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(54) Title: AZAHETEROBICYCLIC COMPOUNDS

(57) Abstract: The invention provides novel substituted azaheterobicyclic compounds according to Formula (I), their manufacture and use for the treatment of hyperproliferative diseases such as cancer, inflammatory or degenerative diseases.



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Azaheterobicyclic compounds

5 *Field of the invention*

The invention relates to a series of novel substituted azaheterobicyclic compounds that are useful in the treatment of hyperproliferative diseases such as cancer, as well as inflammatory or degenerative diseases, in mammals. Also encompassed by the present
10 invention is the use of such compounds in the treatment of hyperproliferative, inflammatory or degenerative diseases in mammals, especially humans, and pharmaceutical compositions containing such compounds.

Summary of the related art

15

Wnt proteins comprise a large family of cysteine-rich secreted ligands that are highly conserved among species. Currently, three different pathways are believed to be activated by Wnt signaling: the canonical Wnt / β -catenin cascade, the noncanonical planar cell polarity pathway, and the Wnt/ Ca^{2+} pathway. Of these three, the canonical
20 pathway is best understood and has the highest cancer relevance. Therefore, this project is focusing on canonical Wnt / β -catenin signaling.

In the canonical pathway, β -catenin is the key mediator of Wnt signaling. In the absence of Wnt ligands, a protein complex, that contains Axin, adenomatous polyposis coli (APC), glycogen synthase kinase 3 β (GSK3 β) and casein kinase 1 (CK1), functions in
25 phosphorylating β -catenin and thereby marking it for destruction via ubiquitination and degradation by the proteasome. Following Wnt binding to a receptor complex composed of members of the Frizzled (Fz) family of seven transmembrane, serpentine receptors and low density lipoprotein receptor-related proteins 5/6 (LRP5/6), Disheveled (Dsh) and Axin are recruited to the plasma membrane. Subsequently, the Axin-APC-GSK3 β
30 complex is inhibited, non-phosphorylated β -catenin accumulates in the cytoplasm and then translocates into the nucleus where it regulates target gene expression in combination with members of the DNA-binding T cell factor / lymphoid enhancer factor (TCF/LEF) family. Many different target genes of canonical Wnt / β -catenin signaling have been described (e.g. c-Myc, Cyclin D1, VEGF, survivin) which are involved in cell

growth, migration and survival (Logan & Nusse, Annu Rev Cell Dev Biol. 2004;20:781-810).

The Wnt / β -catenin signaling cascade is frequently over-activated in different tumor types and several proteins of the pathway act as oncogenes or tumor suppressors (Giles et al., Biochim Biophys Acta. 2003 Jun 5;1653(1):1-24, van Es et al., Curr Opin Genet Dev. 2003 Feb;13(1):28-33).

Most prominently, the tumor suppressor APC is mutated in nearly 60% of all colon cancers. In addition, many colon cancers express mutated β -catenin which cannot be phosphorylated and is therefore stabilized. Furthermore, loss of function mutations of the tumor suppressor Axin have been detected in hepatocellular, lung and colon cancers. Thus, interference with Wnt / β -catenin signaling is a conceivable strategy for the treatment of cancer (reviewed in Dihlmann & von Knebel Doeberitz, Int. J. Cancer: 113, 515-524 (2005), Luu et al., Curr Cancer Drug Targets. 2004 Dec;4(8):653-71).

WO 2010/041054 discloses a series of chemical compounds which act on the Wnt pathway.

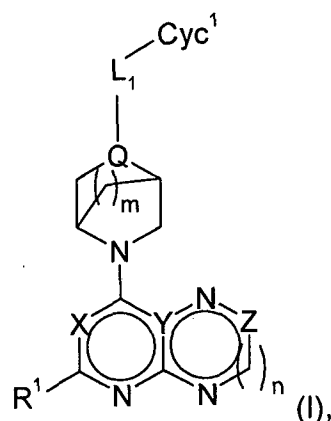
However, as a therapeutic directed to this pathway has yet to be commercialized, a significant unmet medical need still exists, so that further promising Wnt pathway inhibitors have to be identified and developed.

Description of the invention

It is, therefore, the object of the present invention to provide novel Wnt pathway inhibitors useful in the treatment of inflammatory or hyperproliferative diseases, such as cancer in mammals, with superior pharmacological properties both with respect to their activities as well as their solubility, metabolic clearance and bioavailability characteristics.

As a result, this invention provides novel substituted azaheterobicyclic compounds or their stereoisomers or tautomers, or pharmaceutically acceptable salts, that are Wnt pathway inhibitors and useful as medicaments, especially in the treatment of the diseases mentioned above and below.

The compounds are defined by Formula (I):



wherein:

- | | |
|---------------------------------|---|
| X | is CH or N, |
| Y | is C, CH or N, |
| 5 Z | is CH or S, |
| | provided that, if Z is S then Y is not N, |
| Q | is N or CR ² , |
| n | is 0 or 1, |
| m | is 0, 1 or 2, |
| 10 R ¹ | is H, LA, NH ₂ , NH(LA) or N(LA) ₂ , |
| R ² | is H, OH, Hal or NH ₂ , |
| L ₁ , L ₂ | are independently CO, NH, -CONH, -HNCO, -CO(LA), -(LA)CO, -N(LA), LA, or a bond, |
| 15 Cyc ¹ | is a mono- or binuclear, aliphatic or aromatic, 4, 5, 6, 7, 8, 9 or 10 membered homo- or heterocycle, having 0, 1, 2, 3 or 4 N, O and/or S atoms, which may be mono- or independently di- or trisubstituted by Hal, OH, CN, LA, O(LA), and/or monosubstituted by an oxo group or L ₂ -Cyc ² , |
| 20 Cyc ² | is a mono- or binuclear, aliphatic or aromatic, 4, 5, 6, 7, 8, 9 or 10 membered homo- or heterocycle, having 0, 1, 2, 3 or 4 N, O and/or S atoms, which may be mono- or independently di- or trisubstituted by Hal, OH, CN, LA, O(LA), CO(LA), and/or monosubstituted by an oxo group or L ₂ -Cyc ³ , |
| 25 Cyc ³ | is a mononuclear, aliphatic or aromatic, 5 or 6 membered homo- or heterocycle, having 0, 1 or 2 N, O and/or S atoms, which may be mono- or independently di- or trisubstituted by Hal, OH, CN, LA, O(LA), CON(LA), COO(LA), or monosubstituted by an oxo group, |

LA is unbranched or branched alkyl, having 1, 2, 3, 4 or 5 carbon atoms, which may be saturated or partially unsaturated, wherein 1, 2 or 3 H atoms may be replaced by Hal, and/or 1 CH₂ group may be replaced by -O-, -SO₂-, -NH-, or -N(CH₃)-

5 Hal is F, Cl, Br or I, and wherein a circle in a ring system indicates that the said ring system is aromatic.

In general, all residues which occur more than once may be identical or different, i.e. are independent of one another. Above and below, the residues and parameters have the meanings indicated for the Formula (I), unless expressly indicated otherwise. Accordingly, the invention relates, in particular, to the compounds of the Formula (I) in which at least one of the said residues has one of the preferred meanings indicated below.

15 Hal denotes fluorine, chlorine, bromine or iodine, in particular fluorine, chlorine or bromine.

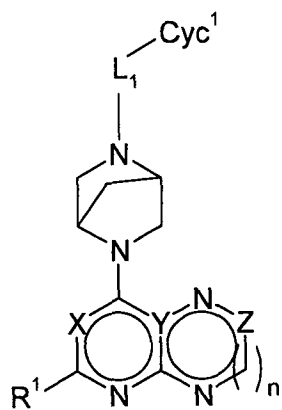
"LA" denotes for example methyl, ethyl, trifluoromethyl, difluoromethyl, 1,1,1-trifluoroethyl, propyl, isopropyl, methoxyethyl, dimethylaminomethyl, butyl, isobutyl, sec-butyl or tert-butyl, isopropenyl, ethenyl, ethynyl or prop-1-ynyl.

"L₁, L₂" are linker moieties and denote for example CO, NH, -CONH, -HNCO, -COCH₂-, CH₂CO, -NCH₂, CH₂-, -COCH₂O, -COCH₂CH₂-, or a bond, wherein the "-" on the left part of the formula indicates connection to the cycle, and the right part is connected to Cyc¹.

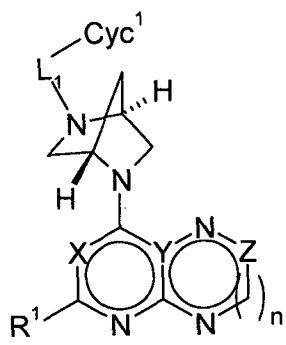
"Cyc¹" and "Cyc²" denote, for example, cyclobutyl, cyclopentyl, cyclohexyl, azetidine-1-, 2- or 3-yl, oxazolidine-2-, 3-, 4- or 5-yl, isoxazolidine-2-, 3-, 4- or 5-yl, 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or -5-furyl, tetrahydro-2- or -3-furyl, tetrahydro-1-, -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3-, 1-, 5- or 6-piperidiny, 2-, 3- or 4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxanyl, 1,3-dioxan-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridazinyl, hexahydro-1-, -2-, -4- or -5-pyrimidinyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, phenyl, 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl,

- 1-, 2- or 3-pyrrolidinyl, 1-, 2, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, pyrazin-2- or 3-yl, pyridazin-3- or 4-yl, 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or 5-yl, 1- or 5-tetrazolyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 2-, 3-, 4-, 5-, 6- or 7-indazolyl, 2-, 3-, 4- or 5-isoindolyl, 2-, 6-, -or 8-purinyl, 1-, 2-, 4- or
- 5 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7- benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolinyl, 3-, 4-, 5-, 6-, 7- or 8-quinolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazoliny, quin-oxalin-2-, 3-, 4- or 5-yl, 4-, 5-, or 6-phthalazinyl, 2-, 3-, 5-, 6-, 7- or 8-2H-benzo-1,4-
- 10 oxazinyl, 1,3-benzodioxol-2-, 4- or 5-yl, indan-1-, 2-, 4- or 5-yl, 2-oxo-1,2-dihydro-thiazolo[5,4-b]pyridin-5, 6, or 7-yl, 7H-pyrrolo[2,3-d]pyrimidin-2, 3, 4 or 6-yl, 1H-pyrrolo[2,3-c]pyridin-2, 3, 4, 5 or 7-yl.
- "Cyc³" denotes, for example, cyclopentyl, cyclohexyl, oxazolidine-2-, 3-, 4- or 5-yl,
- 15 isoxazolidine-2-, 3-, 4- or 5-yl, 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or -5-furyl, tetrahydro-2- or -3-furyl, tetrahydro-1-, -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3-, 1-, 5- or 6-piperidinyl, 2-, 3- or 4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxanyl, 1,3-dioxan-2-, -4- or -5-yl,
- 20 2,3-dihydro-1,4-benzodioxin-2, 3, 5 or 6-yl, naphtalen-1 or 2-yl, hexahydro-1-, -3- or -4-pyridazinyl, hexahydro-1-, -2-, -4- or -5-pyrimidinyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, phenyl, 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2- or 3-pyrrolidinyl, 1-, 2, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, pyrazin-2- or 3-yl, pyridazin-3- or
- 25 4-yl, 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or 5-yl, 1- or 5-tetrazolyl.

In a preferred embodiment the compounds of Formula (I) conform to Formula (IIa) or, more specifically, (IIb)



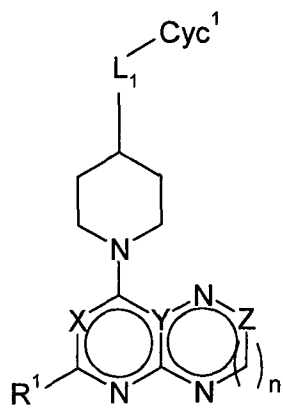
(IIa),



(IIb),

wherein Q is N, m is 1, and the remaining residues have the meaning indicated for Formula (I),

5 or Formula (III)



(III),

wherein Q is CH, m is 0, and the remaining residues have the meaning indicated for Formula (I).

10

Further preferred are compounds of Subformulae 1 to 5 of Formulae (I), (IIa), (IIb) or (III) wherein

15 in Subformula 1

R¹ is H, methyl or NH₂,

X is N,

Y is C,

Z is CH,

20 n is 1,

in Subformula 2

	R ¹	is H, methyl or NH ₂ ,
	X	is CH,
5	Y	is N,
	Z	is CH,
	n	is 0,

in Subformula 3

10	R ¹	is H, methyl or NH ₂ ,
	X	is CH,
	Y	is C,
	Z	is S,
	n	is 0,

15

in Subformula 4

	R ¹	is H, methyl or NH ₂ ,
	X	is CH,
	Y	is C,
20	Z	is CH,
	n	is 1,

in Subformula 5

	R ¹	is H, methyl or NH ₂ ,
25	X	is N,
	Y	is C,
	Z	is S,
	n	is 0,

30 and the remaining residues have the meaning as indicated for Formula (I).

Also preferred are compounds of Subformula 6 of Formula (IIb) wherein

R¹, X, Y, Z, n have the meanings indicated for either of Subformulae 1 to 5,
 L₁ is a bond,

Cyc¹ is phenyl or pyridyl, which may be mono- or independently disubstituted by Hal, methyl, methoxy,
or which may be monosubstituted by pyrazol-1-ylmethyl,
Hal is F, Cl or Br,

5

and the remaining residues have the meaning as indicated for Formula (I).

Also preferred are compounds of Subformulae 7 to 10 of Formula (III) wherein

10 in Subformula 7

R¹, X, Y, Z, n have the meanings indicated for either of Subformulae 1 to 5,

R² is H or OH,

L₁ is a bond, CO, -CONH, CH₂, -CH₂CH₂O, -CONHCH₂,

Cyc¹ is phenyl, pyridyl, piperidine, piperazine, quinoline, thiazole, which
15 may be mono- or independently di- or trisubstituted by Hal, LA, OH,
CN,

Hal is F, Cl or Br,

in Subformula 8

20 R¹, X, Y, Z, n have the meanings indicated for either of Subformulae 1 to 5,

R² is H or OH,

L₁ is a bond, CO, -CONH, CH₂, -CH₂CH₂O, -CONHCH₂,

Cyc¹ is phenyl, pyridyl, piperidine, piperazine, quinoline, thiazole,
[1,2,4]oxadiazol, which is monosubstituted by L₂-Cyc²,

25 L₂ is a bond, -CH₂CH₂O, -CONHCH₂, -COCH₂CH₂, -COCH₂O,
-COCH₂, CO, -CONHCH₂CH₂, -CH₂CONH, -CON(CH₃)CH₂,
-CH₂CH₂OCH₂, CH₂, -CH₂CON(CH₃)CH₂, -CON(CH₃),
-SO₂CH₂CH₂, -CH₂CH₂SO₂,

Cyc² is phenyl, pyridyl, pyrazole, imidazolin-2-one, oxadiazole, furan,
30 2,3-Dihydro-benzo[1,4]dioxin, Benzo[1,3]dioxol, naphthalen,
isoxazol, benzofuran, [1,3,4]thiadiazol, thiazole, which may be
monosubstituted by Hal, LA, CO(LA), O(LA), CN,

in Subformula 9

35 R¹, X, Y, Z, n have the meanings indicated for either of Subformulae 1 to 5,

- R^2 is H or OH,
 L_1 is a bond, CO, -CONH, CH_2 , $-CH_2CH_2O$, $-CONHCH_2$,
 Cyc^1 is phenyl, pyridyl, piperidine, piperazine, quinoline, thiazole, which
 is monosubstituted by L_2-Cyc^2 ,
 5 L_2 is a bond, $-CH_2CH_2O$, $-CONHCH_2$, $-COCH_2CH_2$, $-COCH_2O$,
 $-COCH_2$,
 Cyc^2 is phenyl, pyridyl, pyrazole, imidazolin-2-one, oxadiazole, which
 may be monosubstituted by Hal, LA,
 Hal is F, Cl or Br,
 10 in Subformula 10
 R^1 , X, Y, Z, n have the meanings indicated for either of Subformulae 1 to 5,
 R^2 is H or OH,
 L_1 is a bond, CO, -CONH, CH_2 , $-CH_2CH_2O$, $-CONHCH_2$,
 15 Cyc^1 is phenyl, pyridyl, piperidine, piperazine, quinoline, thiazole, which
 is monosubstituted by L_2-Cyc^2 ,
 L_2 is a bond, $-CH_2CH_2O$, $-CONHCH_2$, $-COCH_2CH_2$, $-COCH_2O$,
 $-COCH_2$,
 Cyc^2 is phenyl, pyridyl, pyrazole, imidazolin-2-one, oxadiazole, which
 20 is monosubstituted by L_2-Cyc^3 ,
 Cyc^3 is phenyl, pyridyl, piperidine which may be mono- or disubstituted
 by Hal, or LA,
 Hal is F, Cl or Br,
 25 and the remaining residues have the meaning as indicated for Formula (I).

The compounds of the Formula (I) may have one or more centres of chirality. They may
 accordingly occur in various enantiomeric forms and be in racemic or optically active
 form. The invention, therefore, also relates to the optically active forms, enantiomers,
 30 racemates, diastereomers, collectively: stereoisomers, of these compounds.
 Since the pharmaceutical activity of the racemates or stereoisomers of the compounds
 according to the invention may differ, it may be desirable to use the enantiomers. In
 these cases, the end product or even the intermediates can be separated into
 enantiomeric compounds by chemical or physical measures known to the person skilled
 35 in the art or even employed as such in the synthesis.

In the case of racemic amines, diastereomers are formed from the mixture by reaction with an optically active resolving agent. Examples of suitable resolving agents are optically active acids, such as the R and S forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid, suitably N-protected amino acids (for example N-benzoylproline or N-benzenesulfonylproline), or the various optically active camphorsulfonic acids. Also advantageous is chromatographic enantiomer resolution with the aid of an optically active resolving agent (for example dinitrobenzoylphenylglycine, cellulose triacetate or other derivatives of carbohydrates or chirally derivatised methacrylate polymers immobilised on silica gel). Suitable eluents for this purpose are aqueous or alcoholic solvent mixtures, such as, for example, hexane/isopropanol/ acetonitrile, for example in the ratio 82:15:3. An elegant method for the resolution of racemates containing ester groups (for example acetyl esters) is the use of enzymes, in particular esterases.

It is well known that atoms may have atomic masses or mass numbers which differ from the atomic masses or mass numbers of the atoms which usually occur naturally. Examples of isotopes which are readily commercially available and which can be incorporated into a compound of the present invention by well-known methods include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, for example ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl , respectively. Incorporation of heavier isotopes, especially deuterium (^2H), into a compound of the invention has therapeutic advantages owing to the higher metabolic stability of this isotope-labeled compound. Higher metabolic stability translates directly into an increased in vivo half-life or lower dosages. Therefore, these isotopes are included in the definition of atoms H, C, N etc., as used in the chemical compounds of this invention.

The compounds of the present invention can be in the form of a prodrug compound. "Prodrug compound" means a derivative that is converted into a biologically active compound according to the present invention under physiological conditions in the living body, e.g., by oxidation, reduction, hydrolysis or the like, each of which is carried out enzymatically, or without enzyme involvement. Examples of prodrugs are compounds, wherein the amino group in a compound of the present invention is acylated, alkylated or phosphorylated, e.g., eicosanoylamino, alanylamino, pivaloyloxymethylamino or wherein the hydroxyl group is acylated, alkylated, phosphorylated or converted into the borate, e.g. acetyloxy, palmitoyloxy, pivaloyloxy, succinyloxy, fumaryloxy, alanyloxy or wherein

the carboxyl group is esterified or amidated, or wherein a sulfhydryl group forms a disulfide bridge with a carrier molecule, e.g. a peptide, that delivers the drug selectively to a target and/or to the cytosol of a cell. These compounds can be produced from compounds of the present invention according to well-known methods. Other examples of prodrugs are compounds, wherein the carboxylate in a compound of the present invention is for example converted into an alkyl-, aryl-, choline-, amino, acyloxymethylester, linolenoyl-ester.

