mg, 0.56 mmol) was dissolved in dichloromethane (5 mL) and trifluoroacetic acid (0.21 mL, 2.81 mmol). The reaction mixture was stirred for 16 hours. The reaction mixture was concentrated *in vacuo* to yield the title compound (142 mg, 93%) as a pale orange solid.

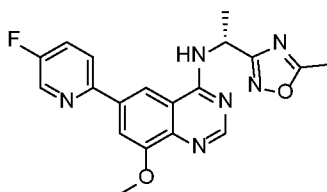
¹H NMR (400 MHz, DMSO): δ 8.76 (d, J = 2.4 Hz, 1 H), 8.39 (d, J = 1.7 Hz, 1 H), 8.29 (dd, J = 9.0 Hz, 4.6 Hz, 1 H), 8.13 (s, 1 H) 8.05 (d, J = 1.7 Hz, 1 H), 7.92 (dt, J = 2.4, 9.1 Hz, 1 H), 5.69 (br s, 1 H), 4.06 (s, 3 H). LCMS (Method 3): [MH⁺] = 272 at 3.08 min.

The following intermediates reported in the table below were synthesised following the same procedure described for the preparation of 6-(5-fluoropyridin-2-yl)-8-methoxyquinazolin-4-ol (Intermediate 23):

Intermediate No.	Chemical Name Structure	Analytical Data ¹ H NMR LC-MS
Intermediate 26	8-Methoxy-6-(5-methylpyridin-2-yl)quinazolin-4-ol 	¹ H NMR (400 MHz, DMSO): δ 8.56 (s, 1 H), 8.33 (s, 1 H), 8.12 (s, 1 H), 7.99-7.93 (m, 1 H), 7.92 (s, 1 H), 7.76-7.73 (m, 1 H), 4.02 (s, 3 H), 2.38 (s, 3 H). LCMS (Method 4): [MH ⁺] = 268 at 2.39 min.
Intermediate 27	6-(5-methylpyrimidin-2-yl)-8-methoxyquinazolin-4-ol 	LCMS (Method 4): [MH ⁺] = 269 at 2.89 min.

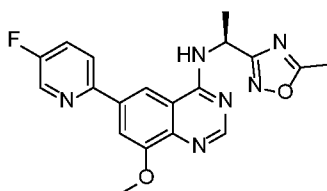
Example 315

(R)-6-(5-fluoropyridin-2-yl)-8-methoxy-N-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine

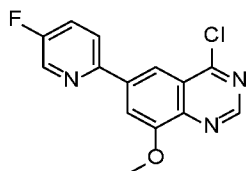


5 **Example 325**

(S)-6-(5-fluoropyridin-2-yl)-8-methoxy-N-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine



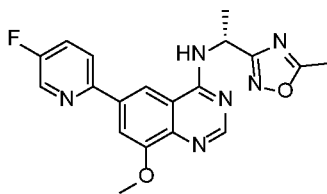
Step 1: Preparation of 4-Chloro-6-(5-fluoropyridin-2-yl)-8-methoxyquinazoline



10

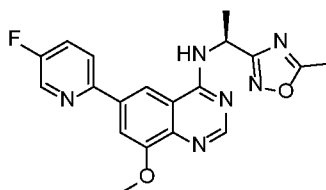
8-Methoxy-6-(5-fluoropyridin-2-yl)quinazolin-4-ol (750 mg, 2.81 mmol) was suspended in thionyl chloride (4.1 mL, 56.12 mmol) and DMF (0.0005 mL, 0.006 mmol) was added. The reaction mixture was heated at 95 °C for 4 hours. The reaction was cooled to room temperature and the solvent was removed *in vacuo* to give 4-chloro-6-(5-fluoropyridin-2-yl)-8-methoxyquinazoline (800 mg, 98%). The crude residue was taken
15 on directly to the next step without further purification.

Step 2: Preparation of (R)-6-(5-fluoropyridin-2-yl)-8-methoxy-N-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine and



and

(*S*)-6-(5-fluoropyridin-2-yl)-8-methoxy-*N*-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine



5

To a mixture of 4-chloro-6-(5-fluoropyridin-2-yl)-8-methoxyquinazoline (100 mg, 0.367 mmol) and *N,N*-diisopropylethylamine (0.32 mL, 1.84 mmol) in 1,4-dioxane (5 mL) was added (*R*)-1-(5-methyl-1,2,4-oxadiazol-3-yl)ethan-1-amine (93 mg, 0.735 mmol). The resulting mixture was stirred at 50 °C for 5 days. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the title compound (25 mg, 19%) as an off white solid.

10

Example 315

(*R*)-6-(5-fluoropyridin-2-yl)-8-methoxy-*N*-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine : ¹H NMR (400 MHz, CDCl₃) δ 8.57 (s, 1 H), 8.54 (d, J=3.8 Hz, 1 H), 7.88 (s, 2 H), 7.69 (s, 1 H), 7.54 (ddd, J=8.6, 8.6, 2.9 Hz, 1 H), 6.82 (s, 1 H), 5.92 - 5.84 (m, 1 H), 4.13 (s, 3 H), 2.65 (s, 3 H), 1.77 (d, J=6.1 Hz, 3 H). LCMS (Method 3): [MH⁺] = 381 at 2.90 min. Chiral analysis (Method 31) at 2.24 min.

15

Example 325

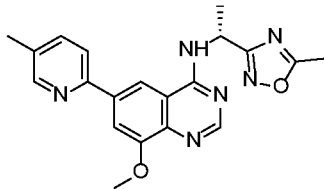
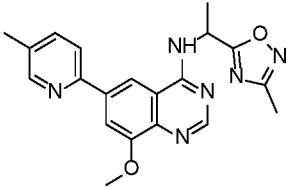
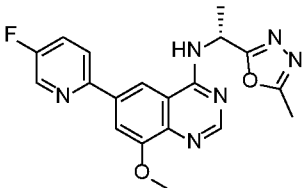
(*S*)-6-(5-fluoropyridin-2-yl)-8-methoxy-*N*-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine

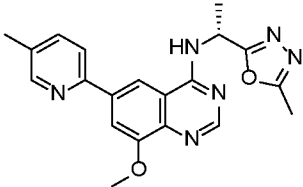
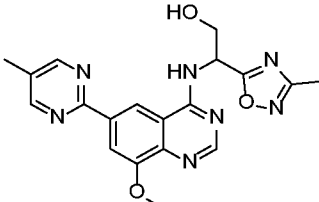
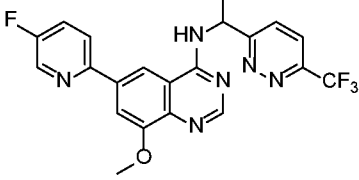
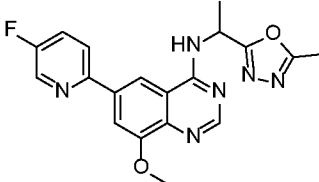
20

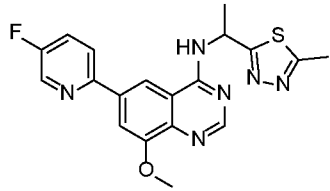
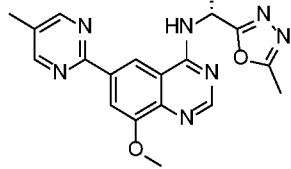
Chiral analysis (Method 31) at 0.58 min.

The following compounds reported in the table below were prepared according to the same procedure described for the preparation of (*R*)-6-(5-fluoropyridin-2-yl)-8-methoxy-*N*-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine.

Some compounds were further purified by preparative chiral SFC to obtain the pure enantiomers.

Example No.	Chemical name Structure	Analytical data ¹ H NMR LC-MS
Example 316 (From Intermediate 26)	(<i>R</i>)-8-methoxy- <i>N</i> -(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)-6-(5-methylpyridin-2-yl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.75-8.71 (m, 1 H), 8.59 (s, 2 H), 8.46-8.45 (m, 1 H), 8.21-8.14 (m, 1 H), 8.05 (d, J = 1.4 Hz, 1 H), 7.82 (dd, J = 1.6, 8.2 Hz, 1 H), 5.82-5.74 (m, 1 H), 4.02 (s, 3 H), 2.58 (s, 3 H), 2.39 (s, 3 H), 1.71-1.68 (m, 3 H). LCMS (Method 3): [MH ⁺] = 377 at 3.64 min. Chiral analysis (Method 38) at 3.10 min.
Example 317 (From Intermediate 26)	8-Methoxy- <i>N</i> -[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]-6-(5-methyl-2-pyridyl)quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.89 (d, J = 7.2 Hz, 1 H), 8.59 (s, 2 H), 8.46 (s, 1 H), 8.15-8.12 (m, 1 H), 8.05 (d, J = 1.5 Hz, 1 H), 7.82 (dd, J = 1.6, 8.2 Hz, 1 H), 5.87-5.78 (m, 1 H), 4.03 (s, 3 H), 2.40 (s, 3 H), 2.33 (s, 3 H), 1.76 (d, J = 7.2 Hz, 3 H). LCMS (Method 4): [MH ⁺] = 377 at 2.91 min.
Example 318 (From Intermediate 23)	6-(5-fluoro-2-pyridyl)-8-methoxy- <i>N</i> -[(1 <i>R</i>)-1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl]quinazolin-4-amine 	¹ H NMR (400 MHz, DMSO): δ 8.84 (d, J = 7.7 Hz, 1 H), 8.75-8.73 (m, 1 H), 8.55 (d, J = 1.5 Hz, 1 H), 8.51 (s, 1 H), 8.28 (dd, J = 4.4, 8.9 Hz, 1 H), 8.01-7.94 (m, 2 H), 5.94-5.85 (m, 1 H), 4.03 (s, 3 H), 2.48 (s, 3 H), 1.74 (d, J = 7.0 Hz, 3 H). LCMS (Method 3): [MH ⁺] = 381 at 3.8 min. Chiral analysis (Method 28) at 3.17 min.