Where tautomerism, e.g., keto-enol tautomerism, of compounds of the present invention or their prodrugs may occur, the individual forms, e.g., the keto or the enol form, are claimed separately and together as mixtures in any ratio. The same applies for stereoisomers, e.g., enantiomers, cis/trans isomers, conformers and the like. If desired, isomers can be separated by methods well known in the art, e.g. by liquid chromatography. The same applies for enantiomers, e.g., by using chiral stationary phases. Additionally, enantiomers may be isolated by converting them into diastereomers, i.e., coupling with an enantiomerically pure auxiliary compound, subsequent separation of the resulting diastereomers and cleavage of the auxiliary residue. Alternatively, any enantiomer of a compound of the present invention may be obtained from stereoselective synthesis using optically pure starting materials

The compounds of the present invention can be in the form of a pharmaceutically acceptable salt, a pharmaceutically acceptable solvate, or a pharmaceutically acceptable solvate of a pharmaceutically acceptable salt.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable bases or acids, including inorganic bases or acids and organic bases or acids. In cases where the compounds of the present invention contain one or more acidic or basic groups, the invention also comprises their corresponding pharmaceutically acceptable salts. Thus, the compounds of the present invention which contain acidic groups can be present in salt form, and can be used according to the invention, for example, as alkali metal salts, alkaline earth metal salts or as ammonium salts. More precise examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. Compounds of the present invention which contain one or more basic groups, i.e. groups which can be protonated, can be present in salt form, and can be used according to the invention in the form of

their addition salts with inorganic or organic acids. Examples of suitable acids include hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfaminic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid, and other acids known to the person skilled in the art. If the compounds of the present invention simultaneously contain acidic and basic groups in the molecule, the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). The respective salts can be obtained by customary methods which are known to a person skilled in the art, for example by contacting these with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange with other salts. The present invention also includes all salts of the compounds of the present invention which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

The term "pharmaceutically acceptable solvates" means addition forms with pharmaceutically acceptable solvents that contain either stoichiometric or non stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate, e.g. a mono- or dihydrate. If the solvent is alcohol, the solvate formed is an alcoholate, e.g., a methanolate or ethanolate. If the solvent is an ether, the solvate formed is an etherate, e.g., diethyl etherate.

Therefore, the following items are also in accordance with the invention:

- a) all stereoisomers or tautomers of the compounds, including mixtures thereof in all ratios,
- b) prodrugs of the compounds, or stereoisomers or tautomers of these prodrugs,
- c) pharmaceutically acceptable salts of the compounds and of the items mentioned under (a) and (b),
- d) pharmaceutically acceptable solvates of the compounds and of the items mentioned under (a), (b) and (c).

It should be understood that all references to compounds above and below are meant to include these items, in particular pharmaceutically acceptable solvates of the compounds, or pharmaceutically acceptable solvates of their pharmaceutically acceptable salts.

5

Furthermore, the present invention relates to pharmaceutical compositions comprising a compound of the present invention, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, as active ingredient, together with a pharmaceutically acceptable carrier.

10

"Pharmaceutical composition" means one or more active ingredients, and one or more inert ingredients that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

15

20 A pharmaceutical composition of the present invention may additionally comprise one or more other compounds as active ingredients, such as one or more additional compounds of the present invention, or other Wnt pathway inhibitors.

The pharmaceutical compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

25

30 In one embodiment, said compounds and pharmaceutical composition are for the treatment of cancer such as brain, lung, colon, epidermoid, squamous cell, bladder, gastric, pancreatic, breast, head & neck, renal, kidney, liver, ovarian, prostate, uterine, oesophageal, testicular, gynecological, thyroid cancer, melanoma, as well as
35 hematologic malignancies such as acute myelogenous leukemia, multiple myeloma,

chronic myelogenous leukemia, myeloid cell leukemia, Kaposi's sarcoma, or any other type of solid or liquid tumors. Preferably, the cancer to be treated is chosen from colon, lung, breast and hematological tumor types.

5 In addition, said compounds and pharmaceutical composition are for the treatment of inflammatory diseases such as multiple sclerosis, rheumatoid arthritis, systemic lupus, inflammatory bowel diseases or degenerative diseases such as osteoarthritis and Alzheimer's disease.

10 This invention also relates to a compound or pharmaceutical composition for inhibiting abnormal cell growth in a mammal which comprises an amount of a compound of the present invention, in combination with an amount of another anti-cancer therapeutic, wherein the amounts of the compound, and of the other anti-cancer therapeutic are together effective in inhibiting abnormal cell growth. Many anti-cancer therapeutics are presently known in the art. In one embodiment, the anti-cancer therapeutic is a
15 chemotherapeutic selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, cell cycle inhibitors, topoisomerase inhibitors, or a biological response modifiers, such as anti-hormones, angiogenesis inhibitors, integrin antagonists, such as cilengitide, and anti-androgens. In another embodiment the anti-cancer therapeutic is an antibody selected from the group
20 consisting of bevacizumab, CD40-specific antibodies, chTNT-1/B, denosumab, zanolimumab, IGF1R-specific antibodies, lintuzumab, edrecolomab, WX G250, rituximab, ticilimumab, trastuzumab and cetuximab. In yet another embodiment the anti-cancer therapeutic is an inhibitor of a protein kinase, such as Akt, Axl, Aurora A, Aurora B, c-Met, dyrk2, epha2, fgfr3, igf1r, IKK2, JNK3, Vegfr1, Vegfr2, Vegfr3 (also known as Flt-4),
25 KDR, MEK, MET, Plk1, RSK1, Src, TrkA, Zap70, cKit, bRaf, EGFR, Jak2, PI3K, NPM-Alk, c-Abl, BTK, FAK, PDGFR, p70S6K, TAK1, LimK, Flt-3, PDK1 and Erk.

This invention further relates to a method for inhibiting abnormal cell growth in a mammal or treating a hyperproliferative disorder that comprises administering to the mammal an
30 amount of a compound of the present invention or pharmaceutical composition, in combination with radiation therapy, wherein the amounts of the compound or pharmaceutical composition, is in combination with the radiation therapy effective in inhibiting abnormal cell growth or treating the hyperproliferative disorder in the mammal. Techniques for administering radiation therapy are known in the art, and these
35 techniques can be used in the combination therapy described herein. The administration

of a compound of the invention, or pharmaceutical composition, in this combination therapy can be determined as described herein. It is believed that the compounds of the present invention can render abnormal cells more sensitive to treatment with radiation for purposes of killing and/or inhibiting the growth of such cells.

5

Accordingly, this invention further relates to a method for sensitizing abnormal cells in a mammal to treatment with radiation which comprises administering to the mammal an amount of a compound of the present invention or pharmaceutical composition, which amount is effective in sensitizing abnormal cells to treatment with radiation. The amount
10 of the compound in this method can be determined according to the means for ascertaining effective amounts of such compounds described herein.

15

In practical use, the compounds of the present invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, *e.g.*, oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like. In the case of oral
20 liquid preparations, any of the usual pharmaceutical media may be employed, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. In the case of oral solid preparations the composition may take forms such as, for example, powders, hard and soft capsules and tablets, with the solid oral
25 preparations being preferred over the liquid preparations.

30

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or
30 nonaqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active
35 compounds can also be administered intranasally as, for example, liquid drops or spray.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Compounds of the present invention may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dose of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules,

creams, ointments, aerosols, and the like. Preferably compounds of the present invention are administered orally.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person skilled in the art.

When treating inflammatory, degenerative or hyperproliferative diseases for which compounds of the present invention are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.01 milligram to about 100 milligram per kilogram of body weight, preferably given as a single daily dose. For most large mammals, the total daily dosage is from about 0.1 milligrams to about 1000 milligrams, preferably from about 0.2 milligram to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 0.2 milligrams to about 200 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

The invention also relates to a set (kit) consisting of separate packs of

- a) an effective amount of a compound according to the invention or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, and
- b) an effective amount of a further medicament active ingredient.

The set comprises suitable containers, such as boxes, individual bottles, bags or ampoules.

By way of example, the set may comprise separate ampoules, each containing an effective amount of a compound according to the invention, and an effective amount of a further medicament active ingredient in dissolved or lyophilised form.

Experimental Section

Some abbreviations that may appear in this application are as follows:

Abbreviations

Designation	
aq.	Aqueous
ATP	Adenosine triphosphate
b	Broad peak
Boc	tert-Butyl carbamate
Boc ₂ O	Di-tert-butyl dicarbonate
calc	Calculated
cHex	Cyclohexane
CDCl ₃	Deutero-Chloroforme
d	Doublet
DCM	Dichloromethane
DME	Ethylene glycol dimethylether
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
EtOAc	Ethyl acetate
EtOH	Ethanol
ESI	Electrospray ionisation
h	Hour
HPLC	High Pressure Liquid Chromatography
LC/MS	Liquid Chromatography coupled to Mass Spectrometry
m	Multiplet
m/z	Mass-to-charge ratio
min	Minute
MS	Mass spectrometry
N	Normal (unit of concentration)
nd	Not determined
NMP	N-Methyl-2-pyrrolidinone
NMR, ¹ H	Nuclear Magnetic Resonance, proton
q	Quartette (or quartet)
R _f	Retention factor
RT	Room temperature
R _t	Retention time
s	Singlet
sat.	Saturated
t	Triplet
tert	Tertiary
TFA	Trifluoro acetic acid
THF	Tetrahydrofuran
UV	Ultraviolet

The compounds of the present invention can be prepared according to the procedures of the following Schemes and Examples, using appropriate materials and are further exemplified by the following specific examples.

- 5 Moreover, by utilizing the procedures described herein, in conjunction with ordinary skills in the art, additional compounds of the present invention claimed herein can be readily prepared. The compounds illustrated in the examples are not, however, to be construed

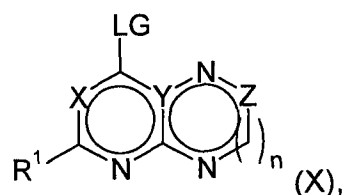
as forming the only genus that is considered as the invention. The examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

The instant compounds are generally isolated in the form of their pharmaceutically acceptable salts, such as those described above. The amine-free bases corresponding to the isolated salts can be generated by neutralization with a suitable base, such as aqueous sodium hydrogencarbonate, sodium carbonate, sodium hydroxide and potassium hydroxide, and extraction of the liberated amine-free base into an organic solvent, followed by evaporation. The amine-free base, isolated in this manner, can be further converted into another pharmaceutically acceptable salt by dissolution in an organic solvent, followed by addition of the appropriate acid and subsequent evaporation, precipitation or crystallization.

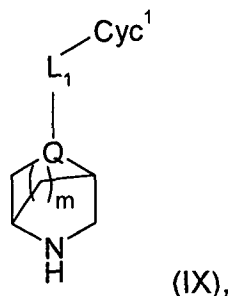
The invention will be illustrated, but not limited, by reference to the specific embodiments described in the following examples. Unless otherwise indicated in the schemes, the variables have the same meaning as described above.

Unless otherwise specified, all starting materials are obtained from commercial suppliers and used without further purifications. Unless otherwise specified, all temperatures are expressed in °C and all reactions are conducted at RT. Compounds were purified by either silica chromatography or preparative HPLC.

The present invention relates also to a process for the manufacture of compounds of Formula (I), wherein a compound of Formula (X)



is reacted with a compound of Formula (IX)



to yield a compound of Formula (I).

LG is a leaving group typically used in nucleophilic aromatic substitutions, preferably Hal,
 5 such as F, Cl or Br.

Examples

10 HPLC method

Solvent A: water + 0.1 % trifluoroacetic acid

Solvent B: acetonitrile + 0.1 % trifluoroacetic acid

Flow: 2 mL/min, wave length: 220nm

15 Gradient: 0.0 min 1 % B
 0.2 min 1 % B
 3.8 min 100 % B
 4.2 min 100% B

Column: Chromolith Speed ROD RP-18e 100-3.0 mm (Merck KGaA)

20

The working examples presented below are intended to illustrate particular embodiments of the invention, and are not intended to limit the scope of the specification or the claims in any way.

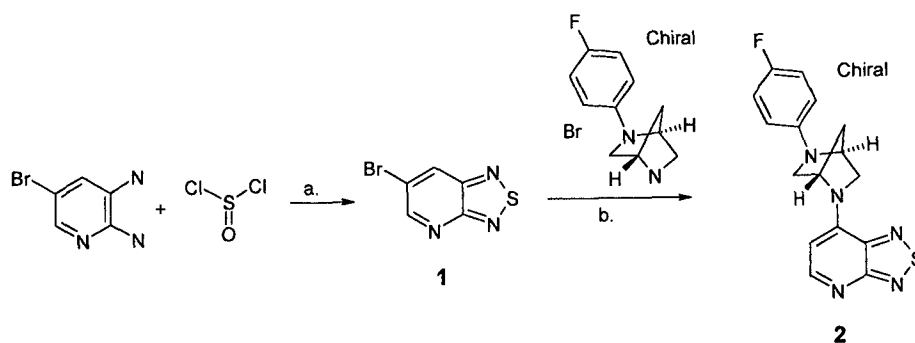
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Chemical Synthesis

In this section experimental details are provided for a number of Example compounds according to Formula (I), and synthetic intermediates thereof.

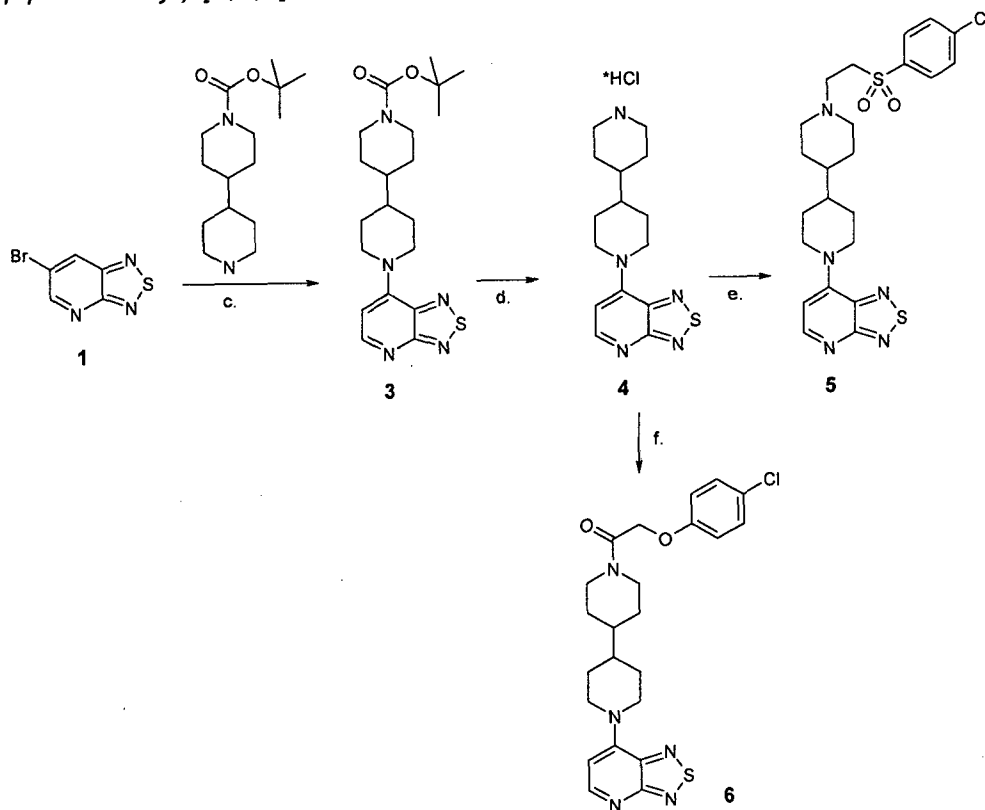
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1. Synthesis of 7-[(1*S*,4*S*)-5-(4-Fluoro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo[3,4-*b*]pyridine **2**



- 5 a. 5-Bromo-pyridine-2,3-diamine (97%, 25.0 g, 129 mmol) was suspended in N,N-dimethyl-formamide (0.94 g, 12.9 mmol) and toluene (150 mL). The suspension was heated to 70°C, thionyl chloride (65.6 g, 550 mmol) was slowly added dropwise (foam formation, color change: brown to orange) and stirring was continued for 18 h at 90°C. The recooled reaction mixture was diluted with tert.-butylmethylether (250 mL),
10 the formed precipitate was filtered off and washed with tert.-butylmethylether and was discarded. The solvent of the filtrate was evaporated under reduced pressure, redissolved in dichloromethane and extracted with saturated NaHCO₃-solution. The organic phase was dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The residue was purified by chromatography
15 (heptane/dichloromethane) to yield in a colorless solid, which was characterized as compound **1** (19.5 g, 90.1 mmol, 70%).
- 20 b. 6-Bromo-[1,2,5]thiadiazolo[3,4-*b*]pyridine **1** (200 mg, 0.93 mmol) and (1*S*,4*S*)-2-(4-fluorophenyl)-2,5-diazabicyclo[2.2.1]heptane hydrobromide (303 mg, 1.11 mmol) were dissolved in water (0.5 mL) and N-ethyl-diisopropyl amine (1.5 mL) and stirred for 2 d at 100°C. Dichloromethane (50 mL) was added to the reaction mixture and extracted with saturated NaHCO₃-solution. The organic phase was dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The residue was purified by chromatography (methanol/dichloromethane) to yield in a colorless solid, which was characterized as compound **2** (77.5 mg, 0.24 mmol, 26%).
- 25 ¹H NMR (500 MHz, DMSO) ppm = 8.45 (s, 1H), 7.06 - 6.87 (m, 2H), 6.71 - 6.54 (m, 2H), 6.39 - 6.06 (m, 1H), 6.58 - 4.89 (m, 1H), 4.73 (s, 1H), 4.45 - 3.32 (m, 3H), 3.10 (s, 1H), 2.24 - 2.08 (m, 2H).

2. Synthesis of 1'-[2-(4-Chloro-benzenesulfonyl)-ethyl]-1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-[4,4']bipiperidiny 5 and 7-(4-{4-[2-(4-Chloro-phenoxy)-ethyl]-piperazin-1-ylmethyl}-piperidin-1-yl)-[1,2,5]thiadiazolo[3,4-b]pyridine 6



- 5 c. 6-Bromo-[1,2,5]thiadiazolo[3,4-b]pyridine 1 (2.90 g, 13.4 mmol) was dissolved in dioxane (50 mL), [4,4']-bipiperidiny-1-carboxylic acid tert-butyl ester (3.60 g, 13.4 mmol), N-ethyldiisopropylamine (8.67 g, 67.1 mmol) and water (30 mmol) were added at room temperature and the reaction mixture was stirred at 100°C for 3 d. To the recooled mixture ethyl acetate was added and washed with water. The organic phase was dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure to result in a red oil. The residue was purified by chromatography (methanol/dichloromethane) to yield in a colorless solid, which was characterized as compound 3 (1.89 g, 4.71 mmol, 35 %).
- 10 d. 1'-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-[4,4']bipiperidiny-1-carboxylic acid tert-butyl ester 3 (1.89 g; 4.71 mmol) was dissolved in dioxane (60 mL) and HCl in dioxane (31.0 ml; ca. 123 mmol) was added at room temperature. The solid formed was redissolved by adding methanol (10 ml) and the reaction mixture was stirred at room temperature for 15 h. The precipitation formed was filtered off and washed with dioxane and diethyl ether. The organic phase was dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure to result in a red oil. The
- 15
- 20

brownish HCl salt of **4** with high purity was used without further purification (1.25 g, 3.67 mmol, 78 %).

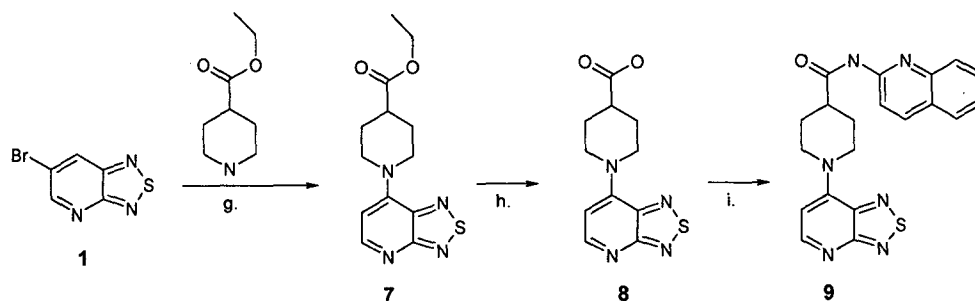
- e. 1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-[4,4']bipiperidinyl hydrochloride **4** (100 mg, 0.29 mmol) was suspended in N,N-dimethylformamide (5 mL), cesium carbonate (479 mg; 1.47 mmol) and 2-chlorethyl-(4-chlorophenyl)-sulphone (70.4 mg; 0.29 mmol) were added and stirred was continued for 15 h at room temperature. Water (10 mL) was added to the mixture, the solid formed was filtered off and washed with water and diethyl ether. The resulting yellow solid was purified by preparative HPLC (acetonitrile/water) to yield in a colorless solid, which was characterized as compound **5** (47.2 mg, 0.09 mmol, 32 %).

¹H NMR (500 MHz, DMSO) ppm = 8.55 (d, J=5.5, 1H), 7.94 - 7.87 (m, 2H), 7.71 (d, J=8.1, 2H), 6.68 (d, J=5.5, 1H), 4.91 - 4.80 (m, 2H), 3.73 - 3.39 (m, 2H), 3.28 - 3.24 (m, 2H), 3.15 - 3.06 (m, 2H), 2.86 - 2.52 (m, 3H), 1.82 - 1.65 (m, 3H), 1.56 - 1.33 (m, 3H), 1.32 - 1.19 (m, 2H), 1.05 - 0.70 (m, 3H).

- f. 1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-[4,4']bipiperidinyl hydrochloride **4** (100 mg, 0.29 mmol) was suspended in dichloromethane (5 mL) and 4-chlorophenoxy acetyl chloride (66.4 mg, 0.32 mmol) was added at RT. To this solution triethyl amine (89.3 mg, 0.88 mmol) was added and stirring was continued for 15 h at room temperature. The mixture was poured onto ice water and extracted with dichloromethane twice. The combined organic layers were washed with saturated NaHCO₃-solution, dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The resulting solid was purified by chromatography (dichloromethane/methanol) to yield in a colorless solid, which was characterized as compound **6** (52.7 mg, 0.11 mmol, 38 %).

¹H NMR (500 MHz, DMSO) ppm = 8.56 (d, J=5.5, 1H), 7.31 (d, J=9.0, 2H), 6.93 (d, J=9.0, 2H), 6.70 (d, J=5.5, 1H), 4.95 - 4.74 (m, 4H), 4.35 (d, J=12.6, 1H), 3.84 (d, J=13.2, 1H), 3.17 - 3.09 (m, 1H), 3.01 - 2.91 (m, 1H), 1.83 (d, J=12.3, 2H), 1.72 (d, J=12.1, 2H), 1.53 - 1.44 (m, 1H), 1.42 - 1.13 (m, 6H), 1.09 - 0.96 (m, 1H).

*Synthesis of 1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid quinolin-2-ylamide **9***



g. 6-Bromo-[1,2,5]thiadiazolo[3,4-b]pyridine **1** (10.0 g, 39.6 mmol) and ethyl 4-piperidinecarboxylate (39.9 g, 218 mmol) were stirred for 18 h at room temperature. Dichloromethane (500 mL) was added to the reaction mixture and washed twice with water followed by saturated NaHCO_3 -solution. The organic phase was dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The residue was purified by chromatography (methanol/dichloromethane) to yield in a colorless solid, which was characterized as compound **7** (10.2 g, 35.0 mmol, 86%).

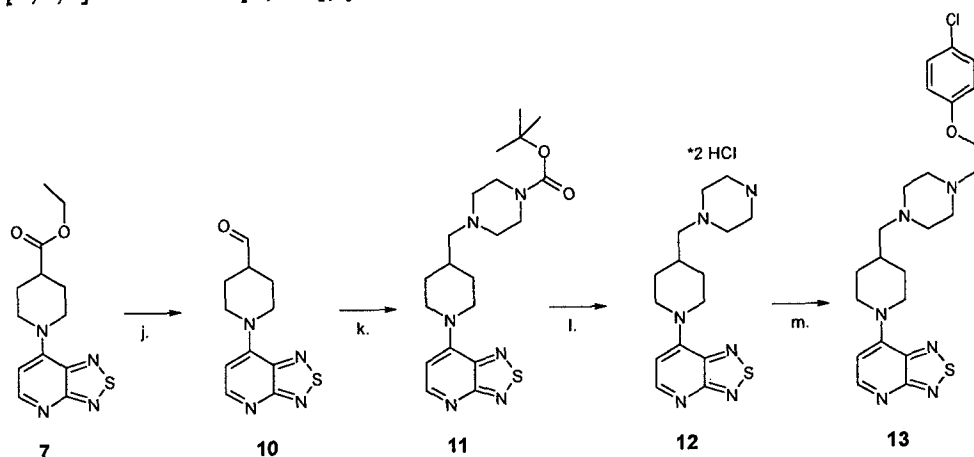
h. 1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid ethyl ester **7** (6.15 g; 21.0 mmol) was dissolved in tetrahydrofurane (50 mL) and lithium hydroxide (98% purity, 1.54 g, 63.1 mmol) and water (10 mL) were added at room temperature. The reaction mixture was stirred at room temperature for 15 h. The solvent was evaporated in vacuo and the remaining aqueous phase titrated to pH2 adding 2N HCl solution. To the mixture slowly added 2 N NaOH solution until neutral pH was reached. The yellow precipitation formed was filtered off and washed with water and diethyl ether and dried. 4.46 g (16.9 mmol, 80%) of a yellowish solid **8** was obtained with high purity was, which was used without further purification.

i. 1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid **8** (50.0 mg; 0.19 mmol) and hydroxybenzotriazole (25.6 mg, 0.19 mmol) were dissolved in N,N-dimethyl-formamide (2 mL). To this solution were added at room temperature 2-aminoquinoline (32.7 mg, 0.23 mmol), 4-methylmorpholine (57.4 mg, 0.57 mmol) and o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluoro-phosphate (108 mg, 0.28 mmol). The reaction mixture was stirred at 50°C for 15 h. To the recooled mixture water was added and the precipitation formed was filtered off and washed with water and diethyl ether and dried in vacuo. 45.1 mg (0.12 mmol, 61%) of a yellowish solid **9** was obtained with high purity.

^1H NMR (500 MHz, DMSO-d_6) ppm = 10.87 (s, 1H), 8.60 (d, $J=5.4$, 1H), 8.36 - 8.27 (m, 2H), 7.93 - 7.89 (m, 1H), 7.83 - 7.80 (m, 1H), 7.73 - 7.69 (m, 1H), 7.51 - 7.46

(m, 1H), 6.77 (d, J=5.5, 1H), 4.91 - 4.84 (m, 2H), 3.38 - 3.30 (m, 2H), 3.04 - 2.96 (m, 1H), 2.06 - 2.00 (m, 2H), 1.88 - 1.78 (m, 2H).

5 *Synthesis of 7-(4-{4-[2-(4-Chloro-phenoxy)-ethyl]-piperazin-1-ylmethyl}-piperidin-1-yl)-[1,2,5]thiadiazolo[3,4-b]pyridine 13*

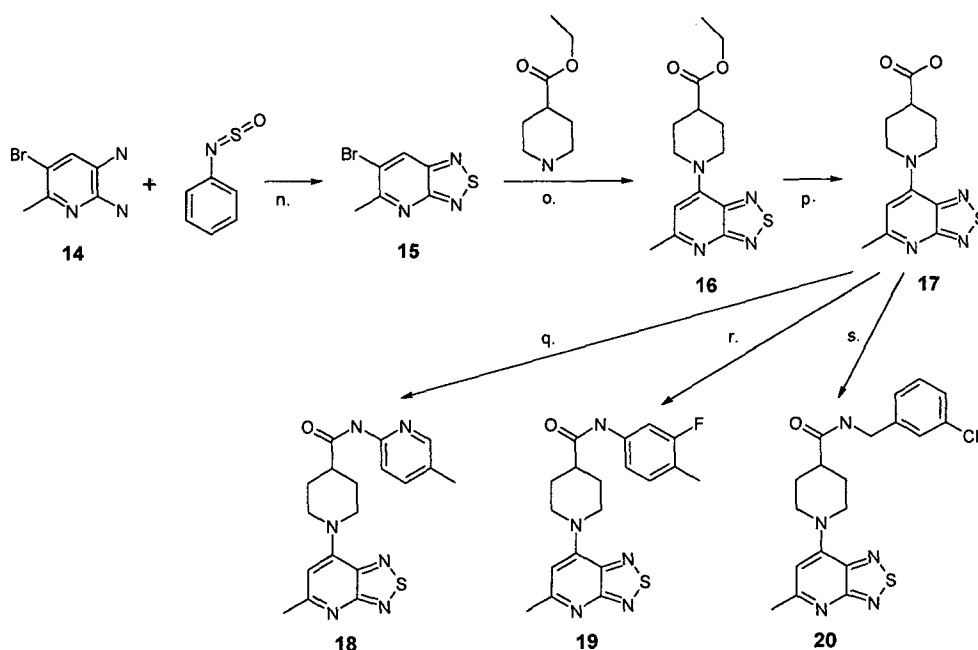


- j. 1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid ethyl ester **7** (3.75 g; 12.8 mmol) was dissolved in dichloromethane (300 mL) and cooled to -78°C. To this mixture diisopropylaluminum hydride (1M in dichloromethane, 36.9 mL, 36.9 mmol) was added dropwise at -78°C. It was stirred for 2 h at -78°C and warmed to room temperature. Methanol (70 mL) and water (70 mL) were added to the mixture and the residue formed filtered off. It was suspended in dichloromethane, filtered off and discarded. The combined filtrate were evaporated to dryness, redissolved in dichloromethane, dried over sodium sulphate, filtered, and the solvent was removed under reduced pressure. 3.02 g (12.1 mmol, 97%) of a yellowish solid **10** was obtained and used without further purification.
- k. 1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carbaldehyde **10** (1.00 g, 4.03 mmol) and tert-Butyl 1-piperazinecarboxylate (0.75 g, 4.03 mmol) were dissolved in N,N-dimethyl-formamide (15 mL) and stirred for 30 min at room temperature. To this solution acetic acid (0.23 mL, 4.04 mmol) and sodium triacetoxyborohydride (95%, 1.71 g, 8.07 mmol) were added and stirring was continued at room temperature for 3 d. 40 mL 1 N NaOH solution was added and stirring continued at room temperature for 4 h. The formed residue was filtered off and washed with water and diethyl ether and dried in vacuo to yield a colorless solid, which was characterized as compound **11** (1.17 g, 2.80 mmol, 69%).

l. 4-(1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidin-4-ylmethyl)-piperazine-1-carboxylic acid tert-butyl ester **11** (1.17 g, 2.80 mmol) was dissolved in dioxane (20 mL), HCl in dioxane (4 N, 20 mL, ca. 80 mmol) was added at room temperature and stirred for 15 h. Diethyl ether (80 mL) was added and the precipitation formed was filtered off and washed with diethyl ether. The colorless Di-HCl salt **12** with high purity was used without further purification (1.385 g, 3.50 mmol, 90 %).

m. 7-(4-Piperazin-1-ylmethyl-piperidin-1-yl)-[1,2,5]thiadiazolo[3,4-b]pyridine dihydrochloride **12** (50 mg, 0.13 mmol), 4-chlorophenyl-2-bromomethylether (36.1 mg, 0.15 mmol) and cesium carbonate (208 mg, 0.64 mmol) were suspended in N,N-dimethyl-formamide (2 mL) at room temperature and stirring was continued for 15 h. Water (18 mL) was added to the mixture and extracted with dichloromethane twice. The combined organic layers were dried over sodium sulphate, filtered and the mixture was evaporated to dryness under reduced pressure. The resulting yellow solid was purified by preparative HPLC (acetonitrile/water/TFA) to yield in a colorless solid, which was characterized as the TFA salt of **13** (19.2 mg, 0.03 mmol, 25 %).
¹H NMR (400 MHz, DMSO) ppm = 8.55 (d, J=7.0, 1H), 7.36 (d, J=8.9, 2H), 7.05 - 6.95 (m, 3H), 5.27 - 4.94 (m, 2H), 4.34 - 4.14 (m, 2H), 3.66 - 2.68 (m, 14H), 2.20 (s, 1H), 2.04 - 1.95 (m, 2H), 1.45 - 1.31 (m, 2H).

20 Synthesis of 1-(5-Methyl-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidine-4-carboxylic acid (5-methyl-pyridin-2-yl)-amide **18**, 1-(5-Methyl-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidine-4-carboxylic acid (3-fluoro-4-methyl-phenyl)-amide **19** and 1-(5-Methyl-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidine-4-carboxylic acid 3-chloro-benzylamide **20**



- n. 5-Bromo-6-methyl-pyridine-2,3-diamine **14** (98%, 1.00 g, 4.85 mmol) was suspended in pyridine (15 mL), N-Thionylaniline (98%, 1.38 g, 9.70 mmol) was added at room temperature and the mixture was stirred for 30 min at 120°C under microwave irradiation. To the recooled mixture water (50 mL) was added and extracted twice with dichloromethane. The combined organic layers were washed with saturated NaHCO₃-solution, dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The residue was purified by chromatography (petrol ether/dichloromethane) to yield in a colorless solid, which was characterized as compound **15** (1.08 g, 4.69 mmol, 97%).
- o. 6-Bromo-5-methyl-[1,2,5]thiadiazolo[3,4-b]pyridine **15** (1.08 g, 4.69 mmol) and ethyl 4-piperidinecarboxylate (98%, 4.08 g, 25.4 mmol) were stirred for 18 h at room temperature. The solvent was removed under reduced pressure and the residue was purified directly by chromatography (methanol/dichloromethane) to yield in a colorless solid, which was characterized as compound **16** (0.81 g, 2.65 mmol, 57%).
- p. 1-(5-Methyl-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidine-4-carboxylic acid ethyl ester **16** (0.81 g; 2.65 mmol) was dissolved in tetrahydrofuran (45 mL) and lithium hydroxide (98% purity, 194 mg, 7.95 mmol) and water (5 mL) were added at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was evaporated in vacuo and the residue was dried in vacuo. The lithium salts containing crude material was used without further purification. 0.92 g (ca. 80% purity, 2.65 mmol, 100%) of a yellowish solid **17** was obtained.
- q. 1-(5-Methyl-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidine-4-carboxylic acid **17** (80%, 156 mg; 0.45 mmol), 2-amino-5-methylpyridine (100 mg, 0.93 mmol) and 4-methylmorpholine (0.15 mL, 1.39 mmol) were dissolved in N,N-dimethyl-formamide (2 mL). To this solution were added at room temperature o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluoro-phosphate (200 mg, 0.61 mmol) and hydroxybenzotriazole (22.0 mg, 0.16 mmol) and the reaction mixture was stirred at room temperature for 15 h. Water and ethyl acetate were added to the mixture. The organic layer was separated, washed with water, saturated NaHCO₃-solution, dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The residue was crystallized from methanol/water to yield in 75.2 mg (0.20 mmol, 45%) of an off-white solid **18** with high purity.
- ¹H NMR (400 MHz, DMSO) ppm = 10.39 (s, 1H), 8.14 (d, J=2.3, 1H), 7.97 (d, J=8.4, 1H), 7.57 (dd, J=8.5, 2.3, 1H), 6.70 (s, 1H), 4.85 - 4.75 (m, 2H), 3.29 - 3.15

(m, 2H), 2.94 - 2.82 (m, 1H), 2.54 (s, 3H), 2.24 (s, 3H), 2.00 - 1.91 (m, 2H), 1.85 - 1.70 (m, 2H).

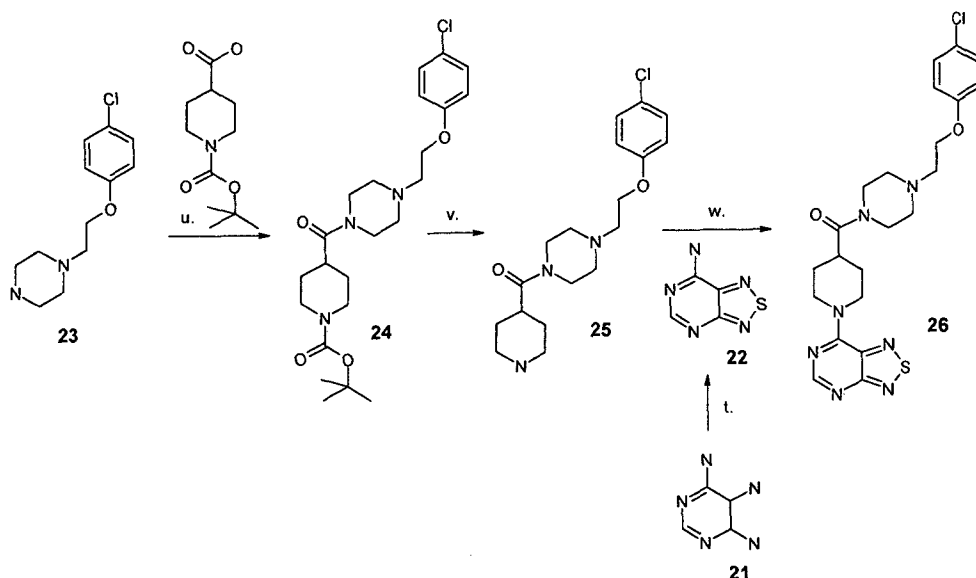
- r. 1-(5-Methyl-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidine-4-carboxylic acid **17** (80%, 62.6 mg; 0.18 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimidhydrochloride (34.4 mg, 0.18 mmol) and hydroxybenzotriazole (24.3 mg, 0.18 mmol) were suspended in N,N-dimethyl-formamide (2 mL). To this solution were added at room temperature 3-fluoro-4-methylaniline (98%, 27.6 mg, 0.22 mmol) and 4-methylmorpholine (72.7 mg, 0.72 mmol) and stirring at room temperature was continued for 3 h. Water (20 ml) was added and the precipitation filtered off and washed with water and diethyl ether. The filter residue was resuspended in diethyl ether, filtered off and dried in vacuo to yield in 30.9 mg (0.08 mmol, 45%) of an off-white solid **19** with high purity.

¹H NMR (500 MHz, DMSO) ppm = 10.04 (s, 1H), 7.58 - 7.50 (m, 1H), 7.25 - 7.14 (m, 2H), 6.71 (s, 1H), 4.81 (d, J=13.1, 2H), 3.28 - 3.22 (m, 2H), 2.76 - 2.65 (m, 1H), 2.54 (s, 3H), 2.16 (s, 3H), 1.96 (d, J=11.0, 2H), 1.85 - 1.73 (m, 2H).

- s. To a solution of 1-(5-Methyl-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidine-4-carboxylic acid (100%, 100 mg, 0.36 mmol), 3-Chloro-benzylamine (105 mg, 0.72 mmol) and 4-Methylmorpholin (0.064 mL, 0.58 mmol) in N,N-Dimethyl-formamide (2 mL), O-(1H-Benzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumtetra fluorborat (83.0 mg, 0.26 mmol) and 1-Hydroxybenzotriazolhydrat (9.00 mg; 0.068 mmol) were added and stirred at room temperature for 18 h. Water was added to the mixture and the resulting precipitate was filtered-off and dried in vacuo. The solid was purified by chromatography (cyclohexane/ethyl acetate) to yield in 48.3 mg (0.12 mmol, 33%) of a colorless solid **20**.

¹H NMR (500 MHz, DMSO) ppm = 8.42 (t, J = 6.0 Hz, 1H), 7.35 (td, J = 7.5, 1.1 Hz, 1H), 7.31 - 7.27 (m, 2H), 7.20 (d, J = 7.6 Hz, 1H), 6.69 (s, 1H), 4.77 (d, J = 13.2 Hz, 2H), 4.27 (d, J = 6.0 Hz, 2H), 3.24 (td, J = 13.2, 2.5 Hz, 2H), 2.65-2.55 (m, 1H), 2.53 (s, 3H), 1.89 (dd, J = 13.2, 2.9 Hz, 2H), 1.78 - 1.68 (m, 2H).