<p>Example 319 (From Intermediate 26)</p>	<p>8-methoxy-<i>N</i>-[(1<i>R</i>)-1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl]-6-(5-methyl-2-pyridyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.85-8.81 (m, 1 H), 8.58 (d, J = 2.2 Hz, 1 H), 8.55 (d, J = 1.5 Hz, 1 H), 8.49-8.49 (m, 1 H), 8.14-8.10 (m, 1 H), 8.05-8.04 (m, 1 H), 7.81 (dd, J = 1.5, 8.2 Hz, 1 H), 5.94-5.85 (m, 1 H), 4.03-4.02 (m, 3 H), 2.40-2.38 (m, 3 H), 1.74 (d, J = 7.0 Hz, 3 H). LCMS (Method 4): [MH⁺] = 377 at 2.55 min. Chiral analysis (Method 38) at 1.98 min.</p>
<p>Example 320 (From Intermediate 27)</p>	<p>2-((8-methoxy-6-(5-methylpyrimidin-2-yl)quinazolin-4-yl)amino)-2-(3-methyl-1,2,4-oxadiazol-5-yl)ethan-1-ol</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.01-8.96 (m, 2 H), 8.86 (s, 2 H), 8.48 (s, 1 H), 8.24 (d, J = 1.2 Hz, 1 H), 5.75 (q, J = 6.5 Hz, 1 H), 5.38 (dd, J = 5.9, 5.9 Hz, 1 H), 4.15-4.06 (m, 2 H), 4.03 (s, 3 H), 2.38 (s, 3 H), 2.33 (s, 3 H). LCMS (Method 3): [MH⁺] = 394 at 3.38 min.</p>
<p>Example 321 (From Intermediate 23)</p>	<p>6-(5-fluoro-2-pyridyl)-8-methoxy-<i>N</i>-[1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl]quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 8.87 (d, J = 7.0 Hz, 1 H), 8.76 (d, J = 3.0 Hz, 1 H), 8.68 (d, J = 1.5 Hz, 1 H), 8.38 (s, 1 H), 8.34 (dd, J = 4.3, 8.9 Hz, 1 H), 8.21 (d, J = 8.8 Hz, 1 H), 8.07 (d, J = 8.8 Hz, 1 H), 8.02-7.96 (m, 2 H), 5.91-5.86 (m, 1 H), 4.01 (s, 3 H), 1.80 (d, J = 7.2 Hz, 3 H). LCMS (Method 4): [MH⁺] = 445 at 3.35 min.</p>
<p>Example 322 (From Intermediate 23)</p>	<p>6-(5-fluoropyridin-2-yl)-8-methoxy-<i>N</i>-(1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, CDCl₃) δ 8.55 (d, J = 2.8 Hz, 1 H), 8.49 (s, 1 H), 7.86 (d, J = 1.9 Hz, 1 H), 7.74 (s, 2 H), 7.48 (ddd, J = 8.4, 8.4, 3.1 Hz, 1 H), 7.05 (s, 1 H), 5.85-5.90 (m, 1 H), 4.13 (s, 3 H), 2.60 (s, 3 H), 1.79 (d, J = 7.9 Hz, 3 H); LCMS (Method 4): [MH⁺] = 381 at 3.37 min.</p>
<p>Example 323</p>	<p>6-(5-fluoropyridin-2-yl)-8-methoxy-<i>N</i>-(1-(5-methyl-1,3,4-</p>	<p>¹H NMR (400 MHz, CDCl₃) δ 8.67 (s, 1 H), 8.56 (d, J = 3.3 Hz, 1 H), 7.93 (s, 1 H), 7.86</p>

<p>(From Intermediate 23)</p>	<p>thiadiazol-2-yl)ethyl)quinazolin-4-amine</p> 	<p>(dd, J = 4.1, 8.7 Hz, 1 H), 7.78 (d, J = 2.5 Hz, 1 H), 7.52 (ddd, J = 8.6, 8.6, 2.8 Hz, 1 H), 7.05 (s, 1 H), 6.09-6.00 (m, 1 H), 4.14 (s, 3 H), 2.78 (s, 3 H), 1.89 (d, J = 7.5 Hz, 3 H). LCMS (Method 4): [MH⁺] = 397 at 3.83 min.</p>
<p>Example 324 (From Intermediate 27)</p>	<p>8-methoxy-N-[(1R)-1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl]-6-(5-methylpyrimidin-2-yl)quinazolin-4-amine</p> 	<p>¹H NMR (400 MHz, DMSO): δ 9.11 (d, J = 7.7 Hz, 1 H), 8.95 (d, J = 1.4 Hz, 1 H), 8.85 (s, 2 H), 8.51 (s, 1 H), 8.23 (d, J = 1.5 Hz, 1 H), 5.91-5.86 (m, 1 H), 4.03 (s, 3 H), 2.38 (s, 3 H), 1.73 (d, J = 7.0 Hz, 3 H). LCMS (Method 4): [MH⁺] = 378 at 2.53 min. Chiral analysis (Method 13) at 1.83 min.</p>

PHARMACOLOGICAL ACTIVITY OF THE COMPOUNDS OF THE INVENTION.

In vitro Electrophysiology Assay for P2X₃

Cells expressing P2X₃ receptors were grown according to standard practice and maintained at 37 °C in a 5% humidified CO₂ atmosphere. The cells were seeded into T175 flask 2 days prior to the day of the assay and dissociated from the flasks using TrypLE when grown to confluence of 80-90%. The dissociated cells were resuspended in serum free media at a cell density of 3x10⁶ cells/ml and loaded onto the Sophion Qube automated patch-clamp system. The extracellular assay buffer contained 145 mM NaCl, 4 mM KCl, 2 mM CaCl₂, 1 mM MgCl₂, 10 mM HEPES, and 10 mM glucose at pH 7.4. The intracellular assay solution contained 140 mM CsF, 10 mM NaCl, 10 mM EGTA, 10 mM HEPES at pH 7.2. Agonist stock solutions were prepared in H₂O and diluted in bath solution prior to use. All antagonists were prepared as 10 mM stock solutions in DMSO and diluted in bath solution prior to use. All experiments were performed under the whole-cell patch clamp configuration at room temperature with 384 individual cells being

voltage clamped at -60 mV simultaneously on the Sophion Qube instrument. Two baseline responses were established with the application of α,β -MeATP (800 nM), with the subsequent agonist applications being washed out using extracellular assay buffer containing 0.5 U/ml apyrase. Following the second agonist application, antagonist was

5 incubated in the absence of α,β -MeATP for 10 minutes. After antagonist preincubation, 800 nM α,β -MeATP and antagonist were co-administered to determine the inhibitory effect of the antagonist. One concentration of an antagonist was assessed against a single cell, with different concentrations of the antagonist applied to other cells on the 384 recording substrate. The control P2X₃ current amplitude was taken from the peak current

10 amplitude from the second agonist response prior to preincubation with antagonist. The peak P2X₃ current amplitude in the presence of antagonist was used to calculate the inhibitory effect at each concentration of the antagonist according to the following equation:

Percentage inhibition of P2X₃ = (P2X₃ control peak amplitude - P2X₃ antagonist peak amplitude) / P2X₃ control peak amplitude * 100

15

Concentration-response curves were constructed from ten different concentrations with each concentration of antagonist tested on at least two individual cells. The concentration of the antagonist to inhibit P2X₃ current by 50% (IC₅₀) was determined by fitting the data with the following equation:

$$20 \quad Y = a + [(b-a) / (1+10^{((\log c-x) d))}]$$

Where 'a' is minimum response, 'b' is maximum response, 'c' is IC₅₀ and 'd' is Hill slope.

The results for individual compounds are provided below in Table 8 and are expressed as range of activity.

25

Table 8

Example No.	h P2X ₃
1	+++
2	+++

3	+++
5	+++
6	+++
7	+++
8	+++
9	++
10	+++
11	+++
12	+++
13	++
14	+++
15	+++
16	+++
17	+++
18	+++
19	+++
20	+++
21	+++
22	+++
23	++
24	++
25	+++
26	++
27	++
28	++
29	+
30	+
31	+++
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39	+++
40	++
41	++
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45	+++
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70	++
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74	+
75	++
76	++
77	+
78	+
79	++
80	+
81	+
82	+
83	+
84	+
85	+
86	+
87	+
88	++
89	+
90	+
91	+
92	+
93	+
94	+
95	++
96	++
97	++

98	++
99	++
100	+
101	+
102	++
103	+
104	++
105	++
106	+
107	+
108	+
109	+
110	++
111	+
113	+++
114	++
115	++
116	+++
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119	++
120	++
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126	++
127	+++
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137	+
138	++
139	++
140	+++
141	++
142	+
143	+++
144	++
145	+++

146	++
147	+++
149	+++
153	+++
154	+++
156	++
157	+++
158	+++
159	+
160	+
161	+++
163	++
163a	++
164	++
165	+++
166	++
167	++
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310	+++
311	++

312	++
313	+++
314	+++
315	+++
316	+++
317	+++
318	++
319	+++
320	++
321	++
322	++
323	+++
324	+++
325	+
326	++

wherein the compounds are classified in term of potency with respect to their inhibitory activity on P2X₃ according to the following classification criterion:

+++ : pIC₅₀ h P2X₃ > 6.5

++ : 6.5 < pIC₅₀ h P2X₃ > 5.5

5 + : 5.5 < pIC₅₀ h P2X₃ > 4.5

In vitro Electrophysiology Assay for P2X_{2/3}

Representative compound of the present invention have been also tested for P2X_{2/3} receptor.

The same assay protocol was used for the P2X_{2/3} assay as the P2X₃ assay with two
10 modifications: 1) 10 μM ATP was used as the agonist; and 2) the mean current amplitude was measured seven seconds after the application of agonist.

The results of Table 9 indicate that representative compounds of the present invention are selective P2X₃ antagonist.

Table 9

Example No.	h P2X₃	h P2X_{2/3}
4	+++	+
19	+++	+
28	++	+

48	+++	+
65	++	+
110	++	+
112	+++	+
116	+++	+
134	+++	+
140	+++	+
145	+++	+
148	+++	++
149	+++	+
150	+++	+
151	+++	+
152	++	+
155	+++	+
175	+++	++
181	+++	++
182	+++	+
184	+++	+
206	+++	+
207	+++	+
208	+++	+
214	+++	+
216	+++	+
217	+++	+
228	+++	+
231	+++	+
240	+++	+
241	+++	++
243	+++	+
244	+++	++
247	+++	+
256	++	+
258	++	+
268	+++	+
282	+++	+
293	++	+
298	+++	+
300	+++	+
314	+++	+
315	+++	+
317	+++	+
319	+++	+
322	++	++
323	+++	+

324	+++	+
-----	-----	---

wherein the compounds are classified in term of potency with respect to their inhibitory activity on P2X₃ or P2X_{2/3} isoforms according to the following classification criterion:

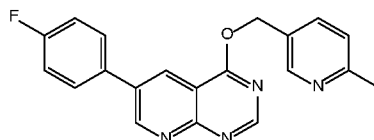
+++: pIC₅₀ h P2X₃ or h P2X_{2/3} > 6.5

5 ++: 6.5 < pIC₅₀ h P2X₃ or h P2X_{2/3} > 5.5

+: 5.5 < pIC₅₀ h P2X₃ or h P2X_{2/3} > 4.5

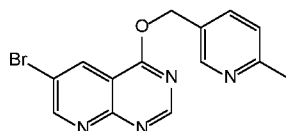
Comparative Example A

6-(4-fluorophenyl)-4-[(6-methyl-3-pyridyl)methoxy]pyrido[2,3-d]pyrimidine



10

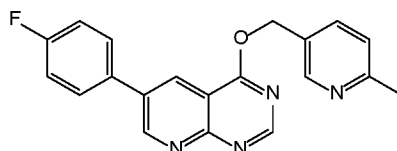
Step 1: Synthesis of 6-bromo-4-[(6-methylpyridin-3-yl)methoxy]pyrido[2,3-d]pyrimidine



6-Bromopyrido[2,3-d]pyrimidin-4(3H)-one (202 mg, 0.89 mmol) (Intermediate 1), 5-
 15 hydroxymethyl-2-methylpyridine (110 mg, 0.89 mmol) and triphenylphosphine (328 mg, 1.25 mmol) were stirred in dry THF (7 mL) and a solution of diisopropyl azodicarboxylate (229 μ L, 1.16 mmol) in dry THF (3 mL) was added dropwise and stirred at room temperature for 6 hours. The reaction was filtered and the precipitate was washed with (2:1) DCM/MeOH (20 mL). The filtrates were combined and the solvent was removed in
 20 vacuo. The residue was purified by chromatography on silica gel eluting with 0-100% EtOAc in DCM to give 6-bromo-4-[(6-methylpyridin-3-yl)methoxy]pyrido[2,3-d]pyrimidine (164 mg, 55%).

¹H NMR (400 MHz, DMSO): δ 9.08 (d, J = 2.6 Hz, 1 H), 8.89 (s, 1 H), 8.67 (d, J = 2.6 Hz, 1 H), 8.55 (d, J = 2.1 Hz, 1 H), 7.72 (dd, J = 2.4, 8.0 Hz, 1 H), 7.24 (d, J = 8.0 Hz, 1 H), 5.20 (s, 2 H), 2.44 (s, 3 H).

Step 2: Synthesis of 6-(4-fluorophenyl)-4-[(6-methyl-3-pyridyl)methoxy]pyrido[2,3-d]pyrimidine

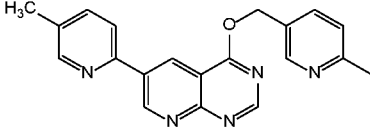


Nitrogen gas was bubbled through a mixture of 6-bromo-4-[(6-methylpyridin-3-yl)methoxy]pyrido[2,3-d]pyrimidine (84 mg, 0.254 mmol), 4-fluorophenylboronic acid, pinacol ester (76 mg, 0.342 mmol) and cesium fluoride (116 mg, 0.761 mmol) in DMF (1 mL) and water (0.3 mL). After 5 min, tetrakis(triphenylphosphine)palladium(0) (29 mg, 0.025 mmol) was added and the resulting mixture was heated at 95 °C for 16 hours. The reaction was diluted with water (6 mL) and EtOAc (3 mL). The aqueous phase was extracted EtOAc (2 × 10 mL). The combined organic phases were passed through a hydrophobic frit, combined and the solvent was removed in vacuo. Purification by reverse phase preparative HPLC afforded 6-(4-fluorophenyl)-4-[(6-methyl-3-pyridyl)methoxy]pyrido[2,3-d]pyrimidine (52 mg, 59%) as a 0.5 eq formate salt.

¹H NMR (400 MHz, DMSO): δ 9.35 (d, J = 2.8 Hz, 1 H), 8.92 (s, 1 H), 8.73 (d, J = 2.5 Hz, 1 H), 8.61 (d, J = 1.5 Hz, 1 H), 8.32 (s, 0.5 H), 7.97 (dd, J = 5.3, 8.6 Hz, 2 H), 7.77 (dd, J = 2.1, 8.0 Hz, 1 H), 7.42 (dd, J = 8.8, 8.8 Hz, 2 H), 7.29 (d, J = 8.1 Hz, 1 H), 5.27 (s, 2 H), 2.49 (s, 3 H).

LCMS (Method 4): [MH⁺] = 347 at 2.82 min.

The following compound reported in the table below was prepared according to the same procedure described for the preparation of 6-(4-fluorophenyl)-4-[(6-methyl-3-pyridyl)methoxy]pyrido[2,3-d]pyrimidine.

Comparative Example No.	Chemical name Structure	Analytical data ¹ H NMR LC-MS
Comparative Example B	 <p data-bbox="475 582 885 728">6-(5-methylpyridin-2-yl)-4-((6-methylpyridin-3-yl)methoxy)pyrido[2,3-d]pyrimidine</p>	¹ H NMR (400 MHz, DMSO): δ 9.70 (d, J = 2.3 Hz, 1 H), 9.14 (d, J = 2.3 Hz, 1 H), 8.92 (s, 1 H), 8.66-8.60 (m, 2 H), 8.18 (d, J = 8.1 Hz, 1 H), 7.83 (d, J = 6.8 Hz, 1 H), 7.78 (dd, J = 1.9, 8.0 Hz, 1 H), 7.29 (d, J = 8.1 Hz, 1 H), 5.27 (s, 2 H), 2.49 (s, 3 H), 2.42 (s, 3 H). LCMS (Method 3): [MH ⁺] = 344 at 3.31 m

The activity of the comparative examples A and B have been tested in the in vitro Electrophysiology Assay for P₂X₃ as described above.

Results for individual compounds are provided below in Table 10 and are expressed as range of activity.

5

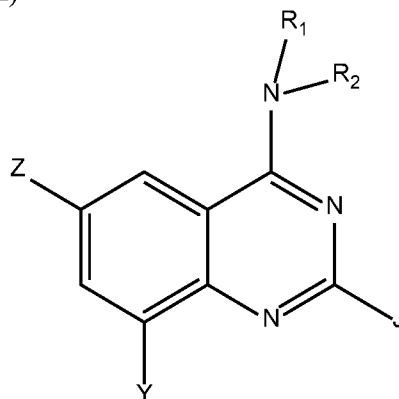
Table 10

Comparative Example No.	h P ₂ X ₃
A	inactive
B	inactive

Inactive: pIC₅₀ h P₂X₃ < 4.5.

CLAIMS

1. A compound of formula (I)



(I)

5 wherein

Z is selected from the group consisting of (C₃-C₈)heterocycloalkyl, (R^AR^B)N-, heteroaryl, aryl,

wherein any of such alkyl, heteroaryl, heterocycloalkyl and aryl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl-, halo, CN, (R^AR^B)NC(O)-, (C₁-C₆)haloalkyl-, R^AO-, (R^AR^B)N(C₁-C₆)alkylene-, (C₃-C₇)cycloalkyl-, R^CSO₂-, (R^AR^B)N-;

R₁ is H or (C₁-C₄)alkyl;

R₂ is selected from the group consisting of (C₁-C₆)alkyl-, heteroaryl(C₁-C₄)alkyl-, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl-, heteroaryl-(C₁-C₆)hydroxyalkyl-, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl-(C₁-C₆)alkyl-, aryl-(C₁-C₄)alkyl-, (R^AR^B)N(C₁-C₆)alkylene-, (R^AR^B)N(O)C(C₁-C₄)alkylene- and R^AO(C₁-C₄)alkylene-

wherein any of such alkyl, alkylene, aryl, heteroaryl and heterocycloalkyl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, R^AO(C₁-C₄)alkylene-, (C₁-C₆)haloalkyl, halo, oxo, R^AO-, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl-, heteroaryl, (R^AR^B)N-, -NHC(O)R^C, -C(O)N(R^AR^B), -SO₂N(R^AR^B), -

O(C₁-C₄)alkylene-N(R^AR^B), aryl optionally substituted by halo, -OR^C, aryl-(C₁-C₄)alkyl-, -C(O)R^A;

R^A and R^B are at each occurrence independently H or selected from the group consisting of (C₁-C₄)alkyl-, (C₃-C₈)cycloalkyl-, (C₁-C₆) haloalkyl, or

5 **R^A and R^B** may form together with the nitrogen atom to which they are attached a 5 or 6 membered saturated heterocyclic monocyclic ring system optionally containing a further heteroatom which is nitrogen or oxygen, which may be optionally substituted by one or more groups selected (C₁-C₄)alkyl and oxo;

10 **R^C** is at each occurrence H or selected from the group consisting of (C₁-C₆)alkyl, (R^AR^B)N-, aryl-(C₁-C₄)alkyl-;

Y is selected from the group consisting of H, -OR^D, R^CSO₂, halo, -NHSO₂R^C, heteroaryl, (C₃-C₈)heterocycloalkyl,

wherein any of such heteroaryl and heterocycloalkyl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, -C(O)N(R^AR^B);

15 **R^D** is selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl-, R^COC(O)(C₁-C₄)alkylene-, (R^AR^B)N(C₁-C₆)alkylene-, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl-(C₁-C₆)alkyl-, R^CO(C₁-C₄)alkylene-, (R^AR^B)N(O)C(C₁-C₄)alkylene-,

20 wherein any of such heterocycloalkyl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl-;

J is H or selected from the group consisting of (C₁-C₆)alkyl, (R^AR^B)N-, (C₁-C₆)haloalkyl, -OR^C and halo.