Synthesis of {4-[2-(4-Chloro-phenoxy)-ethyl]-piperazin-1-yl}-(1-[1,2,5]thiadiazolo[3,4-d]pyrimidin-7-yl)-piperidin-4-yl)-methanone **26**



t. Pyrimidine-4,5,6-triamine **21** (4.00 g, 32.0 mmol) was suspended in thionyl chloride (50 mL) and N,N-dimethyl-formamide (0.23 mL, 3.20 mmol) were added at room temperature. The mixture was stirred min at 80°C for 40 h. The solvent and reagents
 5 were removed under reduced pressure, the residue was resuspended in water/methanol (45 ml, 8:1), brought to pH 8 by adding 1 N NaOH solution and stirring was continued at 60°C for 30 min. The mixture was cooled to 0°C, the precipitation formed filtered off, washed with ice-cold water and dried in vacuo to yield in an orange solid, which was characterized as compound **22** (4.80 g, 31.3 mmol,
 10 98%).

u. 1-Boc-piperazine-4-carboxylic acid (1.20 g, 5.23 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimidhydrochloride (1.00 g, 5.23 mmol) and hydroxybenzotriazole (0.80 mg, 5.23 mmol) were dissolved in N,N-dimethyl-formamide (50 mL). To this solution were added at room temperature 1-[2-(4-chloro-phenoxy)-ethyl]-piperazine
 15 hydrochloride **23** (1.45 g, 5.23 mmol) and 4-methylmorpholine (2.90 mL, 26.1 mmol) and stirring at room temperature was continued for 18 h. Water was added to the mixture and extracted with ethyl acetate twice. The combined layer was washed with saturated NaHCO₃-solution, dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The residue was used without further purification to yield in 2.10 g (94% purity, 4.34 mmol, 83%) of a brownish oil **24**.
 20

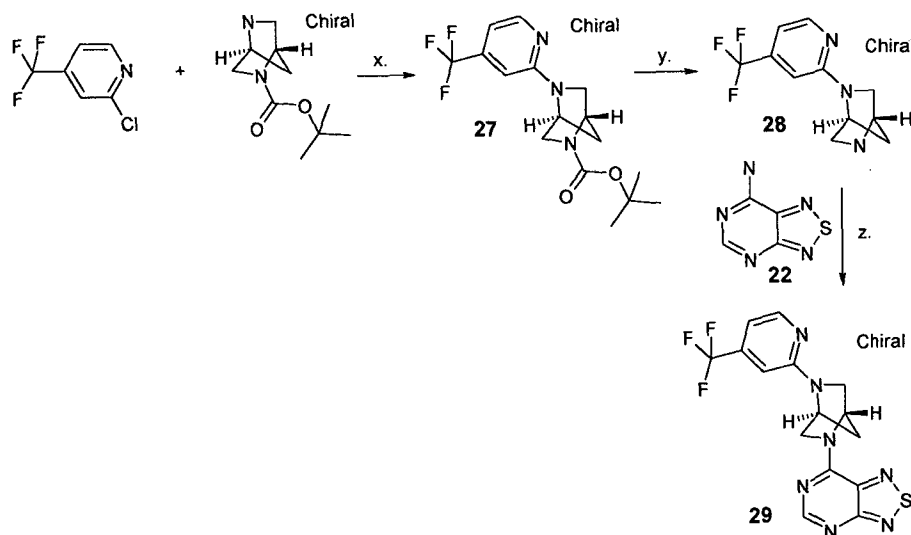
v. 4-[4-[2-(4-Chloro-phenoxy)-ethyl]-piperazine-1-carbonyl]-piperidine-1-carboxylic acid tert-butyl ester **24** (94%, 2.10 g; 4,34 mmol) was dissolved in 2-propanol (25 mL), HCl in 2-propanol (5-6 N, 25 mL, ca. 125-150 mmol) was added at room temperature and stirred for 15 h. Diethyl ether (100 mL) was added and the precipitation formed was

filtered off and washed with diethyl ether. The colorless HCl salt **25** with high purity was used without further purification (1.60 g, 3.75 mmol, 86 %).

w. [1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-ylamine **22** (250 mg, 1.63 mmol) was suspended in methanol (3 mL), {4-[2-(4-Chloro-phenoxy)-ethyl]-piperazin-1-yl}-piperidin-4-yl-methanone hydrochloride **25** (634 mg; 1,63 mmol) was added and the mixture was stirred at 120°C for 72 h. The mixture was evaporated to dryness and the residue was taken up in methanol and diethyl ether. The resulting precipitate was filtered off and discarded. The filtrate was evaporated and the residue was purified preparative HPLC to yield in 104 mg (0.21 mmol, 13%) of a colorless solid **26**.

¹H NMR (500 MHz, DMSO-d₆) ppm = 8.51 (s, 1H), 7.36 - 7.26 (m, 2H), 7.02 - 6.92 (m, 2H), 5.80 - 5.72 (m, 1H), 5.07 (s, 1H), 4.10 (t, J=5.7, 2H), 3.65 (d, J=20.7, 1H), 3.61 - 3.55 (m, 2H), 3.49 - 3.43 (m, 2H), 3.34 - 3.21 (m, 1H), 3.21 - 3.09 (m, 1H), 2.73 (t, J=5.7, 2H), 2.56 - 2.50 (m, 2H), 2.47 - 2.41 (m, 2H), 1.89 - 1.82 (m, 2H), 1.78 - 1.53 (m, 2H).

*Synthesis of 7-[(1S,4S)-5-(4-Trifluoromethyl-pyridin-2-yl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo[3,4-d]pyrimidine **29***



x. Under inert atmosphere (1S,4S)-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester (100 mg, 0.50 mmol), 2-chloro-4-trifluoromethyl-pyridine (0.24 mL, 1.51 mmol), (S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (S)-BINAP (32.0 mg; 0.05 mmol) and sodium tert-butoxide (145 mg, 1.51 mmol) was dissolved in toluene. To this mixture Tris-(dibenzylideneacetone)dipalladium(0) (46.0 mg, 0.05 mmol) was

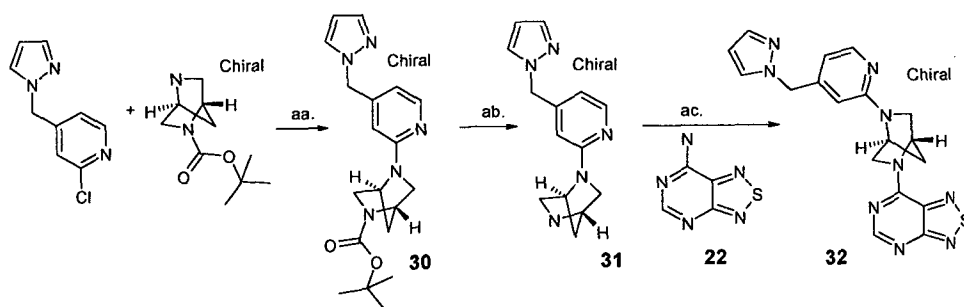
added and stirring was continued at 95 °C for 15 h. To the recooled mixture water and ethyl acetate were added and the organic layer separated. It was washed with water, saturated NaHCO₃-solution, dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure to dryness. The residue was purified by chromatography (n-heptane/ethyl acetate) to yield in a colorless solid, which was characterized as compound **27** (160 mg, 0.47 mmol, 92%).

y. (1S,4S)-5-(4-Trifluoromethyl-pyridin-2-yl)-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester **27** (160 mg; 0,47 mmol) was dissolved in 2-propanol (2 mL), HCl in 2-propanol (5-6 N, 2 mL, ca. 10-12 mmol) was added at room temperature and stirring was continued for 15 h. Additional 2 mL HCl in 2-propanol (5-6 N, ca. 10-12 mmol) was added at room temperature and stirring was continued for 15 h again. Diethyl ether (100 mL) was added and since the precipitation formed could not be filtered off the mixture was completely evaporated to dryness and the crude HCl salt of **28** was used without further purification (88% purity, 148 mg, 0.47 mmol, 100%).

z. [1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-ylamine **22** (72 mg, 0.47 mmol) and (1S,4S)-2-(4-trifluoromethyl-pyridin-2-yl)-2,5-diaza-bicyclo[2.2.1]heptane hydrochloride (88%, 148 mg; 0,47 mmol) were dissolved in methanol and stirred for 2 h at 120°C under microwave irradiation. The solvent was evaporated to dryness under reduced pressure and the residue was purified by preparative HPLC (acetonitrile/water/formic acid) to yield in a colorless solid, which was characterized as compound **29** (18.2 mg, 0.05 mmol, 10%).

¹H NMR (500 MHz, DMSO-d₆) ppm = 8.51 - 8.44 (m, 1H), 8.28 (t, J=5.6, 1H), 6.86 - 6.75 (m, 2H), 6.17 - 5.40 (m, 1H), 5.16 (d, J=12.9, 1H), 4.35 - 4.13 (m, 1H), 3.92 - 3.80 (m, 1H), 3.78 - 3.69 (m, 1H), 3.56 (dd, J=27.3, 9.9, 1H), 2.28 - 2.10 (m, 2H).

*Synthesis of 7-[(1S,4S)-5-(4-Pyrazol-1-ylmethyl-pyridin-2-yl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo[3,4-d]pyrimidine **32***



aa. Under inert atmosphere a mixture of (1S,4S)-2-boc-2,5-diazabicyclo[2.2.1]heptane (97%, 83.7 mg, 0.42 mmol), 1-(3-iodobenzyl)-1H-pyrazole (97%, 100 mg, 0.35 mmol), rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) (97%, 19.7 mg, 0.03 mmol), tris(dibenzylideneacetone)dipalladium(0) (99%, 9.67 mg, 0.01 mmol) and sodium tert-butylat (47.4 mg; 0.49 mmol) in toluene (5 ml) was heated to 110°C for 18 h. After cooling to room temperature, the mixture was filtered through Celite, and the filter cake was rinsed with ethyl acetate. The solvent of the filtrate was removed in vacuo. The residue was purified by preparative HPLC (acetonitrile/water/formic acid) to yield in a colorless solid, which was characterized as compound **30** (26.4 mg, 0.07 mmol, 21%).

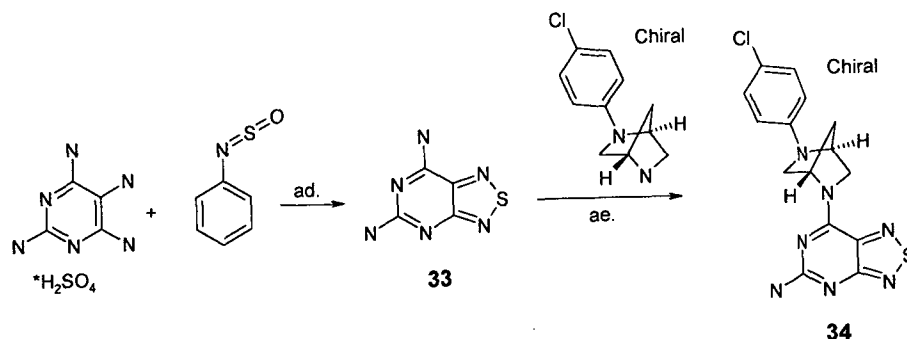
ab. (1S,4S)-5-(3-Pyrazol-1-ylmethyl-phenyl)-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester (13.2 mg, 0.04 mmol) was dissolved in 2-propanole (3 ml), HCl in 2-propanole (5-6 N, 2.00 mL, 10-12 mmol) was added and the mixture was stirred for 18 h at room temperature. The mixture was evaporated to dryness and the crude HCl salt of **31** was used without further purification (92% purity, 11.6 mg, 0.04 mmol, 100%).

ac. [1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-ylamine (5.60 mg, 0.04 mmol) was suspended in methanol (2 ml) and (1S,4S)-2-(3-pyrazol-1-ylmethyl-phenyl)-2,5-diaza-bicyclo[2.2.1]heptane hydrochloride (92%, 11.6 mg; 0.04 mmol) was added. The mixture was heated 4 hours at 120°C under microwave irradiation. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (acetonitrile/water/formic acid) to yield in a colorless solid, which was characterized as compound **32** (4.20 mg, 0.01 mmol, 29%).

¹H NMR (500 MHz, DMSO) ppm = 8.46 (d, J=23.7, 1H), 7.75 (d, J=2.2, 1H), 7.42 (t, J=1.6, 1H), 7.08 (td, J=7.9, 2.5, 1H), 6.67 - 6.50 (m, 2H), 6.46 - 6.37 (m, 1H), 6.30 - 6.19 (m, 1H), 6.14 - 5.44 (m, 1H), 5.28 - 5.11 (m, 2H), 4.73 (d, J=33.5, 1H), 4.29 - 4.09 (m, 1H), 3.94 - 3.67 (m, 2H), 3.16 (dd, J=19.5, 9.2, 1H), 2.27 - 2.03 (m, 2H).

Synthesis of 7-[(1S,4S)-5-(4-Chloro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-

*[1,2,5]thiadiazolo[3,4-d]pyrimidin-5-ylamine **34***

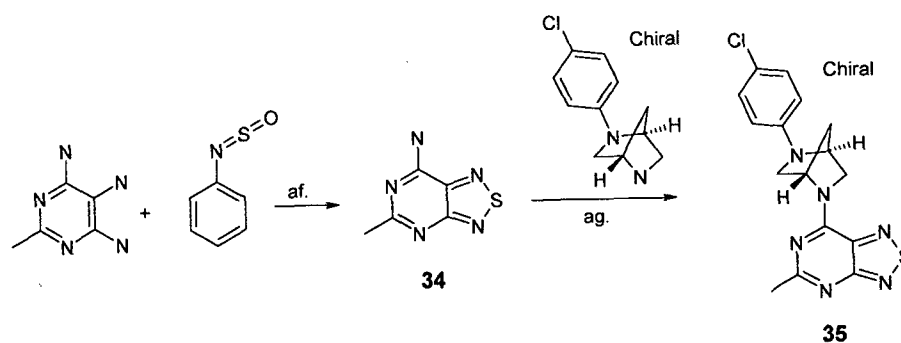


ad. 2,4,5,6-Tetraaminopyrimidine sulfate (98%, 1.00 g, 4.11 mmol) and N-thionylaniline (98%, 1.20 g, 8.23 mmol) were dissolved in dry pyridine (20 mL). The mixture was heated to 100°C for 72 h. To the recooled reaction mixture water was added, the precipitation formed filtered off, washed with water and dried in vacuo. The residue was used without further purification to yield in a light brownish solid, which was characterized as compound **33** (654 mg, 3.89 mmol, 94%) with high purity.

ae. [1,2,5]Thiadiazolo[3,4-d]pyrimidine-5,7-diamine **33** (211 mg, 1.26 mmol) and (1S,4S)-2-(4-chlorophenyl)-2,5-diazabicyclo[2.2.1]heptane hydrobromide (727 mg, 2.51 mmol) were dissolved in methanol (7 mL) and stirred for 16 h at 80°C. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (acetonitrile/water/trifluoroacetic acid) to yield in a colorless solid, which was characterized as the TFA salt of compound **34** (12.8 mg, 0.26 mmol, 21%).

¹H NMR (500 MHz, DMSO) ppm = 8.49 - 7.98 (m, 1H), 7.88 - 7.38 (m, 1H), 7.21 - 7.15 (m, 2H), 6.72 - 6.64 (m, 2H), 6.13 - 5.33 (m, 1H), 4.77 (d, J=35.3, 1H), 4.27 - 4.09 (m, 1H), 3.84 - 3.78 (m, 1H), 3.78 - 3.69 (m, 1H), 3.25 - 3.15 (m, 1H), 2.29 - 2.10 (m, 2H).

Synthesis of 7-[(1S,4S)-5-(4-Chloro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-5-methyl-[1,2,5]thiadiazolo[3,4-d]pyrimidine **35**



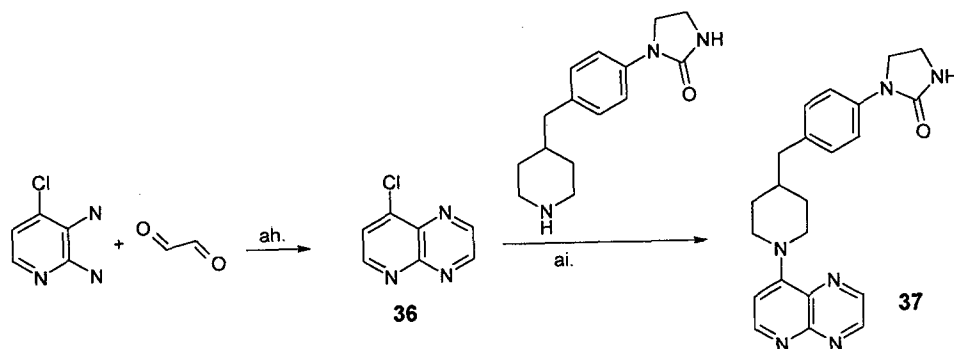
af. 2-Methyl-pyrimidine-4,5,6-triamine (98%, 2.00 g, 14.1 mmol) and N-thionylaniline (98%, 4.00 g, 28.2 mmol) were dissolved in dry pyridine (15 mL). The mixture was heated to 120°C for 20 min under microwave irradiation. To the recooled reaction mixture water was added, the precipitation formed filtered off and washed with water.

5 The residue was resuspended in dichloromethane/methanol (50 mL, 1:1), the precipitation filtered off and discarded. The mixture was evaporated to dryness. The residue was used without further purification to yield in an off-white solid, which was characterized as compound **34** (900 mg, 5.38 mmol, 38%) with high purity.

ag. 5-Methyl-[1,2,5]thiadiazolo[3,4-d]pyrimidin-7-ylamine **34** (225 mg, 1.25 mmol) and (1S,4S)-2-(4-chlorophenyl)-2,5-diazabicyclo[2.2.1]heptane hydrobromide (779 mg, 2.69 mmol) were dissolved in methanol (7 mL) and stirred for 16 h at 80°C. The solvent was removed under reduced pressure and the residue was purified by chromatography (methanol/dichloro methane) to yield in a colorless solid, which was characterized as compound **35** (152 mg, 0.42 mmol, 32%).

15 ¹H NMR (500 MHz, DMSO) ppm = 7.15 (dd, J=9.0, 2.6, 2H), 6.70 - 6.63 (m, 2H), 6.10 - 5.41 (m, 1H), 4.75 (d, J=37.4, 1H), 4.24 - 4.09 (m, 1H), 3.82 - 3.76 (m, 1H), 3.75 - 3.68 (m, 1H), 3.20 - 3.13 (m, 1H), 2.46 (d, J=34.9, 3H), 2.26 - 2.18 (m, 1H), 2.12 (s, 1H).

20 *Synthesis of 1-[4-(1-Pyrido[2,3-b]pyrazin-8-yl-piperidin-4-ylmethyl)-phenyl]-imidazolidin-2-one **37***

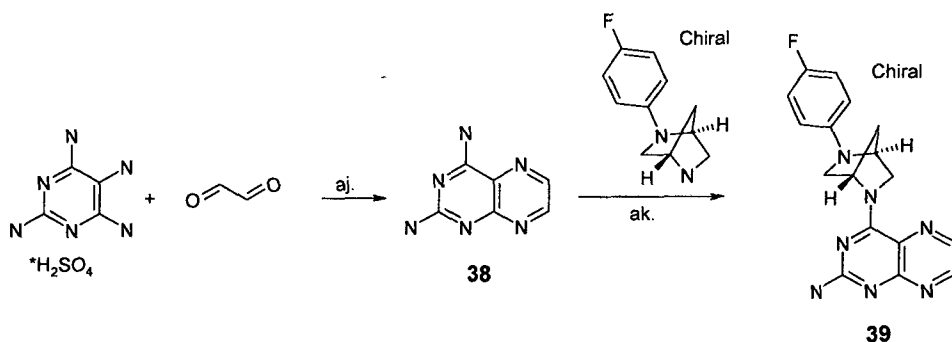


ah. 4-Chloropyridine-2,3-diamine (1.50 g, 10.4 mmol) was dissolved in tetrahydrofuran (70 mL), gluoxale (30% in water, 2.01 g, 10.4 mmol) was added at room temperature and stirring was continued for 18 h at the same temperature. The mixture was evaporated to dryness and the yellowish residue used without further purification. It was characterized as compound **36** with 94% purity (1.50 mg, 8.51 mmol, 82%).

ai. 8-Chloro-pyrido[2,3-b]pyrazine **36** (94%, 53.2 mg, 0.30 mmol), 1-(4-piperidin-4-ylmethyl-phenyl)-imidazolidin-2-one trifluoroacetic acid (113 mg, 0.30 mmol) and N-ethyldiisopropylamin (195 mg, 1.51 mmol) were suspended in water (0.5 mL) and stirred for 16 h at 100°C. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC chromatography (acetonitrile/water/trifluoroacetic acid) to yield in a colorless solid, which was characterized as compound **37** (30.1 mg, 0.07 mmol, 24%).

¹H NMR (500 MHz, DMSO-d₆) ppm = 8.98 (d, J=1.7, 1H), 8.83 (d, J=1.8, 1H), 8.67 (d, J=5.5, 1H), 7.51 - 7.42 (m, 2H), 7.17 - 7.10 (m, 2H), 7.03 (d, J=5.6, 1H), 6.83 (s, 1H), 4.49 - 4.41 (m, 2H), 3.86 - 3.77 (m, 2H), 3.42 - 3.35 (m, 2H), 3.09 - 3.00 (m, 2H), 2.56 - 2.50 (m, 2H), 1.88 - 1.76 (m, 1H), 1.75 - 1.68 (m, 2H), 1.47 - 1.35 (m, 2H).

Synthesis of 4-[(1S,4S)-5-(4-Fluoro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-pteridin-2-ylamine **39**

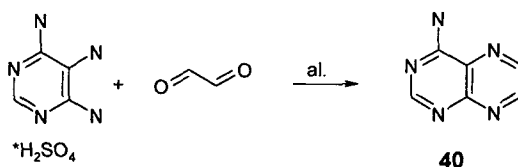


aj. 2,4,5,6-Tetraaminopyrimidine sulfate (97%, 500 mg, 2.10 mmol) was dissolved in tetrahydrofuran (15 mL), gluoxale (30% in water, 406 mg, 2.1 mmol) was added at room temperature and stirring was continued for 18 h at the same temperature. The mixture was evaporated to dryness and the brownish residue was used without further purification. It was characterized as compound **38** with high purity (340 mg, 2.10 mmol, 100%).

ak. Pteridine-2,4-diamine **38** (16.5 mg, 0.10 mmol) and (1S,4S)-2-(4-fluorophenyl)-2,5-diazabicyclo[2.2.1]heptane hydrobromide (27.8 mg, 0.10 mmol) were dissolved in methanol (2 mL) and stirred for 4 d at 100°C. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (acetonitrile/water/trifluoroacetic acid) to yield in a colorless solid, which was characterized as **39** (5.2 mg, 0.015 mmol, 15%).

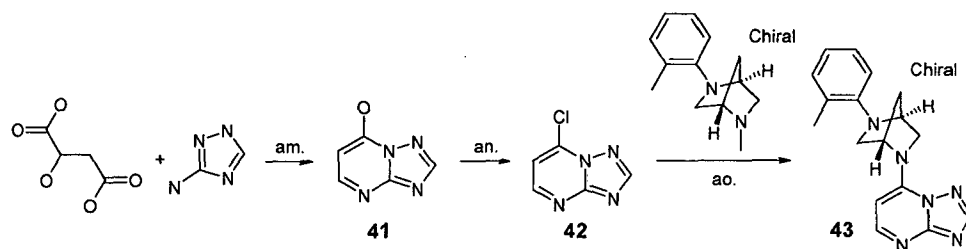
¹H NMR (500 MHz, DMSO, rotamers, d-TFA exchanged) ppm = 8.83 (d, *J* = 2.3 Hz, 0.5H), 8.76 (t, *J* = 2.0 Hz, 1H), 8.67 (d, *J* = 2.3 Hz, 0.5H), 7.00 (q, *J* = 8.5 Hz, 2H), 6.72 – 6.62 (m, 2H), 6.48 (s, 0.5H), 5.54 – 5.48 (m, 0.5H), 4.80 – 4.67 (m, 1H), 4.42 – 4.31 (m, 0.5H), 4.29 – 4.21 (m, 0.5H), 3.94 – 3.73 (m, 2H), 3.28 – 3.18 (m, 1H), 2.30 – 2.06 (m, 2H).

Synthesis of starting material Pteridin-4-ylamine **40**



- 10 **al.** 4,5,6-Tetraaminopyrimidine sulfate (98%, 500 mg, 2.24 mmol) was dissolved in tetrahydrofuran (15 mL), gluoxale (30% in water, 433 mg, 2.24 mmol) was added at room temperature and stirring was continued for 18 h at the same temperature. The mixture was evaporated to dryness and the brownish residue was used without further purification. It was characterized as compound **40** with high purity (329 mg, 15 2.24 mmol, 100%).

Synthesis of 7-((1*S*,4*S*)-5-*o*-Tolyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidine **43**



- 20 **am.** Sulfuric acid (95-98%, 20 mL) was cooled to 2°C and racemic malic acid (5.00 g, 27.3 mmol) was added in small portions keeping the temperature below 10°C. In the same manner 3-amino-1H-1,2,4-triazol (3.14 g, 37.3 mmol) were added. The mixture was warmed to room temperature, stirred for 15 h at the same temperature and then heated to 100°C for 1 h. The recooled reaction mixture was poured onto ice-water and the pH was adjusted to 4 by adding 1 N NaOH solution. The precipitation formed was filtered off, washed with water and dried in vacuo. The colorless residue was
- 25

used without further purification and was characterized as compound **41** (4.00 g, 29.4 mmol, 79%) with high purity.

an. To phosphoryl chloride (36.7 mL, 240 mmol) was added at room temperature in small portions [1,2,4]triazolo[1,5-a]pyrimidin-7-ol **41** and heated to 105°C for 18 h. The precipitation formed after cooling was filtered off and washed with diethyl ether. To the filtrate toluene was added and the solvent and reagents were removed by distillation under reduced pressure. The residue was treated with diethyl ether and the precipitation formed was filtered off again and washed with diethyl ether. The combined solids were dried in vacuo to result in a colorless powder, which was characterized as compound **42** (3.50 g, 21.5 mmol, 73%) with high purity.

ao. 7-Chloro-[1,2,4]triazolo[1,5-a]pyrimidine **42** (50.0 mg, 0.32 mmol) and (1S,4S)-2-(2-methylphenyl)-2,5-diazabicyclo[2.2.1]heptane maleic acid (109 mg, 0.36 mmol) were dissolved in 1-butanol (2 mL), ethyldiisopropyl (0.16 mL, 0.94 mmol) was added and stirred for 30 min at 120°C under microwave irradiation. Ethyl acetate and water were added, the organic layer separated, washed with brine, dried over sodium sulphate, filtered and evaporated to dryness. The residue was purified by chromatography (dichloromethane/methanol) to yield in a colorless solid, which was characterized as **43** (20.8 mg, 0.07 mmol, 21%).

¹H NMR (500 MHz, DMSO) ppm = 8.38 (s, 1H), 8.25 (d, *J* = 5.7 Hz, 1H), 7.05 (t, *J* = 7.4 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.75 (t, *J* = 7.3 Hz, 1H), 6.30 (s, 1H), 4.44 (s, 1H), 4.06 (dd, *J* = 10.5, 5.3 Hz, 1H), 3.64 (dd, *J* = 9.4, 2.3 Hz, 1H), 3.36 (d, *J* = 9.4 Hz, 1H), 3.17 (d, *J* = 5.2 Hz, 1H), 2.20 (s, 4H), 2.11 (s, 2H).

25 Biological Activity

To assess the inhibitory potential of the compounds on the Wnt pathway, IC₅₀-values were determined, as shown in Table 1 below, whereby the following classification is used:

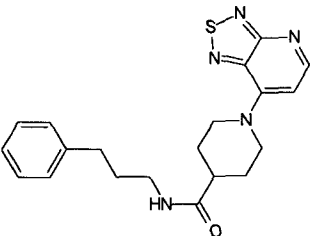
30	IC ₅₀ < 0.05 μM	"A"
	0.05 μM ≤ IC ₅₀ < 0.10 μM	"B"
	0.10 μM ≤ IC ₅₀ < 0.50 μM	"C"
	0.50 μM ≤ IC ₅₀ < 1.00 μM	"D"
35	1.00 μM ≤ IC ₅₀ < 5.00 μM	"E"

1. Cellular Assay for Wnt Pathway Activity

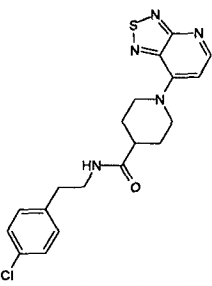
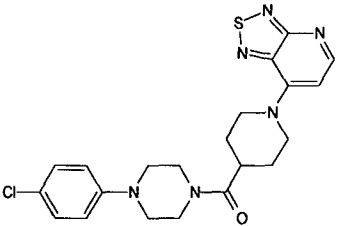
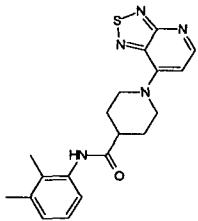
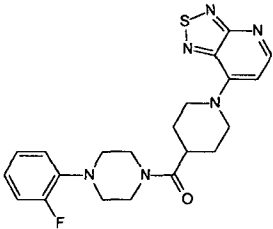
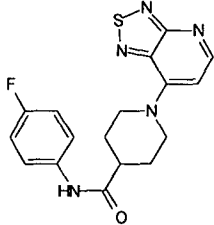
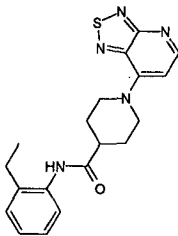
5 Inhibitory activity of the Wnt pathway was assessed using a luciferase reporter cell based assay. A luciferase reporter cell line was developed in the colorectal adenocarcinoma HT29 cells which were stably transfected with the TOPflash plasmid (Merck Millipore, #21-170). This TCF driven reporter construct contains the Firefly luciferase reporter gene which is transcribed upon binding of nuclear β -Catenin to specific TCF binding sites. Due to their APC mutation, HT29 cells have a high constitutive Wnt pathway activation and thus a constitutive luciferase reporter expression which is blocked by treatment with Wnt pathway inhibitors:

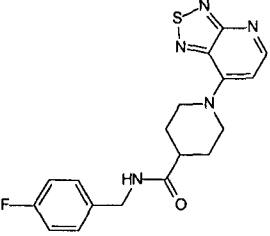
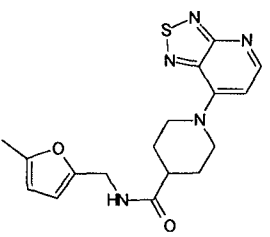
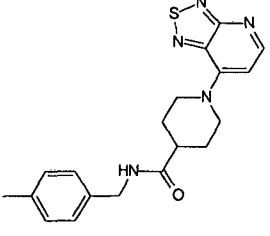
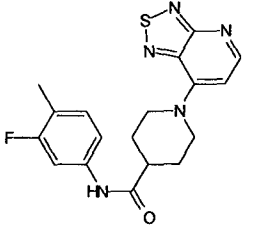
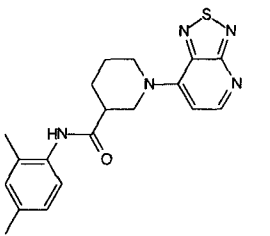
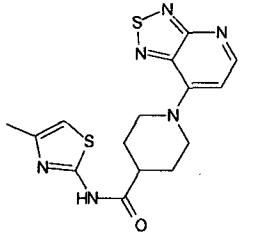
HT29_TOPflash cells are plated in 96 well plates with 2×10^4 cells per well. Next day, cells are treated with a serial-dilution of test compound in seven steps as triplicates with a final DMSO concentration of 0.3%. After 24 hours, cells are lysed with Steady-Glo-Luciferase reagent (Promega, #E2520) for 10 min in the dark. Luciferase activity is detected with the EnVision Microplate Reader according to the manufacturer's instructions. As controls, cells are treated with solvent alone (neutral control) and with the Wnt pathway reference inhibitor ICG-001 (3×10^{-5} M) which serves as pharmacological blank. For analysis, the luciferase activity data of test compound treated samples were normalized against the untreated solvent control and fitted for determination of the IC_{50} values using the Assay Explorer software (Accelrys).

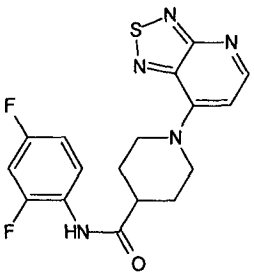
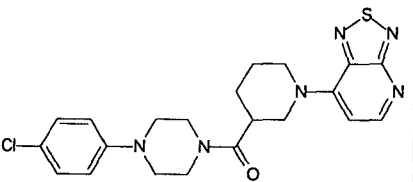
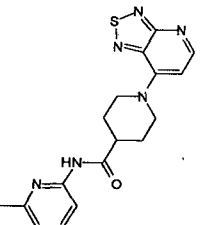
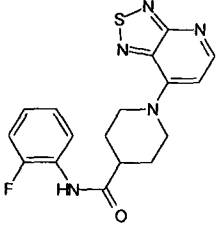
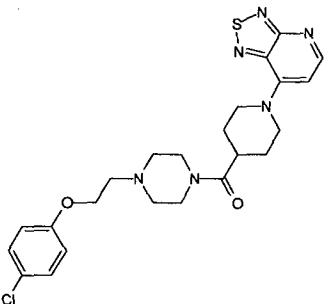
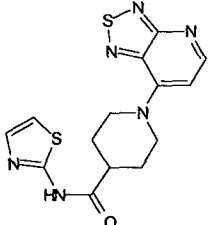
Table 1

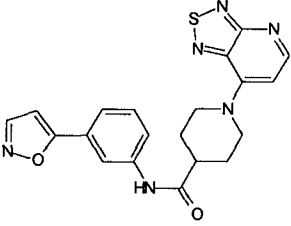
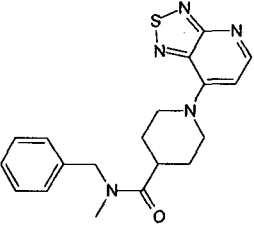
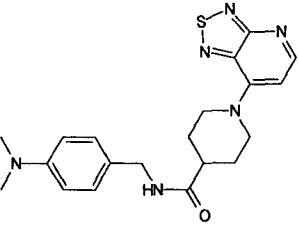
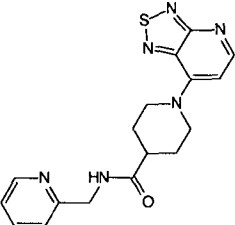
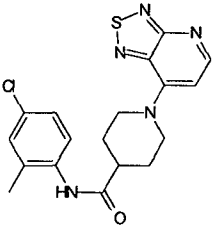
#	Chemical Structure	IC_{50} [μ M]	$[M + 1]^+$	HPLC/ MS Rt [min]	Chemical Name	NMR listing
1		E	502		1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (3-phenyl-propyl)-amide	

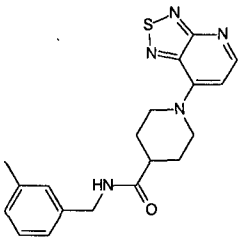
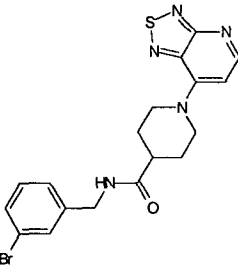
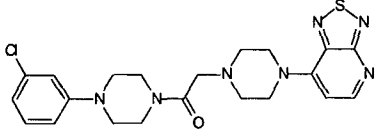
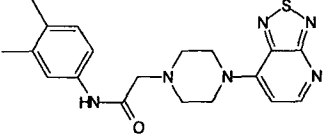
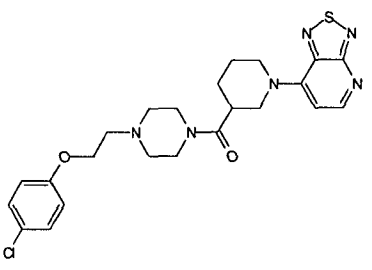
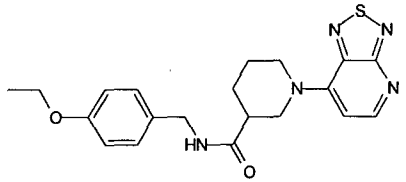
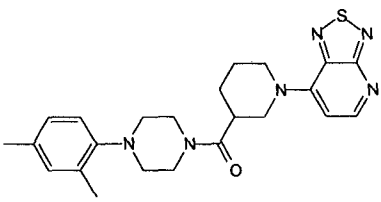
2		D	469		1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid (2,4-dimethyl- phenyl)-amide	
3		C	421		1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid (3-chloro-4- methyl-phenyl)- amide	
4		E	329		1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid 3- methoxy- benzylamide	
5		D	423		1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid (4-chloro- phenyl)-amide	
6		C	335		1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid (1-benzyl- piperidin-4-yl)- amide	
7		C	470		1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid 4- chloro- benzylamide	

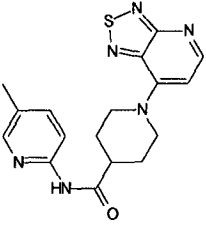
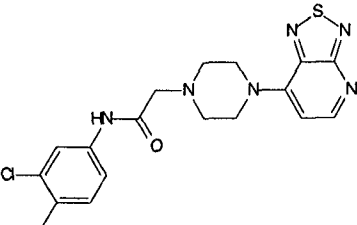
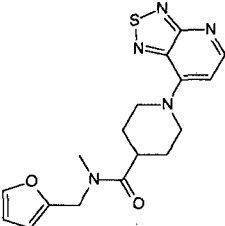
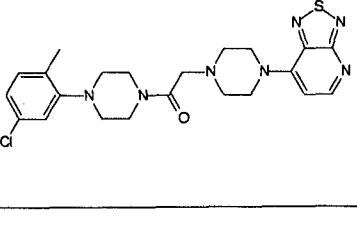
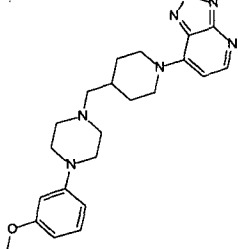
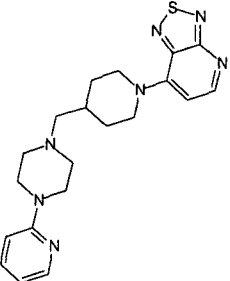
8		C	347		1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid [2-(4-chlorophenyl)-ethyl]-amide	
9		D	326		[4-(4-Chlorophenyl)-piperazin-1-yl]-(1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-piperidin-4-yl)-methanone	
10		D	396		1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (2,3-dimethylphenyl)-amide	
11		D	341		[4-(2-Fluorophenyl)-piperazin-1-yl]-(1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-piperidin-4-yl)-methanone	
12		E	379		1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (4-fluorophenyl)-amide	
13		E	391		1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (2-ethylphenyl)-amide	