2. A compound of formula I according to claim 1 selected selected from the group consisting of:

25 (R)-6-(4-Fluorophenyl)-8-methoxy-N-(1-(6-methylpyridazin-3-yl)ethyl)quinazolin-4-amine,

6-(4-Fluorophenyl)-8-methoxy-N-((2-(trifluoromethyl)pyrimidin-5-yl)methyl)quinazolin-4-amine,

6-(4-Fluorophenyl)-8-methoxy-N-(2-(6-methylpyridin-3-yl)ethyl)quinazolin-4-amine,

5 N-([1,2,4]Triazolo[4,3-a]pyrimidin-3-ylmethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine,

6-[[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]methyl]-1H-pyridin-2-one,

10 6-(4-Fluorophenyl)-8-methoxy-N-[(1-methyl-4-piperidyl)methyl]quinazolin-4-amine,

(R)-5-(1-((6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)amino)ethyl)-2-(trifluoromethyl)pyridine 1-oxide formate,

8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(5-methylpyridin-2-yl)quinazolin-4-amine,

15 8-Methoxy-N-[(6-methylpyridazin-3-yl)methyl]-6-(5-methylpyrimidin-2-yl)quinazolin-4-amine,

8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(5-methylthiazol-2-yl)quinazolin-4-amine,

20 (R)-5-(1-((8-Methoxy-6-(5-methyl-1,3,4-thiadiazol-2-yl)quinazolin-4-yl)amino)ethyl)-2-(trifluoromethyl)pyridine 1-oxide,

8-Methoxy-6-(5-methylpyrimidin-2-yl)-N-[(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl]quinazolin-4-amine,

6-(5-Fluoropyrimidin-2-yl)-8-methoxy-N-[(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl]quinazolin-4-amine,

25 6-(5-Fluoro-2-pyridyl)-8-methoxy-N-[(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl]quinazolin-4-amine,

8-Methoxy-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-6-(5-methylpyrimidin-2-yl)quinazolin-4-amine,

8-Methoxy-6-(1-methylpyrazol-3-yl)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]quinazolin-4-amine,

5 6-(5-Fluoro-2-pyridyl)-8-methoxy-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]quinazolin-4-amine,

6-(5-Chloropyridin-2-yl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

10 (R)-6-(4-fluorophenyl)-8-methoxy-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine,

6-(4-fluorophenyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

(R)-6-(4-Fluorophenyl)-8-methoxy-4-((1-(2-(trifluoromethyl)pyrimidin-5yl)ethyl)-amino)-quinazolin-2-ol,

15 6-(4-fluorophenyl)-8-(2-methoxyethoxy)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine,

6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-(oxetan-3-ylmethoxy)quinazolin-4-amine,

20 6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-tetrahydropyran-4-yloxy-quinazolin-4-amine,

2-[6-(4-fluorophenyl)-4-[(6-methylpyridazin-3-yl)methylamino]quinazolin-8-yl]oxyacetic acid, sodium salt,

6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-pyrrolidin-3-yloxy-quinazolin-4-amine,

25 6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-(morpholin-2-ylmethoxy)quinazolin-4-amine,

6-(5-methylpyridin-2-yl)-N-((6-methylpyridin-3-yl)methyl)quinazolin-4-amine,

N-((6-methylpyridazin-3-yl)methyl)-6-(5-methylpyridin-2-yl)quinazolin-4-amine,

5 N-((6-methylpyridin-3-yl)methyl)-6-(5-methylthiophen-2-yl)quinazolin-4-amine,

N-((6-methylpyridin-3-yl)methyl)-6-(p-tolyl)quinazolin-4-amine,

(R)-6-(4-fluorophenyl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine,

10 6-(4-fluorophenyl)-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine,

6-(4-fluorophenyl)-N-((6-methylpyridin-3-yl)methyl)quinazolin-4-amine formate,

Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine

Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine,

Single enantiomer 1 of 2-((6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)amino)-2-(3-methyl-1,2,4-oxadiazol-5-yl)ethan-1-ol,

20 Single enantiomer 2 of 2-((6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)amino)-2-(3-methyl-1,2,4-oxadiazol-5-yl)ethan-1-ol,

Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,3,4-thiadiazol-2-yl)ethyl)quinazolin-4-amine,

Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,3,4-thiadiazol-2-yl)ethyl)quinazolin-4-amine,

Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(3-methyl-1,2,4-

oxadiazol-5-yl)ethyl)quinazolin-4-amine,

Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine,

6-(3,5-Difluoropyridin-2-yl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

6-(3-Fluoro-5-methyl-2-pyridyl)-8-methoxy-N-[(6-methylpyridazin-3-yl)methyl] quinazolin-4-amine,

6-(5-Ethylthiazol-2-yl)-8-methoxy-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine,

(R)-8-methoxy-6-(1-methyl-1H-1,2,4-triazol-3-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine,

(R)-8-methoxy-6-(1-methyl-1H-pyrazol-3-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine,

(R)-8-methoxy-6-(1-methyl-1H-1,2,4-triazol-3-yl)-N-(1-(6-methylpyridazin-3-yl)ethyl)quinazolin-4-amine,

(R)-6-(5-fluoropyridin-2-yl)-8-methoxy-N-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine,

(R)-8-methoxy-N-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)-6-(5-methylpyridin-2-yl)quinazolin-4-amine,

8-Methoxy-N-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]-6-(5-methyl-2-pyridyl)quinazolin-4-amine,

6-(5-fluoro-2-pyridyl)-8-methoxy-N-[(1R)-1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl]quinazolin-4-amine,

8-methoxy-N-[(1R)-1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl]-6-(5-methyl-2-pyridyl)quinazolin-4-amine,

6-(5-fluoro-2-pyridyl)-8-methoxy-N-[1-[6-(trifluoromethyl)pyridazin-3-

yl]ethyl]quinazolin-4-amine,

6-(5-fluoropyridin-2-yl)-8-methoxy-N-(1-(5-methyl-1,3,4-oxadiazol-2-

yl)ethyl]quinazolin-4-amine,

6-(5-fluoropyridin-2-yl)-8-methoxy-N-(1-(5-methyl-1,3,4-thiadiazol-2-

5 yl)ethyl]quinazolin-4-amine,

8-methoxy-N-[(1R)-1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl]-6-(5-

methylpyrimidin-2-yl)quinazolin-4-amine,

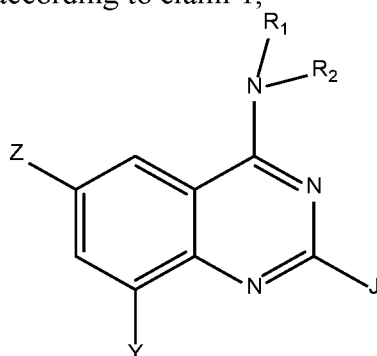
(S)-6-(5-fluoropyridin-2-yl)-8-methoxy-N-(1-(5-methyl-1,2,4-oxadiazol-3-

yl)ethyl]quinazolin-4-amine,

10 8-Methoxy-N-[(1S)-1-(6-methylpyridazin-3-yl)ethyl]-6-(5-

methylpyrimidin-2-yl)quinazolin-4-amine .

3. A compound of formula I according to claim 1,



(I)

15 wherein

Z is selected from the group consisting of heteroaryl, aryl, (R^AR^B)N-, (C₃-C₈)heterocycloalkyl,

wherein any of such heteroaryl, aryl and heterocycloalkyl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, halo, CN,

20 (R^AR^B)NC(O)-;

R₁ is H or (C₁-C₄)alkyl;

R₂ is selected from the group consisting of heteroaryl(C₁-C₄)alkyl-,

(R^AR^B)N(O)C(C₁-C₄)alkylene-,

wherein any of such heteroaryl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, halo, (C₁-C₆) haloalkyl;

R^A and R^B are at each occurrence independently H, (C₁-C₄)alkyl- and
 5 (C₃-C₈)cycloalkyl-, or R^A and R^B may form together with the nitrogen atom to which they are attached a 5 or 6 membered saturated heterocyclic monocyclic ring system optionally containing a further heteroatom which is oxygen or nitrogen, which may be optionally substituted by one or more groups selected from oxo, (C₁-C₄)alkyl;

10 **Y** is H;

J is H or selected from the group consisting of (C₁-C₄)alkyl, (R^AR^B)N-, halo, (C₁-C₆)haloalkyl.

4. A compound of formula I according to claim 2 selected selected from the group consisting of:

15 6-(5-methylpyridin-2-yl)-N-((6-methylpyridin-3-yl)methyl)quinazolin-4-amine,

N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)-6-(5-methylpyridin-2-yl)quinazolin-4-amine,

20 N-((6-methylpyridazin-3-yl)methyl)-6-(5-methylpyridin-2-yl)-2-(trifluoromethyl)quinazolin-4-amine,

N-((6-methylpyridazin-3-yl)methyl)-6-(5-methylpyridin-2-yl)quinazolin-4-amine,

N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)-6-(5-methylthiazol-2-yl)quinazolin-4-amine,

25 2-chloro-6-(4-fluorophenyl)-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine,

N2-cyclopropyl-6-(4-fluorophenyl)-N4-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazoline-2,4-diamine,

6-(4-fluorophenyl)-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)-2-morpholinoquinazolin-4-amine,

5 2-((2-(cyclopropylamino)-6-(4-fluorophenyl)quinazolin-4-yl)amino)propanamide,

N-cyclopropyl-2-((2-(cyclopropylamino)-6-(4-fluorophenyl)quinazolin-4-yl)amino)propanamide,

10 6-(4-fluorophenyl)-2-methyl-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

N-((6-methylpyridin-3-yl)methyl)-6-(5-methylthiophen-2-yl)quinazolin-4-amine,

N-((6-methylpyridin-3-yl)methyl)-6-(p-tolyl)quinazolin-4-amine,

15 N-((6-methylpyridazin-3-yl)methyl)-6-(2-methylpyrimidin-5-yl)quinazolin-4-amine,

(R)-6-(4-fluorophenyl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine,

6-(4-fluorophenyl)-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine,

20 2-(4-(((6-methylpyridin-3-yl)methyl)amino)quinazolin-6-yl)benzotrile,

2-(4-(((6-methylpyridin-3-yl)methyl)amino)quinazolin-6-yl)benzamide,

6-(4-fluorophenyl)-N-((6-methylpyridin-3-yl)methyl)quinazolin-4-amine formate,

6-(4-fluorophenyl)-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

25 N-((3,5-difluoropyridin-2-yl)methyl)-6-(4-fluorophenyl)quinazolin-4-amine hydrochloride,

6-(4-fluorophenyl)-N-methyl-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine,