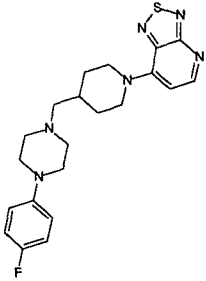
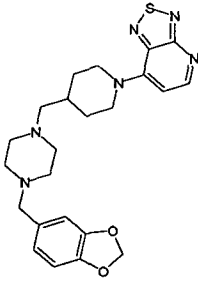
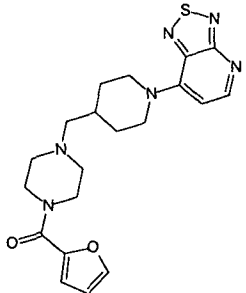
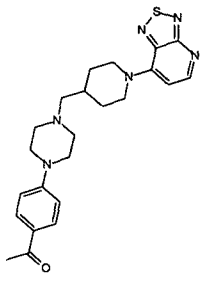
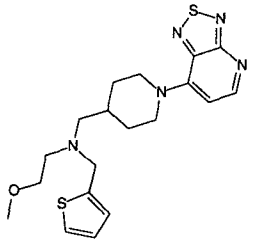
14		E	380	2,00	1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid 4-fluorobenzylamide	
15		E	347		1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (5-methyl-furan-2-ylmethyl)-amide	
16		D	347		1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid 4-methylbenzylamide	
17		D	489	2,24	1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (3-fluoro-4-methyl-phenyl)-amide	
18		E	347		1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-3-carboxylic acid (2,4-dimethyl-phenyl)-amide	
19		C	313		1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (4-methyl-thiazol-2-yl)-amide	

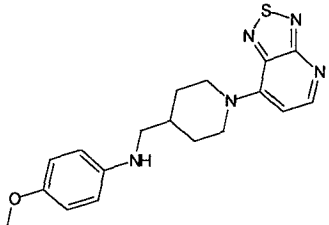
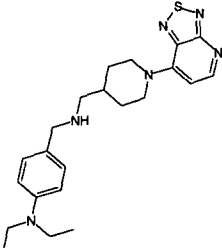
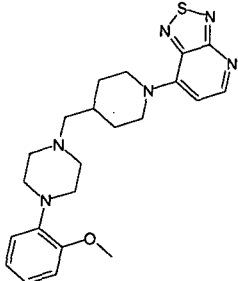
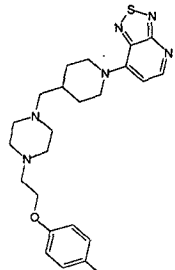
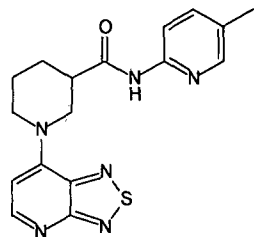
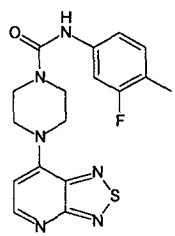
20		E	417	2,02	1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid (2,4-difluoro- phenyl)-amide	
21		D	322		[4-(4-Chloro- phenyl)- piperazin-1-yl]- (1- [1,2,5]thiadiazolo [3,4-b]pyridin-7- yl-piperidin-3-yl)- methanone	
22		C	352		1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid (6-methyl-pyridin- 2-yl)-amide	
23		E	332		1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid (2-fluoro-phenyl)- amide	
24		A	286	0,56	{4-[2-(4-Chloro- phenoxy)-ethyl]- piperazin-1-yl]- (1- [1,2,5]thiadiazolo [3,4-b]pyridin-7- yl-piperidin-4-yl)- methanone	¹ H NMR (400 MHz, DMSO-d ₆) ppm = 8.62-8.55 (m, 1H), 7.32 (d, J=8 Hz, 2H), 6.95 (d, J=8 Hz, 2H), 6.75-6.67 (m, 1H), 4.90-4.75 (m, 2H), 4.12-4.02 (m, 2H), 3.55-3.25 (m, 8H), 3.10-3.00 (m, 1H), 2.75-2.65 (m, 2H), 2.45-2.35 (m, 2H), 1.81-1.61 (m, 4H).
25		D	365		1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid thiazol-2-ylamide	

26		C	348		1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid (3-isoxazol-5-yl- phenyl)-amide	
27		C	363		1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid benzyl-methyl- amide	
28		E	322		1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid 4- dimethylamino- benzylamide	
29		D	399		1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid (pyridin-2- ylmethyl)-amide	
30		C	312		1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid (4-chloro-2- methyl-phenyl)- amide	

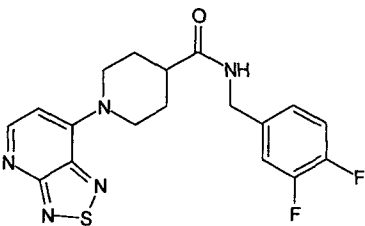
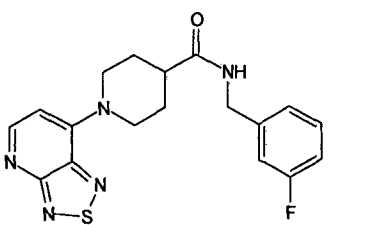
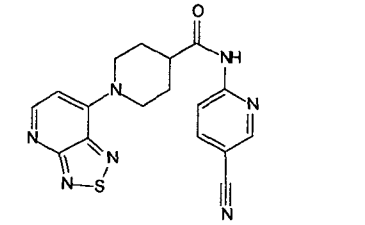
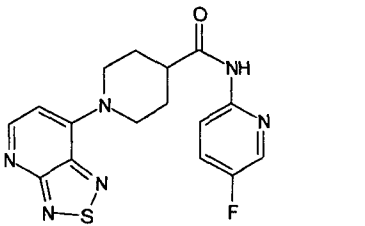
31		D	396		1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid 3-methyl-benzylamide	
32		B	328		1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid 3-bromo-benzylamide	
33		E	338		1-[4-(3-Chloro-phenyl)-piperazin-1-yl]-2-(4-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperazine-1-yl-ethanone	
34		E	382		N-(3,4-Dimethyl-phenyl)-2-(4-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperazine-1-yl-ethanone	
35		C	328		{4-[2-(4-Chloro-phenoxy)-ethyl]-piperazin-1-yl}-1-(1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidin-3-yl-methanone	
36		D	307		1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-3-carboxylic acid 4-ethoxy-benzylamide	
37		C	312		[4-(2,4-Dimethyl-phenyl)-piperazin-1-yl]-1-(1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidin-3-yl-methanone	

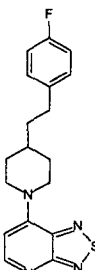
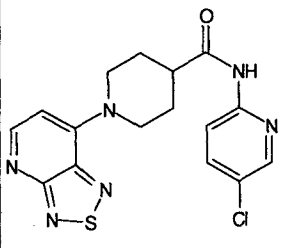
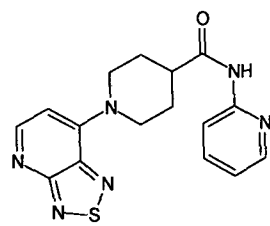
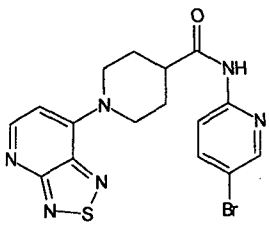
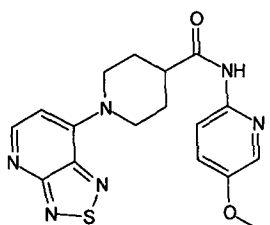
38		C	377	1,56	1- [1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (5-methyl-pyridin-2-yl)-amide	¹ H NMR (400 MHz, DMSO) ppm = 10.40 (s, 1H), 8.59 (d, J=5.5, 1H), 8.14 (d, J=2.3, 1H), 7.97 (d, J=8.5, 1H), 7.62 - 7.53 (m, 1H), 6.75 (d, J=5.5, 1H), 4.93 - 4.78 (m, 2H), 3.26 (d, J=2.7, 2H), 2.96 - 2.84 (m, 1H), 2.24 (s, 3H), 2.04 - 1.91 (m, 2H)
39		E	441		N-(3-Chloro-4-methyl-phenyl)-2-(4-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperazin-1-yl)-acetamide	
40		D	379		1- [1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid furan-2-ylmethylmethyl-amide	
41		E	381		1-[4-(5-Chloro-2-methyl-phenyl)-piperazin-1-yl]-2-(4-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperazin-1-yl)-ethanone	
42		D	378		7-[4-[4-(3-Methoxy-phenyl)-piperazin-1-ylmethyl]-piperidin-1-yl]-[1,2,5]thiadiazolo[3,4-b]pyridine	
43		D	456		7-[4-(4-Pyridin-2-yl)-piperazin-1-ylmethyl]-piperidin-1-yl]-[1,2,5]thiadiazolo[3,4-b]pyridine	

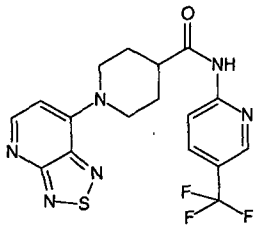
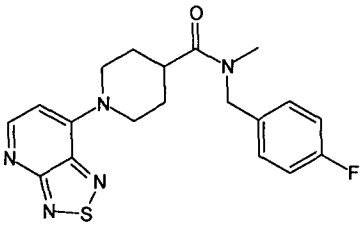
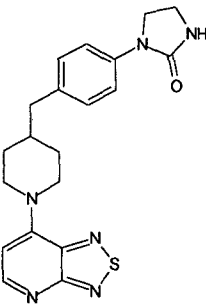
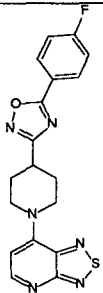
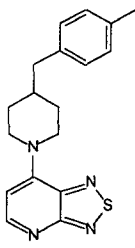
44		E	381		7-{4-[4-(4-Fluorophenyl)-piperazin-1-ylmethyl]-piperidin-1-yl}-[1,2,5]thiadiazolo[3,4-b]pyridine	
45		C	407	1,60	7-[4-(4-Benzo[1,3]dioxol-5-ylmethyl)-piperazin-1-ylmethyl]-piperidin-1-yl]-[1,2,5]thiadiazolo[3,4-b]pyridine	¹ H NMR (500 MHz, DMSO) ppm = 8.53 (d, J=7.1, 1H), 7.06 - 6.88 (m, 4H), 6.05 (s, 2H), 5.24 - 4.98 (m, 2H), 4.01 (s, 2H), 3.63 - 3.52 (m, 8H), 3.08 - 2.94 (m, 4H), 2.24 - 2.11 (m, 1H), 2.06 - 1.93 (m, 2H), 1.45 - 1.30 (m, 2H).
46		C	426	1,49	Furan-2-yl-[4-(1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-piperidin-4-ylmethyl)-piperazin-1-yl]-methanone	¹ H NMR (500 MHz, DMSO) ppm = 8.57 (d, J=6.8, 1H), 7.89 (d, J=1.6, 1H), 7.12 (d, J=3.5, 1H), 6.99 (d, J=6.9, 1H), 6.70 - 6.65 (m, 1H), 5.30 - 4.93 (m, 2H), 3.97 (s, 2H), 3.58 - 3.48 (m, 4H), 3.17 (s, 4H), 3.09 - 3.04 (m, 2H), 2.40 - 2.29 (m, 1H)
47		C	377		1-{4-[4-(1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidin-4-ylmethyl)-piperazin-1-yl]-phenyl}-ethanone	
48		E	422		(2-Methoxyethyl)-(1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-piperidin-4-ylmethyl)-thiophen-2-ylmethyl-amine	

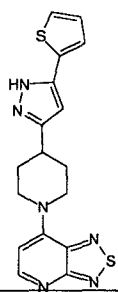
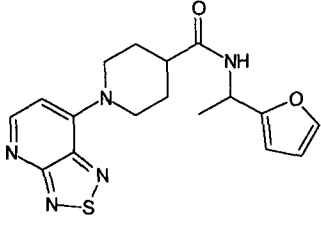
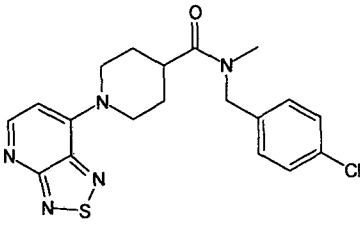
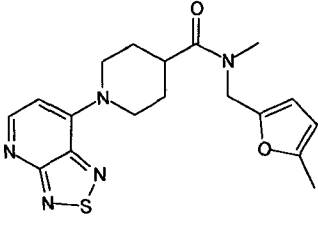
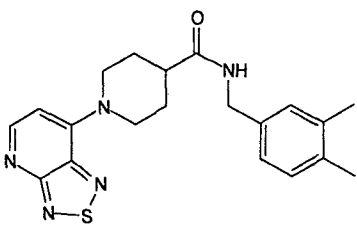
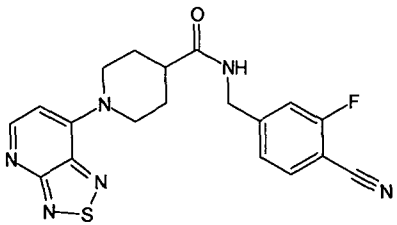
49		E	370		(4-Methoxy-phenyl)-(1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-piperidin-4-ylmethyl)-amine	
50		E	421		Diethyl-(4-(((1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-piperidin-4-ylmethyl)-amino)-methyl)-phenyl)-amine	
51		E	423		7-{4-[4-(2-Methoxy-phenyl)-piperazin-1-ylmethyl]-piperidin-1-yl}-[1,2,5]thiadiazolo[3,4-b]pyridine	
52		B	422	1,89	7-(4-{4-[2-(4-Chloro-phenoxy)-ethyl]-piperazin-1-ylmethyl}-piperidin-1-yl)-[1,2,5]thiadiazolo[3,4-b]pyridine	¹ H NMR (400 MHz, DMSO) ppm = 8.55 (d, J=7.0, 1H), 7.36 (d, J=8.9, 2H), 7.05 - 6.95 (m, 3H), 5.27 - 4.94 (m, 2H), 4.34 - 4.14 (m, 2H), 3.66 - 2.68 (m, 14H), 2.20 (s, 1H), 2.04 - 1.95 (m, 2H), 1.45 - 1.31 (m, 2H).
53		E	562	1,58	1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-3-carboxylic acid (5-methyl-pyridin-2-yl)-amide	
54		E	417	2,10	4-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperazine-1-carboxylic acid (3-fluoro-4-methyl-phenyl)-amide	

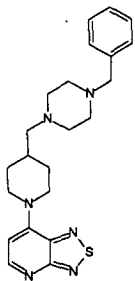
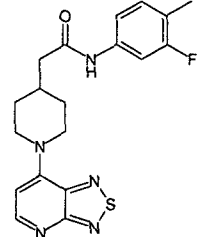
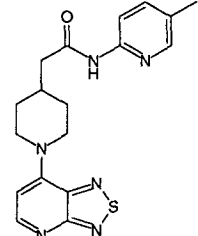
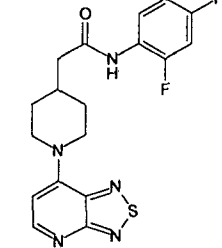
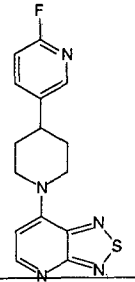
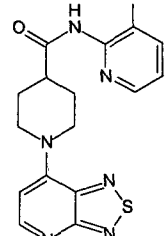
55		C	592	2,09	1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid 2,4,5-trifluoro- benzylamide	¹ H NMR (500 MHz, DMSO) ppm = 8.57 (d, J=5.4, 1H), 8.44 - 8.36 (m, 1H), 7.56 - 7.47 (m, 1H), 7.37 - 7.29 (m, 1H), 6.74 (d, J=5.5, 1H), 4.86 - 4.75 (m, 2H), 4.26 (d, J=5.7, 2H), 3.32 (s, 1H), 3.26 (d, J=2.7, 1H), 2.65 - 2.57 (m, 1H), 1.94 - 1.84
56		C	411	2,28	1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid 4- trifluoromethyl- benzylamide	
57		C		2,14	1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid 3- chloro- benzylamide	¹ H NMR (500 MHz, DMSO) ppm = 8.58 (d, J=5.5, 1H), 8.47 - 8.39 (m, 1H), 7.38 - 7.32 (m, 1H), 7.32 - 7.26 (m, 2H), 7.23 - 7.17 (m, 1H), 6.74 (d, J=5.5, 1H), 4.82 (d, J=13.2, 2H), 4.27 (d, J=5.9, 2H), 3.32 (d, J=2.7, 1H), 3.27 (d, J=2.7, 1H), 2.67
58		B		2,26	1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid 3- trifluoromethyl- benzylamide	¹ H NMR (500 MHz, DMSO) ppm = 8.67 - 8.53 (m, 1H), 8.50 (t, J=6.0, 1H), 7.63 - 7.52 (m, 4H), 6.74 (d, J=5.4, 1H), 4.82 (d, J=13.2, 2H), 4.36 (d, J=5.9, 2H), 3.33 (d, J=2.6, 1H), 3.28 (d, J=2.7, 1H), 2.68 - 2.59 (m, 1H), 1.94 - 1.87 (m, 2H), 1.80
59		C		1,64	(4- Benzo[1,3]dioxol- 5-ylmethyl- piperazin-1-yl)- (1- [1,2,5]thiadiazolo [3,4-b]pyridin-7- yl-piperidin-4-yl)- methanone	¹ H NMR (400 MHz, DMSO) ppm = 8.56 (d, J=6.7, 1H), 7.11 - 6.89 (m, 4H), 6.08 (s, 2H), 5.13 - 4.94 (m, 2H), 4.52 - 4.17 (m, 4H), 3.66 - 3.53 (m, 4H), 3.32 - 3.05 (m, 4H), 2.95 (s, 1H), 1.92 (d, J=11.5, 2H), 1.84 -

						1.69 (m, 2H).
60		E		2,09	1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid 3,4-difluoro- benzylamide	
61		C		1,99	1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid 3- fluoro- benzylamide	1H NMR (400 MHz, DMSO) ppm = 8.58 (d, J=5.4, 1H), 8.47 - 8.37 (m, 1H), 7.42 - 7.29 (m, 1H), 7.12 - 6.99 (m, 3H), 6.74 (d, J=5.5, 1H), 4.87 - 4.77 (m, 2H), 4.29 (d, J=5.9, 2H), 3.33 (d, J=2.7, 1H), 3.28 - 3.24 (m, 1H), 2.68 - 2.57 (m, 1H), 1.95
62		C		1,89	1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid (5-cyano-pyridin- 2-yl)-amide	1H NMR (500 MHz, DMSO) ppm = 11.11 (s, 1H), 8.80 (d, J=2.0, 1H), 8.56 (d, J=7.0, 1H), 8.27 - 8.19 (m, 2H), 7.00 (d, J=7.0, 1H), 5.29 - 4.96 (m, 2H), 3.69 - 3.60 (m, 2H), 3.11 - 3.04 (m, 1H), 2.16 - 2.09 (m, 2H), 1.92 - 1.82 (m, 2H).
63		C		1,88	1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid (5-fluoro-pyridin- 2-yl)-amide	

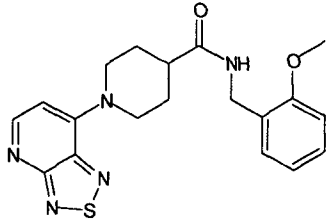
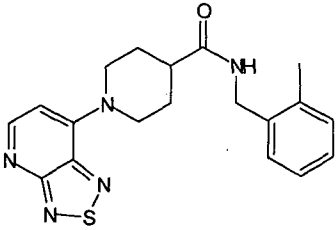
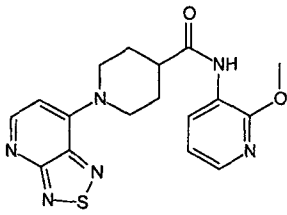
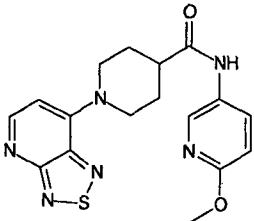
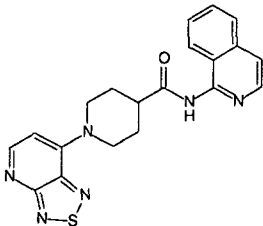
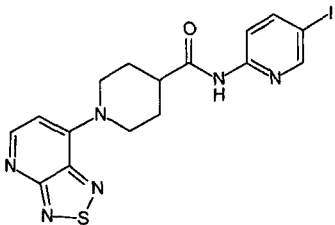
64		E		2,56	7-[4-[2-(4-Fluorophenyl)-ethyl]-piperidin-1-yl]-[1,2,5]thiadiazolo[3,4-b]pyridine	
65		C		2,07	1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (5-chloro-pyridin-2-yl)-amide	1H NMR (500 MHz, DMSO) ppm = 10.71 (s, 1H), 8.59 (d, J=5.5, 1H), 8.36 (d, J=2.6, 1H), 8.11 (d, J=8.9, 1H), 7.91 - 7.85 (m, 1H), 6.76 (d, J=5.5, 1H), 4.85 (d, J=13.3, 2H), 3.37 (s, 1H), 3.27 (d, J=2.6, 1H), 2.97 - 2.88 (m, 1H), 2.04 - 1.94 (m, 2
66		D		1,48	1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid pyridin-2-ylamide	
67		A		2,12	1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (5-bromo-pyridin-2-yl)-amide	1H NMR (500 MHz, DMSO) ppm = 10.70 (s, 1H), 8.59 (d, J=5.5, 1H), 8.43 (d, J=2.5, 1H), 8.07 (d, J=8.9, 1H), 8.01 - 7.96 (m, 1H), 6.75 (d, J=5.5, 1H), 4.85 (d, J=13.3, 2H), 3.32 (d, J=2.7, 1H), 3.27 (d, J=2.6, 1H), 2.97 - 2.88 (m, 1H), 2.04 - 1.9
68		C		1,67	1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (5-methoxy-pyridin-2-yl)-amide	1H NMR (500 MHz, DMSO) ppm = 10.38 (s, 1H), 8.60 (d, J=5.4, 1H), 8.09 - 7.98 (m, 2H), 7.46 - 7.36 (m, 1H), 6.76 (d, J=5.5, 1H), 4.92 - 4.79 (m, 2H), 3.81 (s, 3H), 3.31 - 3.25 (m, 2H), 2.95 - 2.83 (m, 1H), 1.97 (dd, J=13.7, 3.8, 2H), 1.86 - 1.73

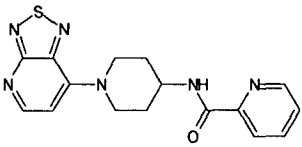
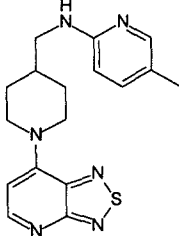
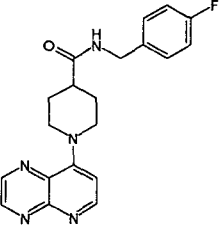
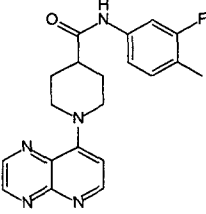
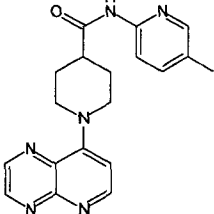
69		A		2,25	1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid (5- trifluoromethyl- pyridin-2-yl)- amide	1H NMR (500 MHz, DMSO) ppm = 11.00 (s, 1H), 8.71 (s, 1H), 8.59 (d, J=5.5, 1H), 8.27 (d, J=8.8, 1H), 8.20 - 8.10 (m, 1H), 6.77 (d, J=5.6, 1H), 4.86 (d, J=13.2, 2H), 3.38 - 3.30 (m, 2H), 3.04 - 2.90 (m, 1H), 2.07 - 1.95 (m, 2H), 1.88 - 1.72 (m, 2
70		D		2,14	1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid (4-fluoro-benzyl)- methyl-amide	
71		B		2,11	1-[4-(1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidin-4- ylmethyl)- phenyl]- imidazolidin-2- one	1H NMR (500 MHz, DMSO) ppm = 8.49 (d, J=7.3, 1H), 7.47 (d, J=8.6, 2H), 7.12 (d, J=8.5, 2H), 7.02 (d, J=7.5, 1H), 6.96 - 6.75 (m, 1H), 5.39 - 4.97 (m, 1H), 3.86 - 3.78 (m, 2H), 3.59 - 3.52 (m, 3H), 3.41 - 3.36 (m, 2H), 2.56 - 2.51 (m, 2H), 2.11
72		D		2,34	7-{4-[5-(4-Fluoro- phenyl)- [1,2,4]oxadiazol- 3-yl]-piperidin-1- yl}- [1,2,5]thiadiazolo [3,4-b]pyridine	
73		E		2,56	7-[4-(4-Methyl- benzyl)-piperidin- 1-yl]- [1,2,5]thiadiazolo [3,4-b]pyridine	

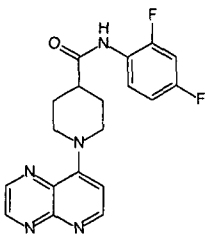
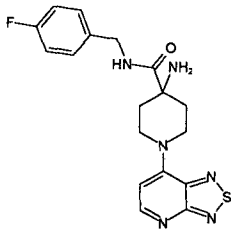
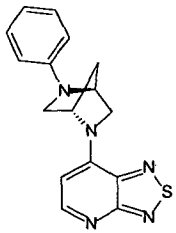
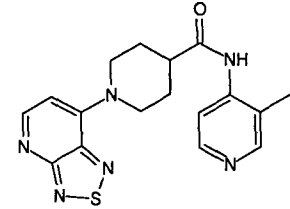
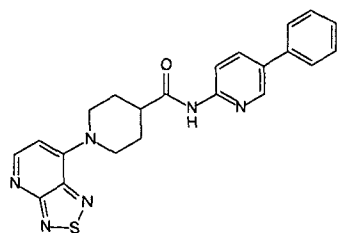
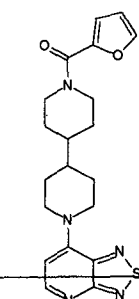
74		E		2,12	7-[4-(5-Thiophen-2-yl-1H-pyrazol-3-yl)-piperidin-1-yl]-[1,2,5]thiadiazolo[3,4-b]pyridine	
75		E		1,91	1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (1-furan-2-yl-ethyl)-amide	
76		C		2,28	1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (4-chloro-benzyl)-methyl-amide	
77		D		2,05	1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid methyl-(5-methyl-furan-2-ylmethyl)-amide	
78		D		2,22	1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid 3,4-dimethyl-benzylamide	
79		E		1,96	1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid 4-cyano-3-fluoro-benzylamide	

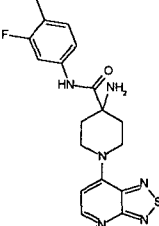
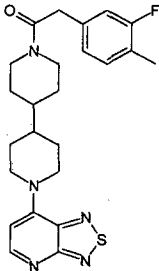
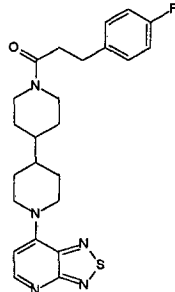
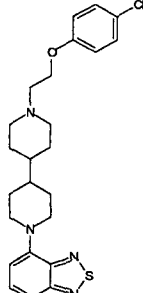
80		D		1,62	7-[4-(4-Benzyl-piperazin-1-ylmethyl)-piperidin-1-yl]-[1,2,5]thiadiazolo[3,4-b]pyridine	
81		E		2,31	N-(3-Fluoro-4-methyl-phenyl)-2-(1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-piperidin-4-yl)-acetamide	
82		D		1,65	N-(5-Methyl-pyridin-2-yl)-2-(1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-piperidin-4-yl)-acetamide	
83		E		2,09	N-(2,4-Difluoro-phenyl)-2-(1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-piperidin-4-yl)-acetamide	
84		D		1,89	6-Fluoro-1'-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-1',2',3',4',5',6'-hexahydro-[3,4']bipyridinyl	
85		D		1,86	1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (3-bromo-pyridin-2-yl)-amide	

86		C		2,07	1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid (benzofuran-5- ylmethyl)-amide	
87		C		2,41	1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid (2-fluoro-4- trifluoromethyl- phenyl)-amide	1H NMR (500 MHz, DMSO) ppm = 10.19 (s, 1H), 8.55 - 8.16 (m, 1H), 7.76 - 7.70 (m, 1H), 7.56 (dd, J=8.5, 2.0, 1H), 7.08 (d, J=7.4, 1H), 5.30 - 5.05 (m, 1H), 3.85 - 3.71 (m, 2H), 3.66 - 3.56 (m, 1H), 3.19 - 3.12 (m, 1H), 2.22
88		A		1,81	1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid quinolin-2- ylamide	1H NMR (500 MHz, DMSO-d6) ppm = 10.87 (s, 1H), 8.60 (d, J=5.4, 1H), 8.36 - 8.27 (m, 2H), 7.93 - 7.89 (m, 1H), 7.83 - 7.80 (m, 1H), 7.73 - 7.69 (m, 1H), 7.51 - 7.46 (m, 1H), 6.77 (d, J=5.5, 1H), 4.91 - 4.84 (m, 2H), 3.38 - 3.30 (m, 2H), 3.04 - 2.96 (m, 1H), 2.06 - 2.00 (m, 2H), 1.88 - 1.78 (m, 2H).
89		E		2,01	1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-pyrrolidine-3- carboxylic acid 4- fluoro- benzylamide	
90		C		1,97	1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid 2- fluoro- benzylamide	

91		E		1,97	1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid 2- methoxy- benzylamide	
92		B		2,02	1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid 2- methyl- benzylamide	1H NMR (500 MHz, DMSO-d6) ppm = 8.57 (d, J=5.5, 1H), 8.23 (t, J=5.6, 1H), 7.21 - 7.10 (m, 4H), 6.73 (d, J=5.5, 1H), 4.86 - 4.77 (m, 2H), 4.24 (d, J=5.7, 2H), 3.33 - 3.24 (m, 2H), 2.68 - 2.58 (m, 1H), 2.25 (s, 3H), 1.94 - 1.85 (m, 2H), 1.82 - 1.70 (m, 2H).
93		E		1,89	1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid (2-methoxy- pyridin-3-yl)- amide	
94		E		1,76	1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid (6-methoxy- pyridin-3-yl)- amide	
95		E		1,73	1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid isoquinolin-1- ylamide	
96		C		2,15	1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid (5-iodo-pyridin-2- yl)-amide	

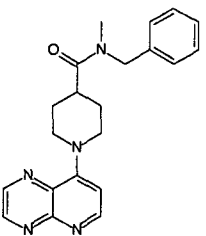
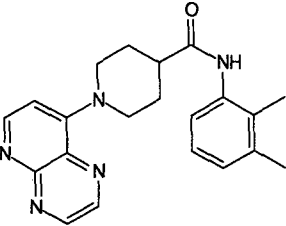
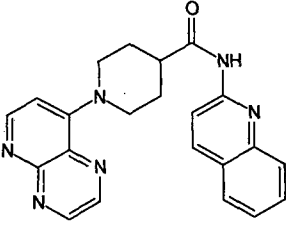
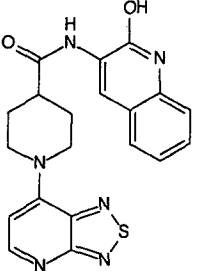
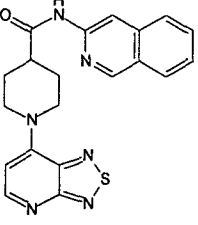
97		D		1,73	Pyridine-2-carboxylic acid (1- [1,2,5]thiadiazolo [3,4-b]pyridin-7-yl-piperidin-4-yl)-amide	
98		E		1,65	(5-Methyl-pyridin-2-yl)-(1- [1,2,5]thiadiazolo [3,4-b]pyridin-7-yl-piperidin-4-ylmethyl)-amine	
99		E		1,98	1-Pyrido[2,3-b]pyrazin-8-yl-piperidine-4-carboxylic acid 4-fluoro-benzylamide	
100		C		2,27	1-Pyrido[2,3-b]pyrazin-8-yl-piperidine-4-carboxylic acid (3-fluoro-4-methyl-phenyl)-amide	¹ H NMR (500 MHz, DMSO-d ₆) ppm = 10.04 (s, 1H), 9.00 (d, J=1.7, 1H), 8.85 (d, J=1.7, 1H), 8.73 (d, J=5.4, 1H), 7.56 (dd, J=12.4, 2.0, 1H), 7.27 - 7.14 (m, 2H), 7.09 (d, J=5.4, 1H), 4.53 - 4.45 (m, 2H), 3.22 - 3.12 (m, 2H), 2.72 - 2.62 (m, 1H), 2.17 (s, 3H), 1.98 - 1.83 (m, 4H).
101		C		1,55	1-Pyrido[2,3-b]pyrazin-8-yl-piperidine-4-carboxylic acid (5-methyl-pyridin-2-yl)-amide	

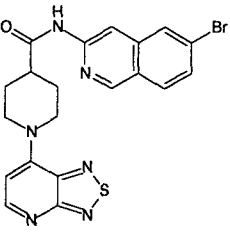
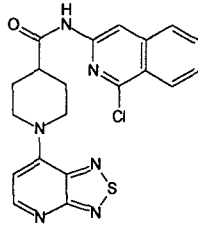
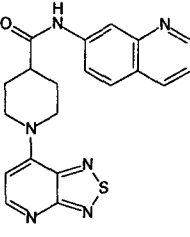
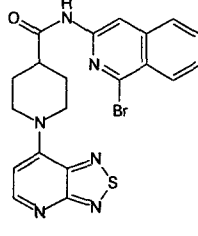
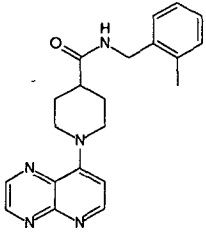
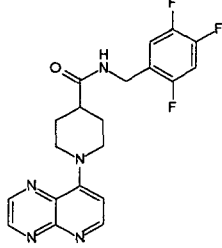
102		E		2,00	1-Pyrido[2,3-b]pyrazin-8-yl-piperidine-4-carboxylic acid (2,4-difluorophenyl)-amide	
103		E		1,72	4-Amino-1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid 4-fluorobenzylamide	
104		A		2,12	7-((1S,4S)-5-Phenyl-2,5-diazabicyclo[2.2.1]hept-2-yl)-[1,2,5]thiadiazolo[3,4-b]pyridine	1H NMR (500 MHz, DMSO) ppm = 8.54 - 8.44 (m, 1H), 7.22 - 7.11 (m, 2H), 7.07 - 6.57 (m, 1H), 6.72 - 6.62 (m, 3H), 6.39 - 5.42 (m, 1H), 4.92 - 4.83 (m, 1H), 4.50 - 4.29 (m, 1H), 4.05 - 3.71 (m, 2H), 3.30 - 3.16 (m, 1H), 2.35 - 2.21 (m, 2H).
105		E		1,51	1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (3-methyl-pyridin-4-yl)-amide	
106		C		2,15	1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (5-phenyl-pyridin-2-yl)-amide	
107		C		2,08	Furan-2-yl-(1'-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-[4,4']bipiperidinyl-1-yl)-methanone	1H NMR (500 MHz, DMSO) ppm = 8.55 (d, J=5.4, 1H), 7.80 (dd, J=1.6, 0.8, 1H), 6.93 (dd, J=3.4, 0.9, 1H), 6.70 (d, J=5.5, 1H), 6.62 - 6.57 (m, 1H), 4.87 (d, J=12.8, 2H), 4.43 -

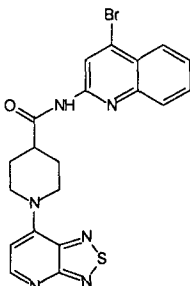
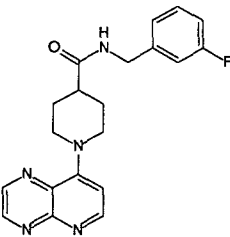
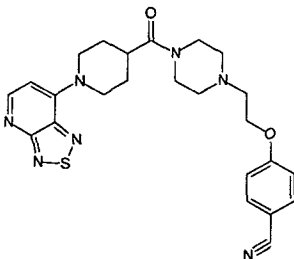
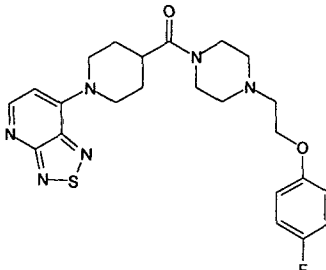
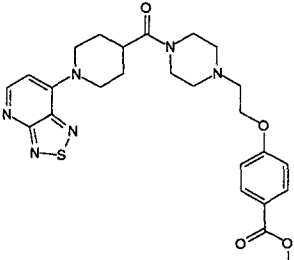
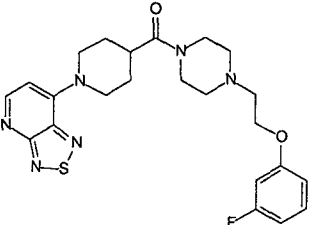
						4.25 (m, 2H), 3.19 - 3.08 (m, 2H), 3.05 - 2.69 (m, 2H), 1.89 - 1.82 (m)
108		E		1,87	4-Amino-1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (3-fluoro-4-methyl-phenyl)-amide	
109		A		2,43	2-(3-Fluoro-4-methyl-phenyl)-1-(1'-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-[4,4']bipiperidinyl-1-yl)-ethanone	1H NMR (500 MHz, DMSO) ppm = 8.48 (d, J=7.4, 1H), 7.19 (t, J=8.0, 1H), 7.02 (d, J=7.6, 1H), 7.00 - 6.91 (m, 2H), 5.72 - 4.69 (m, 2H), 4.45 - 4.37 (m, 1H), 3.99 - 3.90 (m, 1H), 3.66 (s, 2H), 3.57 - 3.50 (m, 2H), 2.95 - 2.86 (m, 1H), 2.47 - 2.42
110		A		2,38	3-(4-Fluorophenyl)-1-(1'-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-[4,4']bipiperidinyl-1-yl)-propan-1-one	1H NMR (500 MHz, DMSO) ppm = 8.49 (d, J=7.4, 1H), 7.30 - 7.22 (m, 2H), 7.12 - 7.00 (m, 3H), 5.71 - 4.68 (m, 1H), 4.47 - 4.38 (m, 1H), 3.86 (d, J=14.0, 1H), 3.59 - 3.50 (m, 3H), 2.91 - 2.82 (m, 1H), 2.82 - 2.75 (m, 2H), 2.64 - 2.54 (m, 2H), 2.46
111		B		2,12	1'-[2-(4-Chlorophenoxy)-ethyl]-1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-[4,4']bipiperidinyl	1H NMR (500 MHz, DMSO) ppm = 8.62 - 8.49 (m, 1H), 7.39 - 7.23 (m, 2H), 7.06 - 6.87 (m, 2H), 6.77 - 6.63 (m, 1H), 4.96 - 4.77 (m, 2H), 4.11 - 3.98 (m, 2H), 3.17 - 3.10 (m, 2H), 3.00 - 2.89 (m, 4H), 2.66 - 2.62 (m, 2H), 2.00 - 1.59 (m, 5H), 1.49