(R)-6-(3,3-difluoropyrrolidin-1-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine,

5 (R)-6-morpholino-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine,

(R)-1-methyl-4-(4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazolin-6-yl)piperazin-2-one,

N-((6-methylpyridazin-3-yl)methyl)-6-morpholinoquinazolin-4-amine,

10 Single enantiomer 1 of 6-(4-fluorophenyl)-N-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]quinazolin-4-amine,

Single enantiomer 2 of 6-(4-fluorophenyl)-N-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]quinazolin-4-amine,

15 Single enantiomer 1 of N2-cyclopropyl-6-(4-fluorophenyl)-N4-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]quinazoline-2,4-diamine,

Single enantiomer 2 of N2-cyclopropyl-6-(4-fluorophenyl)-N4-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]quinazoline-2,4-diamine,

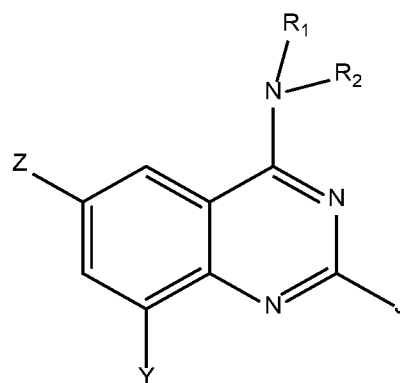
Single enantiomer 1 of 6-(4-fluorophenyl)-N-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]-2-morpholino-quinazolin-4-amine,

20 Single enantiomer 2 of 6-(4-fluorophenyl)-N-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]-2-morpholino-quinazolin-4-amine,

6-(4-fluorophenyl)-N2,N2-dimethyl-N4-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]quinazoline-2,4-diamine,

25 6-(4-fluorophenyl)-N2,N2-dimethyl-N4-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]quinazoline-2,4-diamine.

5. A compound of formula I according to claim 1,



(I)

wherein

Z is selected from the group consisting of heteroaryl and aryl,

5 wherein any of such heteroaryl and aryl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, halo, CN, (R^AR^B)NC(O)-, (C₁-C₆)haloalkyl, R^AO-, (R^AR^B)N(C₁-C₆)alkylene-, (C₃-C₇)cycloalkyl-, R^CSO₂-, (R^AR^B)N-;

R₁ is H or (C₁-C₄)alkyl,

10 **R₂** is selected from the group consisting of (C₁-C₆)alkyl, heteroaryl(C₁-C₄)alkyl-, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl, heteroaryl-(C₁-C₆)hydroxyalkyl, aryl-(C₁-C₄)alkyl-, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl-(C₁-C₆)alkyl-, (R^AR^B)N(C₁-C₆)alkylene-; R^AO(C₁-C₄)alkylene,

wherein any of such alkyl, alkylene, aryl, heteroaryl, cycloalkyl and

15 heterocycloalkyl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, R^AO(C₁-C₄)alkylene, (C₁-C₆)haloalkyl, oxo, R^AO-, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl, heteroaryl, aryl optionally substituted by halo, R^CO-, (R^AR^B)N-, -NHC(O)R^C, -C(O)N(R^AR^B), halo, -SO₂N(R^AR^B), -O(R^AO(C₁-C₄)alkylene-N(R^AR^B), aryl-(C₁-C₄)alkyl-, -C(O)R^A,

20 **R^A** and **R^B** are at each occurrence independently H or selected from the group consisting of (C₁-C₄)alkyl-, aryl, (C₁-C₆) haloalkyl, or

R^A and R^B may form together with the nitrogen atom to which they are

attached a 6 membered saturated heterocyclic monocyclic ring system optionally containing a further heteroatom which is nitrogen or oxygen, which may be optionally substituted by (C₁-C₄)alkyl- and oxo;

R^C is H or selected from the group consisting of (C₁-C₆)alkyl, (R^AR^B)N-, aryl-
5 (C₁-C₄)alkyl-,

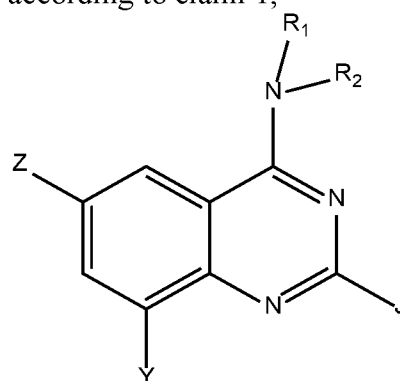
Y is selected from the group consisting of -OR^D, R^CSO₂-, halo, -NHSO₂R^C, heteroaryl, (C₃-C₈)heterocycloalkyl,

wherein any of such heteroaryl and heterocycloalkyl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, -C(O)N(R^AR^B);

10 **J** is H or selected from the group consisting of (C₁-C₆)alkyl, -OR^C,

R^D is H or (C₁-C₆)alkyl.

6. A compound of formula I according to claim 1,



(I)

15 wherein

Z is selected from the group consisting of heteroaryl and aryl, wherein any of such heteroaryl and aryl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, halo, CN, (R^AR^B)NC(O)-, (C₁-C₆)haloalkyl, R^AO-, (R^AR^B)N(C₁-C₆)alkylene-, (C₃-C₇)cycloalkyl-, R^CSO₂-,
20 (R^AR^B)N-;

R₁ is H,

R₂ is selected from the group consisting of (C₁-C₆)alkyl, heteroaryl(C₁-

C₄)alkyl-, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl, heteroaryl-(C₁-C₆)hydroxyalkyl, aryl-(C₁-C₄)alkyl-, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl-(C₁-C₆)alkyl-, (R^AR^B)N(C₁-C₆)alkylene-; R^AO(C₁-C₄)alkylene,

wherein any of such alkyl, alkylene, aryl, heteroaryl, cycloalkyl and heterocycloalkyl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, R^AO(C₁-C₄)alkylene, (C₁-C₆)haloalkyl, oxo, R^AO-, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl, heteroaryl, aryl optionally substituted by halo, R^CO-, (R^AR^B)N-, -NHC(O)R^C, -C(O)N(R^AR^B), halo, -SO₂N(R^AR^B), -O(R^AO(C₁-C₄)alkylene-N(R^AR^B), aryl-(C₁-C₄)alkyl-, -C(O)R^A,

10 **R^A and R^B** are at each occurrence independently H or selected from the group consisting of (C₁-C₄)alkyl-, aryl, (C₁-C₆) haloalkyl, or

R^A and R^B may form together with the nitrogen atom to which they are attached a 6 membered saturated heterocyclic monocyclic ring system optionally containing a further heteroatom which is nitrogen or oxygen, which may be optionally substituted by (C₁-C₄)alkyl- and oxo;

15 **R^C** is H or selected from the group consisting of (C₁-C₆)alkyl, (R^AR^B)N-, aryl-(C₁-C₄)alkyl-,

Y is selected from the group consisting of -OR^D, R^CSO₂-, halo, -NHSO₂R^C, heteroaryl, (C₃-C₈)heterocycloalkyl,

20 wherein any of such heteroaryl and heterocycloalkyl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, -C(O)N(R^AR^B);

J is H or selected from the group consisting of (C₁-C₆)alkyl, -OR^C,

R^D is H or (C₁-C₆)alkyl.

7. A compound of formula I according to claims 5 and 6, selected from the group consisting of:

25

(R)-6-(4-Fluorophenyl)-8-methoxy-2-methyl-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine

(R)-6-(4-Fluorophenyl)-8-methoxy-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)-amino)-quinazolin-2-ol ,

5 (R)-6-(4-Fluorophenyl)-2,8-dimethoxy-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine ,

6-(4-Fluorophenyl)-8-methoxy-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine ,

10 6-(4-Fluorophenyl)-8-methoxy-N-((5-methylpyridin-2-yl)methyl)quinazolin-4-amine,

N-((6-(Difluoromethoxy)pyridin-3-yl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine,

(R)-6-(4-Fluorophenyl)-8-methoxy-N-(1-(6-methylpyridazin-3-yl)ethyl)quinazolin-4-amine,

15 6-(4-Fluorophenyl)-8-methoxy-N-((6-methylpyridin-3-yl)methyl)quinazolin-4-amine,

4-(((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)methyl)-1-methylpyridin-2(1H)-one,

20 N-((2-(Dimethylamino)pyrimidin-5-yl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine,

N-((5-Chloropyrimidin-2-yl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine,

5-(((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)methyl)-N-methylpicolinamide,

25 6-(4-Fluorophenyl)-8-methoxy-N-((2-methylpyrimidin-5-yl)methyl)quinazolin-4-amine,,

N-(1-(3-Ethyl-1,2,4-oxadiazol-5-yl)ethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine,

6-(4-Fluorophenyl)-8-methoxy-N-(1-(6-methoxypyridin-3-yl)ethyl)quinazolin-4-amine,

5 6-(4-Fluorophenyl)-8-methoxy-N-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine,

6-(4-Fluorophenyl)-8-methoxy-N-(1-(6-methylpyridin-3-yl)ethyl)quinazolin-4-amine,

10 2-(((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)-2-(3-methyl-1,2,4-oxadiazol-5-yl)ethan-1-ol,

6-(4-Fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine,

N-(Cyclopropylmethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine,

15 6-(4-Fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)quinazolin-4-amine,

6-(4-Fluorophenyl)-8-methoxy-N-((2-(trifluoromethyl)pyrimidin-5-yl)methyl)quinazolin-4-amine,

6-(4-Fluorophenyl)-8-methoxy-N-((6-(trifluoromethyl)pyridin-3-yl)methyl)quinazolin-4-amine,

20 6-(4-Fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,3,4-thiadiazol-2-yl)ethyl)quinazolin-4-amine,

6-(4-Fluorophenyl)-N-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)ethyl)-8-methoxyquinazolin-4-amine,

25 N-(((6-(Dimethylamino)pyridin-3-yl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine,

6-(4-Fluorophenyl)-8-methoxy-N-[[5-(trifluoromethyl)-3-pyridyl]methyl]quinazolin-4-amine,

3-((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)tetrahydrothiophene 1,1-dioxide,

5 6-(4-Fluorophenyl)-8-methoxy-N-((tetrahydro-2H-pyran-4-yl)methyl)quinazolin-4-amine,

Single enantiomer 1 of 3-((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)tetrahydrothiophene 1,1-dioxide,

10 Single enantiomer 2 of 3-((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)tetrahydrothiophene 1,1-dioxide,

N-(5-(((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)methyl)pyridin-2-yl)acetamide,

6-(4-Fluorophenyl)-8-methoxy-N-(2-(6-methylpyridin-3-yl)ethyl)quinazolin-4-amine,

15 6-(4-Fluorophenyl)-8-methoxy-N-(1-methylpiperidin-4-yl)quinazolin-4-amine,

N1-(6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)-N3,N3-dimethylpropane-1,3-diamine,

20 (S)-2-(((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)-2-(6-methoxypyridin-3-yl)ethan-1-ol,

6-(4-Fluorophenyl)-8-methoxy-N-((6-morpholinopyridazin-3-yl)methyl)quinazolin-4-amine,

6-(4-Fluorophenyl)-8-methoxy-N-((6-methoxypyridin-3-yl)methyl)quinazolin-4-amine,

25 N-(4-ethoxybenzyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine,

6-(4-Fluorophenyl)-8-methoxy-N-(2-methyl-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl)quinazolin-4-amine,

6-(4-Fluorophenyl)-8-methoxy-N-[[2-(trifluoromethyl)-4-pyridyl]methyl]quinazolin-4-amine,

5 6-(4-Fluorophenyl)-8-methoxy-N-((1-methyl-1H-tetrazol-5-yl)methyl)quinazolin-4-amine,

6-(4-Fluorophenyl)-8-methoxy-N-((1-methyl-1H-pyrazol-4-yl)methyl)quinazolin-4-amine,

10 4-(2-((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)ethyl)morpholin-3-one,

6-(4-Fluorophenyl)-8-methoxy-N-((1-methyl-1H-1,2,4-triazol-5-yl)methyl)quinazolin-4-amine ,

6-(4-Fluorophenyl)-8-methoxy-N-((2-methyl-2H-tetrazol-5-yl)methyl)quinazolin-4-amine,

15 6-(4-Fluorophenyl)-8-methoxy-N-((1-methyl-1H-1,2,4-triazol-3-yl)methyl)quinazolin-4-amine,

6-(4-Fluorophenyl)-N-(imidazo[1,2-a]pyrimidin-6-ylmethyl)-8-methoxyquinazolin-4-amine,

20 6-(4-Fluorophenyl)-8-methoxy-N-((6-(2,2,2-trifluoroethoxy)pyridazin-3-yl)methyl)quinazolin-4-amine,

N-((4-Ethyl-4H-1,2,4-triazol-3-yl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine,

N-([1,2,4]Triazolo[4,3-a]pyrimidin-3-ylmethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine,

25 3-(((6-(4-Fluorophenyl)-8-methoxyquinazolin-4-yl)amino)methyl)-6-methylpyridin-2(1H)-one,

6-(4-Fluorophenyl)-8-methoxy-N-((3-(pyridin-4-yl)-1,2,4-oxadiazol-5-yl)methyl)quinazolin-4-amine,

6-(4-Fluorophenyl)-8-methoxy-N-((3-(piperidin-1-ylmethyl)-1,2,4-oxadiazol-5-yl)methyl)quinazolin-4-amine,

5 6-(4-Fluorophenyl)-8-methoxy-N-((1-methyl-1H-1,2,3-triazol-4-yl)methyl)quinazolin-4-amine,

6-(4-Fluorophenyl)-8-methoxy-N-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)methyl)quinazolin-4-amine,

10 6-(4-Fluorophenyl)-8-methoxy-N-((4-(trifluoromethyl)pyridin-3-yl)methyl)quinazolin-4-amine,

6-(4-Fluorophenyl)-8-methoxy-N-((2-(trifluoromethyl)pyridin-3-yl)methyl)quinazolin-4-amine,

N-((5,6-Dimethylpyridin-3-yl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine,

15 6-(4-Fluorophenyl)-8-methoxy-N-[(1-methylimidazol-2-yl)methyl]quinazolin-4-amine,

6-(4-Fluorophenyl)-8-methoxy-N-(2-phenylcyclopropyl)quinazolin-4-amine,

20 N-[(3-Chloro-4-pyridyl)methyl]-6-(4-fluorophenyl)-8-methoxy-quinazolin-4-amine,

2-(3-Chloro-4-pyridyl)-2-[[6-(4-fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]ethanol,

N-[(3S,4R)-4-Ethoxytetrahydrofuran-3-yl]-6-(4-fluorophenyl)-8-methoxy-quinazolin-4-amine,

25 N-[(1,1-Dioxothian-4-yl)methyl]-6-(4-fluorophenyl)-8-methoxy-quinazolin-4-amine,

4-[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]-1-methyl-
piperidin-2-one,

6-[[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]methyl]-1H-
pyridin-2-one,

5 3-[[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]methyl]-1,4-
dihydro-1,2,4-triazol-5-one,

N-[[1-(4-Chlorophenyl)cyclopropyl]methyl]-6-(4-fluorophenyl)-8-methoxy-
quinazolin-4-amine,

(5R)-5-[[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-
10 yl]amino]methyl]pyrrolidin-2-one,

(1S)-2-[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]-1-phenyl-
ethanol,

N'-[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]-N,N-dimethyl-1-(4-
pyridyl)ethane-1,2-diamine,

15 (2S)-2-[[6-(4-fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]-4-methyl-
pentanamide,

6-(4-Fluorophenyl)-8-methoxy-N-(2H-tetrazol-5-ylmethyl)quinazolin-4-
amine,

20 6-(4-Fluorophenyl)-8-methoxy-N-[(2-methylindazol-6-
yl)methyl]quinazolin-4-amine,

N-[2-[4-(Dimethylamino)phenyl]ethyl]-6-(4-fluorophenyl)-8-methoxy-
quinazolin-4-amine,

4-[[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]methyl]-N,N-
dimethyl-benzenesulfonamide,

25 6-(4-Fluorophenyl)-8-methoxy-N-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-
6-yl)quinazolin-4-amine,

N-[(1R,5S)-8-Benzyl-8-azabicyclo[3.2.1]octan-3-yl]-6-(4-fluorophenyl)-8-methoxy-quinazolin-4-amine,

N-[[4-[2-(dimethylamino)ethoxy]phenyl]methyl]-6-(4-fluorophenyl)-8-methoxy-quinazolin-4-amine,

5 6-(4-Fluorophenyl)-8-methoxy-N-(3-pyrrolidin-1-ylpropyl)quinazolin-4-amine,

(1S,2R)-1-[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]indan-2-ol,

10 6-(4-Fluorophenyl)-8-methoxy-N-[(4-methyl-2,3-dihydro-1,4-benzoxazin-7-yl)methyl]quinazolin-4-amine,

N-[(6-Chloroimidazo[1,2-a]pyridin-2-yl)methyl]-6-(4-fluorophenyl)-8-methoxy-quinazolin-4-amine,

N-[(4-Benzyloxyphenyl)methyl]-6-(4-fluorophenyl)-8-methoxy-quinazolin-4-amine,

15 N-[(1-Benzylazetid-3-yl)methyl]-6-(4-fluorophenyl)-8-methoxy-quinazolin-4-amine,

6-(4-Fluorophenyl)-8-methoxy-N-[(2R)-tetrahydrofuran-2-yl]methyl]quinazolin-4-amine,

20 N-[Cyclohexyl(phenyl)methyl]-6-(4-fluorophenyl)-8-methoxy-quinazolin-4-amine,

3-(3-Chlorophenyl)-3-[[6-(4-fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]propan-1-ol,

6-(4-Fluorophenyl)-8-methoxy-N-[(1-methylbenzimidazol-5-yl)methyl]quinazolin-4-amine,

25 6-(4-Fluorophenyl)-8-methoxy-N-[2-(4-methylpiperazin-1-yl)-1-phenylethyl]quinazolin-4-amine,

6-(4-Fluorophenyl)-8-methoxy-N-[(1S)-1-methyl-2-pyrrolidin-1-yl-ethyl]quinazolin-4-amine,

6-(4-Fluorophenyl)-8-methoxy-N-[(1-methylindazol-7-yl)methyl]quinazolin-4-amine,

5 6-(4-Fluorophenyl)-8-methoxy-N-[(1-methylazetid-3-yl)methyl]quinazolin-4-amine,

(1R,2S)-1-[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]indan-2-ol,

10 3-[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]-1-methyl-pyrrolidin-2-one,

6-(4-Fluorophenyl)-8-methoxy-N-(1-tetrahydropyran-4-ylethyl)quinazolin-4-amine,

N-[[3-Chloro-5-(trifluoromethyl)-2-pyridyl]methyl]-6-(4-fluorophenyl)-8-methoxy-quinazolin-4-amine,

15 1-[4-[[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]methyl]-1-piperidyl]ethanone,

2,2-Difluoro-3-[[6-(4-fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]propan-1-ol,

20 6-(4-Fluorophenyl)-8-methoxy-N-(2-piperazin-1-ylethyl)quinazolin-4-amine,

6-(4-Fluorophenyl)-8-methoxy-N-(pyrrolidin-3-ylmethyl)quinazolin-4-amine,

6-(4-Fluorophenyl)-8-methoxy-N-(pyrrolidin-2-ylmethyl)quinazolin-4-amine,

25 6-(4-Fluorophenyl)-8-methoxy-N-(1-methyl-2-morpholino-ethyl)quinazolin-4-amine,

(S)-6-(4-Fluorophenyl)-8-methoxy-N-((tetrahydrofuran-2-yl)methyl)quinazolin-4-amine,

6-(4-Fluorophenyl)-8-methoxy-N-((1-methylpyrrolidin-3-yl)methyl)quinazolin-4-amine,

5 N1,N1-Diethyl-N3-(6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)propane-1,3-diamine,

(R)-6-(4-Fluorophenyl)-8-methoxy-N-(1-methylpiperidin-3-yl)quinazolin-4-amine,

10 6-(4-Fluorophenyl)-8-methoxy-N-((1-methylpiperidin-2-yl)methyl)quinazolin-4-amine,

6-(4-Fluorophenyl)-8-methoxy-N-(2-(1-methylazetidid-3-yl)ethyl)quinazolin-4-amine,

2-[[6-(4-Fluorophenyl)-8-methoxy-quinazolin-4-yl]amino]-2-tetrahydropyran-4-yl-ethanol formate ,

15 6-(4-Fluorophenyl)-8-methoxy-N-[(1-methyl-4-piperidyl)methyl]quinazolin-4-amine,

6-(4-Fluorophenyl)-8-methoxy-N-[(1-methylindazol-4-yl)methyl]quinazolin-4-amine,

20 (R)-5-(1-((6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)amino)ethyl)-2-(trifluoromethyl)pyridine 1-oxide formate,

6-(4-fluorophenyl)-8-methoxy-N-(2-morpholinoethyl)quinazolin-4-amine,

N-(((1r,4r)-4-Aminocyclohexyl)methyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine ,

25 8-Methoxy-6-(5-methyl-1,3,4-thiadiazol-2-yl)-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine ,

8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(5-methylpyridin-2-yl)quinazolin-4-amine,

6-(8-Methoxy-4-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-6-yl)nicotinonitrile,

5 6-(5-(Difluoromethyl)pyridin-2-yl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

6-(8-Methoxy-4-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-6-yl)pyridin-3-ol,

10 6-(5-(Difluoromethoxy)pyridin-2-yl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(5-(methylsulfonyl)pyridin-2-yl)quinazolin-4-amine,

6-(8-Methoxy-4-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-6-yl)nicotinamide,

15 6-(8-Methoxy-4-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-6-yl)-N-methylnicotinamide,

8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(5-(trifluoromethoxy)pyridin-2-yl)quinazolin-4-amine,

20 6-[5-(Dimethylamino)-2-pyridyl]-8-methoxy-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine,

6-(5-Cyclopropylpyridin-2-yl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

6-(5-Chloropyridin-2-yl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

25 8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(6-methylpyridin-3-yl)quinazolin-4-amine,

8-Methoxy-6-(5-methyl-1,3,4-oxadiazol-2-yl)-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

8-Methoxy-6-(1-methyl-1H-pyrazol-3-yl)-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

5 6-(1,5-Dimethyl-1H-pyrazol-3-yl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

8-Methoxy-6-(6-methoxypyridazin-3-yl)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine,

10 8-Methoxy-6-(6-methylpyridazin-3-yl)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine,

8-Methoxy-N-[(6-methylpyridazin-3-yl)methyl]-6-(5-methylpyrimidin-2-yl)quinazolin-4-amine,

6-(5-Fluoro-2-pyridyl)-8-methoxy-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine,

15 6-(5-Fluoropyrimidin-2-yl)-8-methoxy-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine,

6-[8-Methoxy-4-[(6-methylpyridazin-3-yl)methylamino]quinazolin-6-yl]pyridazin-3-ol,

20 8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(5-(trifluoromethyl)pyridin-2-yl)quinazolin-4-amine,

8-Methoxy-6-(5-methoxypyridin-2-yl)-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(5-methylthiazol-2-yl)quinazolin-4-amine ,

25 8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(4-(trifluoromethyl)thiazol-2-yl)quinazolin-4-amine,

6-(1,3-Dimethyl-1H-pyrazol-4-yl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(4-methylthiazol-2-yl)quinazolin-4-amine,

5 8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(2-methylthiazol-5-yl)quinazolin-4-amine,

(R)-5-(1-((8-Methoxy-6-(5-methyl-1,3,4-thiadiazol-2-yl)quinazolin-4-yl)amino)ethyl)-2-(trifluoromethyl)pyridine 1-oxide,

(R)-8-Methoxy-6-(5-methyl-1,3,4-thiadiazol-2-yl)-N-(1-(6-
10 methylpyridazin-3-yl)ethyl)quinazolin-4-amine,

(R)-8-Methoxy-6-(5-methyl-1,3,4-thiadiazol-2-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine ,

8-Methoxy-6-(5-methylpyrimidin-2-yl)-N-[(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl]quinazolin-4-amine,

15 6-(5-Fluoropyrimidin-2-yl)-8-methoxy-N-[(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl]quinazolin-4-amine,

6-(5-Fluoro-2-pyridyl)-8-methoxy-N-[(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl]quinazolin-4-amine,

8-Methoxy-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-6-(5-
20 methylpyrimidin-2-yl)quinazolin-4-amine,

8-Methoxy-6-(1-methylpyrazol-3-yl)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]quinazolin-4-amine,

6-[5-(Difluoromethyl)-2-pyridyl]-8-methoxy-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]quinazolin-4-amine,

25 8-Methoxy-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-6-(5-methyl-2-pyridyl)quinazolin-4-amine,

6-(5-Fluoro-2-pyridyl)-8-methoxy-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]quinazolin-4-amine,

8-Methoxy-6-(3-methylisothiazol-5-yl)-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

5 (R)-8-methoxy-6-(5-methylpyridin-2-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine,

(R)-8-methoxy-6-(5-methylthiazol-2-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine,

10 (R)-8-methoxy-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazolin-6-ol,

(R)-8-methoxy-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine,

8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(5-(trifluoromethyl)thiazol-2-yl)quinazolin-4-amine,

15 8-Methoxy-6-(1-methyl-1H-pyrazol-4-yl)-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine ,

6-(4,5-Dimethylthiazol-2-yl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

20 6-(4-Fluoro-3-methylphenyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine ,

6-(2,4-Difluorophenyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

6-(4-Fluoro-3-methoxyphenyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

25 6-(4-Fluoro-2-methylphenyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

6-(4-Fluoro-2-(trifluoromethyl)phenyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

6-(3-Fluorophenyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

5 6-(2,4-Difluorophenyl)-8-methoxy-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]quinazolin-4-amine,

6-[4-[(Dimethylamino)methyl]phenyl]-8-methoxy-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine formate,

10 4-[8-Methoxy-4-[(6-methylpyridazin-3-yl)methylamino]quinazolin-6-yl]-N,N-dimethyl-benzamide,

6-[4-(Dimethylamino)phenyl]-8-methoxy-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine,

8-Methoxy-6-(4-methoxyphenyl)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine,

15 Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine,

Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine, 6-(3,4-Difluorophenyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

20 6-(4-Fluoro-2-methoxyphenyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine ,

8-Methoxy-N-((6-methylpyridazin-3-yl)methyl)-6-(2,4,6-trifluorophenyl)quinazolin-4-amine,

25 2-(8-Methoxy-4-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-6-yl)-5-methylbenzotrile,

5-Fluoro-2-(8-methoxy-4-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-6-yl)benzotrile,

5-Fluoro-2-(8-methoxy-4-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-6-yl)phenol,

5 (R)-6-(4-fluorophenyl)-8-methoxy-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine,

6-(4-fluorophenyl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

10 (R)-6-(4-Fluorophenyl)-8-methoxy-2-methyl-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine ,

(R)-6-(4-Fluorophenyl)-8-methoxy 4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)-amino)-quinazolin-2-ol ,

6-(4-fluorophenyl)-8-iodo-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

15 6-(4-fluorophenyl)-N-((6-methylpyridazin-3-yl)methyl)-8-(methylsulfonyl)quinazolin-4-amine,

(R)-N-(6-(4-fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazolin-8-yl)methanesulfonamide,

20 N-(6-(4-fluorophenyl)-4-oxo-3,4-dihydroquinazolin-8-yl)methanesulfonamide,

(R)-6-(4-fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazoline-8-sulfonamide,

(R)-6-(4-fluorophenyl)-8-(1-methyl-1H-pyrazol-4-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine ,

25 (R)-6-(4-Fluorophenyl)-8-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine,

(R)-6-(4-Fluorophenyl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)-8-(1,3,5-trimethyl-1H-pyrazol-4-yl)quinazolin-4-amine,

(R)-6-(4-Fluorophenyl)-8-(pyridin-4-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine,

5 (R)-4-(6-(4-Fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazolin-8-yl)-N,N-dimethylbenzamide,

(R)-6-(4-fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)-quinazolin-8-ol ,

10 6-(4-fluorophenyl)-4-(((6-methylpyridazin-3-yl)methyl)amino)quinazolin-8-ol,

((R)-8-methoxy-6-(3-methyl-1H-pyrazol-1-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine,

(R)-8-methoxy-6-(5-methyl-1H-pyrazol-1-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine,

15 (R)-8-Methoxy-6-(4-methyl-1H-imidazol-1-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine ,

(R)-8-methoxy-6-(5-methyl-1H-imidazol-1-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine ,

20 (R)-8-Methoxy-6-(4-methyl-1H-pyrazol-1-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine ,

Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine,

Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine ,

25 Single enantiomer 1 6-(4-fluorophenyl)-8-methoxy-N-(1-(6-methylpyridin-3-yl)ethyl)quinazolin-4-amine,

Single enantiomer 2 6-(4-fluorophenyl)-8-methoxy-N-(1-(6-methylpyridin-3-yl)ethyl)quinazolin-4-amine ,

Single enantiomer 1 6-(4-fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine,

5 Single enantiomer 2 6-(4-fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine,

Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)quinazolin-4-amine,

10 Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)quinazolin-4-amine,

Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(6-methoxypyridin-3-yl)ethyl)quinazolin-4-amine,

Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(6-methoxypyridin-3-yl)ethyl)quinazolin-4-amine ,

15 Single enantiomer 1 of 2-(((6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)amino)-2-(3-methyl-1,2,4-oxadiazol-5-yl)ethan-1-ol,

Single enantiomer 2 of 2-(((6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)amino)-2-(3-methyl-1,2,4-oxadiazol-5-yl)ethan-1-ol ,

20 Single enantiomer 1 of N-(1-(3-ethyl-1,2,4-oxadiazol-5-yl)ethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine,

Single enantiomer 2 of N-(1-(3-ethyl-1,2,4-oxadiazol-5-yl)ethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine ,

Single enantiomer 1 of N-(1-cyclopropylethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine,

25 Single enantiomer 2 of N-(1-cyclopropylethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine,

Single enantiomer of N3-(6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)-N1,N1-dimethylbutane-1,3-diamine,

Single enantiomer 2 of N3-(6-(4-fluorophenyl)-8-methoxyquinazolin-4-yl)-N1,N1-dimethylbutane-1,3-diamine ,

5 Single enantiomer 1 of 6-(4-fluorophenyl)-N-[1-(3-isopropyl-1,2,4-oxadiazol-5-yl)ethyl]-8-methoxy-quinazolin-4-amine ,

Single enantiomer 2 of 6-(4-fluorophenyl)-N-[1-(3-isopropyl-1,2,4-oxadiazol-5-yl)ethyl]-8-methoxy-quinazolin-4-amine ,

10 Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-N-[2-methyl-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl]quinazolin-4-amine,

Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-N-[2-methyl-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl]quinazolin-4-amine,

Single enantiomer 1 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,3,4-thiadiazol-2-yl)ethyl)quinazolin-4-amine,

15 Single enantiomer 2 of 6-(4-fluorophenyl)-8-methoxy-N-(1-(5-methyl-1,3,4-thiadiazol-2-yl)ethyl)quinazolin-4-amine,

(R)-6-(4-Fluorophenyl)-8-iodo-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine,,

20 (R)-6-(4-fluorophenyl)-8-(methylsulfonyl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine,

6-(4-Fluorophenyl)-8-methoxy-N-(1-(3-(pyridin-4-yl)-1,2,4-oxadiazol-5-yl)ethyl)quinazolin-4-amine,

6-(4-fluorophenyl)-8-methoxy-N-(2-(3-methyl-1,2,4-oxadiazol-5-yl)propan-2-yl)quinazolin-4-amine,

25 (rac)-N-(1-(4H-1,2,4-triazol-3-yl)ethyl)-6-(4-fluorophenyl)-8-methoxyquinazolin-4-amine,

(S)-6-(4-fluorophenyl)-8-methoxy-N-(1-(5-methyl-4H-1,2,4-triazol-3-yl)ethyl)quinazolin-4-amine,

6-(3,5-Difluoropyridin-2-yl)-8-methoxy-N-((6-methylpyridazin-3-yl)methyl)quinazolin-4-amine,

5 6-(3-Fluoro-5-methyl-2-pyridyl)-8-methoxy-N-[(6-methylpyridazin-3-yl)methyl] quinazolin-4-amine,

6-(5-Ethylthiazol-2-yl)-8-methoxy-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine,(R)-8-methoxy-6-(1-methyl-1H-1,2,4-triazol-3-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine,(R)-8-

10 methoxy-6-(1-methyl-1H-pyrazol-3-yl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine,

(R)-8-methoxy-6-(1-methyl-1H-1,2,4-triazol-3-yl)-N-(1-(6-methylpyridazin-3-yl)ethyl)quinazolin-4-amine,

(R)-6-(5-fluoropyridin-2-yl)-8-methoxy-N-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine,

15

(R)-8-methoxy-N-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)-6-(5-methylpyridin-2-yl)quinazolin-4-amine,

8-Methoxy-N-[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]-6-(5-methyl-2-pyridyl)quinazolin-4-amine,

20

6-(5-fluoro-2-pyridyl)-8-methoxy-N-[(1R)-1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl]quinazolin-4-amine,

8-methoxy-N-[(1R)-1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl]-6-(5-methyl-2-pyridyl)quinazolin-4-amine,

25

2-((8-methoxy-6-(5-methylpyrimidin-2-yl)quinazolin-4-yl)amino)-2-(3-methyl-1,2,4-oxadiazol-5-yl)ethan-1-ol,

6-(5-fluoro-2-pyridyl)-8-methoxy-N-[1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl]quinazolin-4-amine,

6-(5-fluoropyridin-2-yl)-8-methoxy-N-(1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)quinazolin-4-amine,

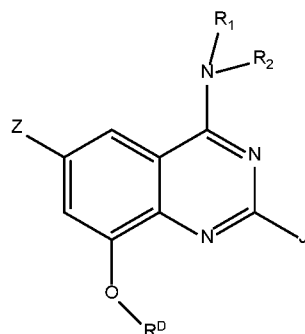
5 6-(5-fluoropyridin-2-yl)-8-methoxy-N-(1-(5-methyl-1,3,4-thiadiazol-2-yl)ethyl)quinazolin-4-amine,

8-methoxy-N-[(1R)-1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl]-6-(5-methylpyrimidin-2-yl)quinazolin-4-amine,

10 (S)-6-(5-fluoropyridin-2-yl)-8-methoxy-N-(1-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)quinazolin-4-amine,

8-Methoxy-N-[(1S)-1-(6-methylpyridazin-3-yl)ethyl]-6-(5-methylpyrimidin-2-yl)quinazolin-4-amine .

8. A compound of formula (I) according to claim 1, wherein Y is $-OR^D$, represented by formula (Ia)



15

(Ia)

wherein

Z is selected from the group consisting of aryl,

wherein any of such aryl may be optionally substituted by one or more groups
20 selected from halo;

R₁ is H,

R₂ is selected from the group consisting of heteroaryl(C₁-C₄)alkyl-,

wherein any of such heteroaryl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl, C₁-C₆haloalkyl;

R^A and R^B are at each occurrence independently H or selected from the group consisting of (C₁-C₄)alkyl-;

5 **R^C** is at each occurrence H or selected from the group consisting of (C₁-C₆)alkyl;

R^D is selected in the group consisting of H, (C₁-C₆)alkyl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl-, **R^C**OC(O)(C₁-C₄)alkylene-, (R^AR^B)N(C₁-C₆)alkylene-, (C₃-C₈)heterocycloalkyl, **R^C**O(C₁-C₄)alkylene-, (R^AR^B)N(O)C(C₁-C₄)alkylene-, (C₃-C₈)cycloalkyl-(C₁-C₆)alkyl-,
 10 wherein any of such heterocycloalkyl may be optionally substituted by one or more groups selected from (C₁-C₃)alkyl;

J is H.

9. A compound of formula I according to claim 4, selected from:

15 (R)-6-(4-Fluorophenyl)-8-((tetrahydro-2H-pyran-4-yl)oxy)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)quinazolin-4-amine,

(R)-4-(2-(1,1-dioxidothiomorpholino)ethyl)-8-(4-fluorophenyl)-3-oxo-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide,

20 6-(4-fluorophenyl)-8-isopropoxy-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine,

8-(cyclopropylmethoxy)-6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine,

25 2-[6-(4-fluorophenyl)-4-[(6-methylpyridazin-3-yl)methylamino]quinazolin-8-yl]oxyethanol,

2-[6-(4-fluorophenyl)-4-[(6-methylpyridazin-3-yl)methylamino]quinazolin-8-yl]oxy-N,N-dimethyl-acetamide,

6-(4-fluorophenyl)-8-(2-methoxyethoxy)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine,

5 6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-(oxetan-3-ylmethoxy)quinazolin-4-amine,

6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-tetrahydropyran-4-yloxy-quinazolin-4-amine,

10 6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-(2-morpholinoethoxy)quinazolin-4-amine,

6-(4-fluorophenyl)-8-[(1-methyl-4-piperidyl)oxy]-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine,

8-[3-(dimethylamino)propoxy]-6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine,

15 ethyl 2-[6-(4-fluorophenyl)-4-[(6-methylpyridazin-3-yl)methylamino]quinazolin-8-yl]oxyacetate,

8-ethoxy-6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine,

20 2-[6-(4-fluorophenyl)-4-[(6-methylpyridazin-3-yl)methylamino]quinazolin-8-yl]oxyacetic acid, sodium salt,

8-(azetidin-3-ylmethoxy)-6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine,

6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-pyrrolidin-3-yloxy-quinazolin-4-amine,

25 6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-(morpholin-2-ylmethoxy)quinazolin-4-amine,

8-(azetidin-3-yloxy)-6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine,

6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-(4-piperidyloxy)quinazolin-4-amine,

5 6-(4-fluorophenyl)-8-[(1-methylazetidin-3-yl)methoxy]-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine,

6-(4-fluorophenyl)-8-[(4-methylmorpholin-2-yl)methoxy]-N-[(6-methylpyridazin-3-yl)methyl]quinazolin-4-amine,

10 6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-(1-methylpyrrolidin-3-yl)oxy-quinazolin-4-amine,

R)-2-((6-(4-fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazolin-8-yl)oxy)acetamide,

(R)-2-((6-(4-fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazolin-8-yl)oxy)-1-(pyrrolidin-1-yl)ethan-1-one,

15 (R)-N,N-diethyl-2-((6-(4-fluorophenyl)-4-((1-(2-(trifluoromethyl)pyrimidin-5-yl)ethyl)amino)quinazolin-8-yl)oxy)acetamide,

6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-[(3S)-pyrrolidin-3-yl]oxy-quinazolin-4-amine,

20 6-(4-fluorophenyl)-N-[(6-methylpyridazin-3-yl)methyl]-8-[(3R)-pyrrolidin-3-yl]oxy-quinazolin-4-amine

10. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, either alone or in combination with another one or more active ingredient, in admixture with one or more pharmaceutically acceptable carrier or excipient.

25 11. The pharmaceutical composition according to claim 10 for oral administration.

12. A compound according to any one of claims 1 to 9 or a pharmaceutical composition

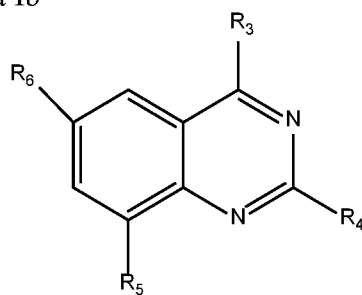
according to claims 10 and 11 for use as a medicament.

13. A compound according to any one of claims 1 to 9 or a pharmaceutical composition according to claims 10 and 11 for the use in treatment of any disease wherein the P2X₃ receptors are involved.

5 14. A compound according to any one of claims 1 to 9 or a pharmaceutical composition according to claims 10 and 11 for use in the prevention and/or treatment of respiratory diseases including cough, sub-acute or chronic cough, treatment-resistant cough, idiopathic chronic cough, post-viral cough, iatrogenic cough, asthma, idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease
10 (COPD) and cough associated with respiratory diseases such as COPD, asthma and bronchospasm.

15. A compound or a pharmaceutical composition according to claim 14 for use in the treatment of chronic cough.

16. A compound of formula Ib



15

(Ib)

wherein

R₃ is OH or halo,

R₄ is H or OH,

20 **R₅** is halo or -OMe,

R₆ is halo or Z,

Z is as defined above.

17. Use of compounds of formula (Ib) according to claim 16, as intermediate in the preparation of compounds of formula (I) as described in claim 1.