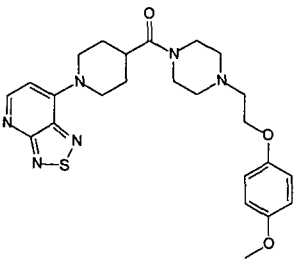
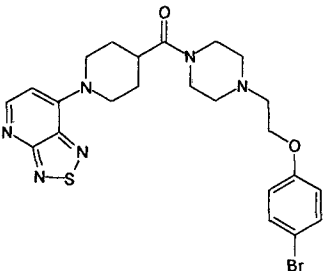
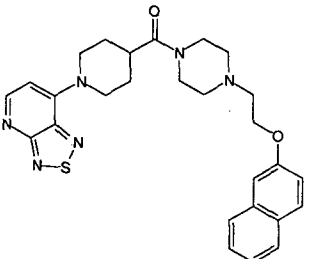
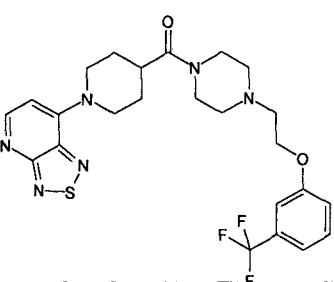
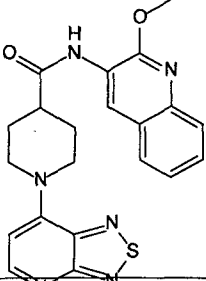
112		D		1,74	7-{4-[4-(2-Benzoyloxy-ethyl)-piperazin-1-ylmethyl]-piperidin-1-yl}-[1,2,5]thiadiazolo[3,4-b]pyridine	
113		C		1,77	7-(4-{4-[2-(4-Fluoro-phenoxy)-ethyl]-piperazin-1-ylmethyl}-piperidin-1-yl)-[1,2,5]thiadiazolo[3,4-b]pyridine	¹ H NMR (400 MHz, DMSO) ppm = 8.55 (d, J=6.9, 1H), 7.20 - 7.09 (m, 2H), 7.05 - 6.92 (m, 3H), 5.29 - 4.96 (m, 2H), 4.22 (s, 2H), 3.65 - 3.45 (m, 4H), 3.43 - 2.99 (m, 10H), 2.26 - 2.11 (m, 1H), 2.00 (d, J=12.8, 2H), 1.46 - 1.30 (m, 2H).
114		C		1,62	7-{4-[4-(4-Methoxy-benzyl)-piperazin-1-ylmethyl]-piperidin-1-yl}-[1,2,5]thiadiazolo[3,4-b]pyridine	¹ H NMR (400 MHz, DMSO) ppm = 8.56 (d, J=7.0, 1H), 7.39 (d, J=7.6, 2H), 7.06 - 6.98 (m, 3H), 5.27 - 4.94 (m, 2H), 3.90 - 3.67 (m, 10H), 3.19 (s, 7H), 2.14 (s, 1H), 2.00 (d, J=12.8, 2H), 1.37 (d, J=10.8, 2H).
115		D		1,34	7-[4-(4-Pyridin-3-ylmethyl)-piperazin-1-ylmethyl]-piperidin-1-yl]-[1,2,5]thiadiazolo[3,4-b]pyridine	
116		D		2,15	1-Pyrido[2,3-b]pyrazin-8-yl-piperidine-4-carboxylic acid 4-chloro-benzylamide	

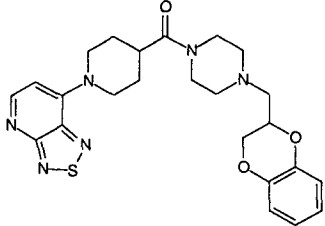
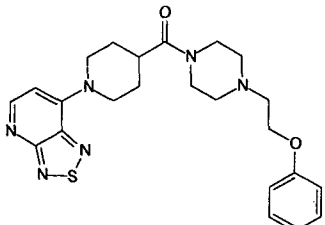
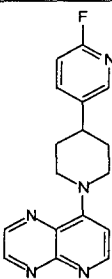
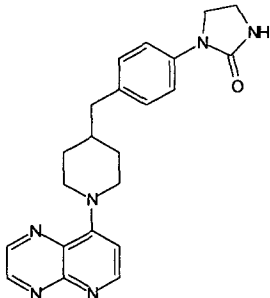
117		C		2,12	1-Pyrido[2,3-b]pyrazin-8-yl-piperidine-4-carboxylic acid 3-chloro-benzylamide	
118		D		2,29	1-Pyrido[2,3-b]pyrazin-8-yl-piperidine-4-carboxylic acid 3-trifluoromethyl-benzylamide	
119		C		2,21	1-Pyrido[2,3-b]pyrazin-8-yl-piperidine-4-carboxylic acid 3-bromo-benzylamide	1H NMR (500 MHz, DMSO-d6) ppm = 8.99 (d, J=1.7, 1H), 8.84 (d, J=1.7, 1H), 8.71 (d, J=5.4, 1H), 8.43 (t, J=6.0, 1H), 7.46 - 7.41 (m, 2H), 7.33 - 7.23 (m, 2H), 7.07 (d, J=5.4, 1H), 4.49 - 4.41 (m, 2H), 4.28 (d, J=6.0, 2H), 3.19 - 3.10 (m, 2H), 2.59 - 2.51 (m, 1H), 1.91 - 1.78 (m, 4H).
120		E		2,26	1-Pyrido[2,3-b]pyrazin-8-yl-piperidine-4-carboxylic acid 4-trifluoromethyl-benzylamide	
121		D		2,07	1-Pyrido[2,3-b]pyrazin-8-yl-piperidine-4-carboxylic acid 3-methyl-benzylamide	

122		E		2,06	1-Pyrido[2,3-b]pyrazin-8-yl-piperidine-4-carboxylic acid benzyl-methyl-amide	
123		E		2,05	1-Pyrido[2,3-b]pyrazin-8-yl-piperidine-4-carboxylic acid (2,3-dimethylphenyl)-amide	
124		A		1,14	1-Pyrido[2,3-b]pyrazin-8-yl-piperidine-4-carboxylic acid quinolin-2-ylamide	1H NMR (400 MHz, DMSO-d6) ppm = 10.86 (s, 1H), 9.03 - 8.97 (m, 1H), 8.88 - 8.83 (m, 1H), 8.73 (d, J=5.4, 1H), 8.38 - 8.28 (m, 2H), 7.91 (d, J=8.1, 1H), 7.82 (d, J=8.4, 1H), 7.76 - 7.66 (m, 1H), 7.49 (t, J=7.6, 1H), 7.11 (d, J=5.5, 1H), 4.51 (d, J=12.3, 2H), 3.17 (td, J=12.5, 2.7, 2H), 3.03 - 2.86 (m, 1H), 2.04 - 1.83 (m, 4H).
125		B		2,06	1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (2-hydroxyquinolin-3-yl)-amide	1H NMR (500 MHz, DMSO) ppm = 12.27 (s, 1H), 9.50 (s, 1H), 8.63 (s, 1H), 8.55 (d, J=7.3, 1H), 7.61 (dd, J=8.0, 1.4, 1H), 7.44 - 7.38 (m, 1H), 7.31 (d, J=8.1, 1H), 7.22 - 7.16 (m, 1H), 7.08 (d, J=7.4, 1H), 5.50 - 4.95 (m, 1H), 3.78 - 3.66 (m, 2H)
126		C		1,96	1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid isoquinolin-3-ylamide	

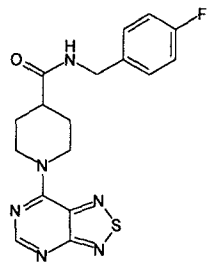
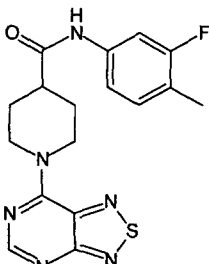
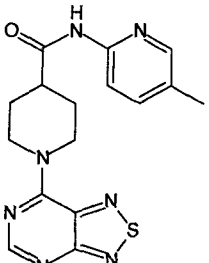
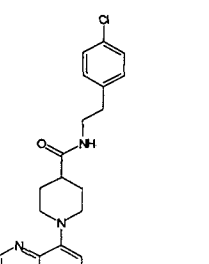
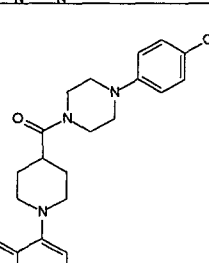
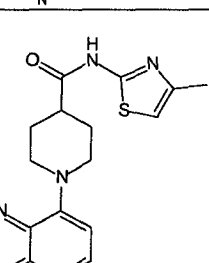
127		E		2,38	1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (6-bromo-isoquinolin-3-yl)-amide	
128		E		2,44	1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (1-chloro-isoquinolin-3-yl)-amide	
129		D		1,65	1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid quinolin-7-ylamide	
130		E		2,48	1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (1-bromo-isoquinolin-3-yl)-amide	
131		D		2,07	1-Pyrido[2,3-b]pyrazin-8-yl-piperidine-4-carboxylic acid 2-methyl-benzylamide	
132		D		2,11	1-Pyrido[2,3-b]pyrazin-8-yl-piperidine-4-carboxylic acid 2,4,5-trifluoro-benzylamide	

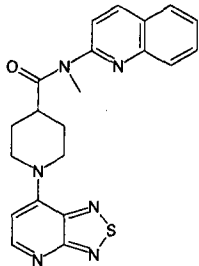
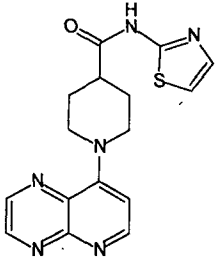
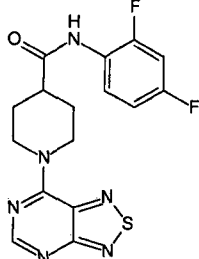
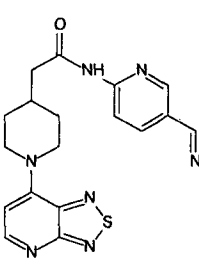
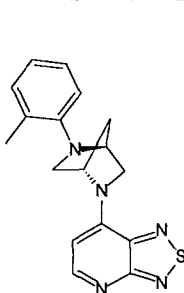
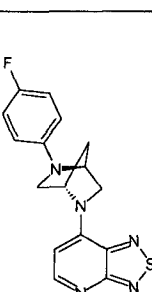
133		C		2,39	1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (4-bromo-quinolin-2-yl)-amide	
134		E		1,97	1-Pyrido[2,3-b]pyrazin-8-yl-piperidine-4-carboxylic acid 3-fluoro-benzylamide	
135		C		1,71	4-{2-[4-(1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl)-piperidine-4-carbonyl]-piperazin-1-yl}-ethoxy}-benzonitrile	
136		C		1,86	{4-[2-(4-Fluorophenoxy)-ethyl]-piperazin-1-yl}-(1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidine-4-yl)-methanone	1H NMR (500 MHz, DMSO-d6) ppm = 8.55 (d, J=7.0, 1H), 7.23 - 7.14 (m, 2H), 7.08 - 6.97 (m, 3H), 5.15 - 5.01 (m, 2H), 4.34 (t, J=4.9, 4H), 3.66 (t, J=12.1, 2H), 3.59 - 3.47 (m, 3H), 3.32 - 3.28 (m, 5H), 3.28 - 3.20 (m, 1H), 1.99 - 1.89 (m, 2H), 1.85 - 1.73 (m, 2H).
137		E		1,80	4-{2-[4-(1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl)-piperidine-4-carbonyl]-piperazin-1-yl}-ethoxy}-benzoic acid methyl ester	
138		C		1,81	{4-[2-(3-Fluorophenoxy)-ethyl]-piperazin-1-yl}-(1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidine-4-yl)-methanone	1H NMR (500 MHz, DMSO-d6) ppm = 8.56 (d, J=6.7, 1H), 7.41 - 7.31 (m, 1H), 6.98 - 6.80 (m, 4H), 5.04 (s, 2H), 4.38 (t, J=4.9, 2H), 3.69 - 3.45 (m, 12H), 3.27

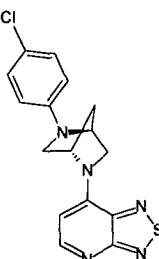
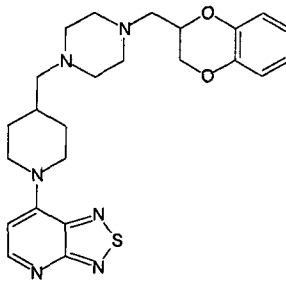
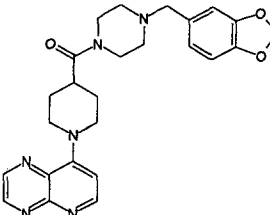
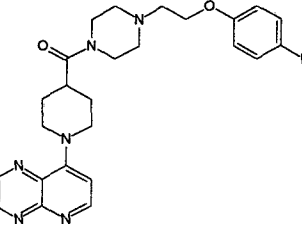
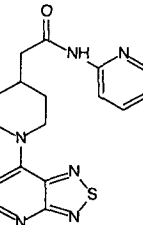
						- 3.18 (m, 1H), 1.97 - 1.88 (m, 2H), 1.84 - 1.72 (m, 2H).
139		C		1,78	{4-[2-(4-Methoxy- phenoxy)-ethyl]- piperazin-1-yl}- (1- [1,2,5]thiadiazolo [3,4-b]pyridin-7- yl-piperidin-4-yl)- methanone	¹ H NMR (500 MHz, DMSO-d ₆) ppm = 8.56 (d, J=6.6, 1H), 7.01 - 6.85 (m, 5H), 5.01 (s, 2H), 4.28 (t, J=4.9, 2H), 3.71 (s, 3H), 3.64 - 3.39 (m, 11H), 3.27 - 3.15 (m, 2H), 1.95 - 1.88 (m, 2H), 1.83 - 1.71 (m, 2H).
140		A		1,98	{4-[2-(4-Bromo- phenoxy)-ethyl]- piperazin-1-yl}- (1- [1,2,5]thiadiazolo [3,4-b]pyridin-7- yl-piperidin-4-yl)- methanone	¹ H NMR (400 MHz, DMSO-d ₆) ppm = 8.56 (d, J=6.8, 1H), 7.56 - 7.47 (m, 2H), 7.04 - 6.92 (m, 3H), 5.04 (s, 2H), 4.35 (t, J=4.9, 2H), 3.66 - 3.43 (m, 7H), 3.37 - 3.12 (m, 6H), 1.97 - 1.88 (m, 2H), 1.85 - 1.70 (m, 2H).
141		C		2,11	{4-[2-(Naphthalen-2- yloxy)-ethyl]- piperazin-1-yl}- (1- [1,2,5]thiadiazolo [3,4-b]pyridin-7- yl-piperidin-4-yl)- methanone	
142		C		2,05	(1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidin-4-yl)- {4-[2-(3- trifluoromethyl- phenoxy)-ethyl]- piperazin-1-yl}- methanone	
143		C		2,34	1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid (2-methoxy- quinolin-3-yl)- amide	¹ H NMR (500 MHz, DMSO) ppm = 9.58 (s, 1H), 8.82 (s, 1H), 8.60 (d, J=5.6, 1H), 7.85 - 7.78 (m, 1H), 7.73 (d, J=8.2, 1H), 7.60 - 7.54 (m, 1H), 7.44 - 7.37 (m, 1H), 6.80 (d, J=5.6, 1H), 4.99 - 4.82 (m,

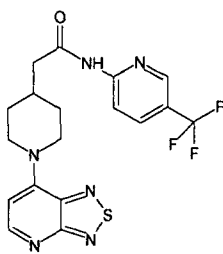
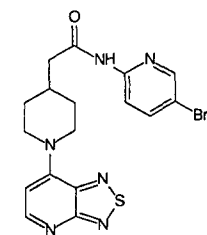
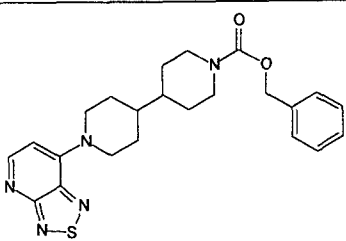
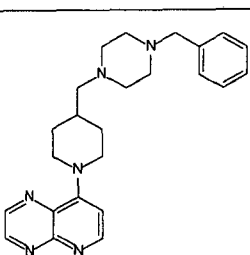
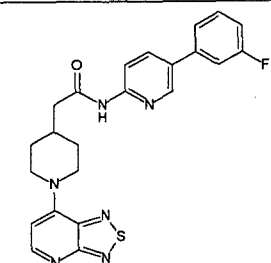
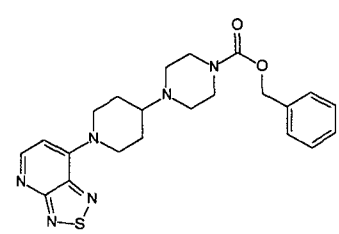
						2H), 4.10 (s, 3H), 3.41 - 3.35 (m, 2H), 3.17
144		C		1,77	[4-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)-piperazin-1-yl]-(1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-piperidin-4-yl)-methanone	
145		C		1,76	[4-(2-Phenoxyethyl)-piperazin-1-yl]-(1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-piperidin-4-yl)-methanone	
146		D		1,93	8-(6-Fluoro-3',4',5',6'-tetrahydro-2'H-[3,4']bipyridinyl-1'-yl)-pyrido[2,3-b]pyrazine	
147		A		2,12	1-[4-(1-Pyrido[2,3-b]pyrazin-8-yl-piperidin-4-ylmethyl)-phenyl]-imidazolidin-2-one	1H NMR (500 MHz, DMSO-d6) ppm = 8.98 (d, J=1.7, 1H), 8.83 (d, J=1.8, 1H), 8.67 (d, J=5.5, 1H), 7.51 - 7.42 (m, 2H), 7.17 - 7.10 (m, 2H), 7.03 (d, J=5.6, 1H), 6.83 (s, 1H), 4.49 - 4.41 (m, 2H), 3.86 - 3.77 (m, 2H), 3.42 - 3.35 (m, 2H), 3.09 - 3.00 (m, 2H), 2.56 - 2.50 (m, 2H), 1.88 - 1.76 (m, 1H), 1.75 - 1.68 (m, 2H), 1.47 - 1.35 (m, 2H).

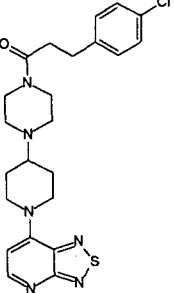
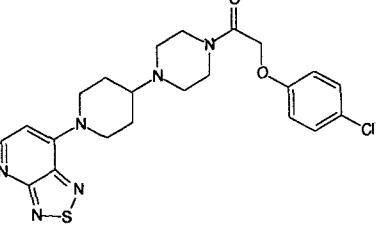
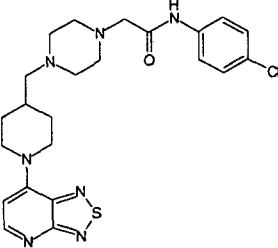
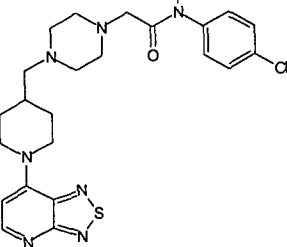
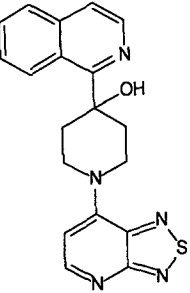
148		E		1,72	7-{4-[4-(2-Phenoxy-ethyl)-piperazin-1-ylmethyl]-piperidin-1-yl}-[1,2,5]thiadiazolo[3,4-b]pyridine	
149		C		1,73	7-(4-{4-[2-(4-Methoxy-phenoxy)-ethyl]-piperazin-1-ylmethyl}-piperidin-1-yl)-[1,2,5]thiadiazolo[3,4-b]pyridine	
150		E		1,95	7-(4-{4-[2-(4-Bromo-phenoxy)-ethyl]-piperazin-1-ylmethyl}-piperidin-1-yl)-[1,2,5]thiadiazolo[3,4-b]pyridine	
151		E		1,79	7-(4-{4-[2-(3-Fluoro-phenoxy)-ethyl]-piperazin-1-ylmethyl}-piperidin-1-yl)-[1,2,5]thiadiazolo[3,4-b]pyridine	
152		C		1,63	4-{2-[4-(1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl)-piperidin-4-ylmethyl]-piperazin-1-yl}-ethoxybenzonitrile	¹ H NMR (500 MHz, DMSO-d ₆) ppm = 8.53 (d, J=7.3, 1H), 7.84 - 7.77 (m, 2H), 7.17 (d, J=8.8, 2H), 7.08 - 7.03 (m, 1H), 4.42 (s, 2H), 3.71 - 3.49 (m, 14H), 3.12 - 2.96 (m, 2H), 2.39 - 2.28 (m, 1H), 2.19 - 2.07 (m, 2H), 1.54 - 1.37 (m, 2H).
153		C		2,19	1-Pyrido[2,3-b]pyrazin-8-yl-piperidine-4-carboxylic acid (4-chloro-2-methyl-phenyl)-amide	

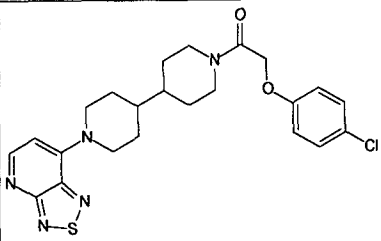
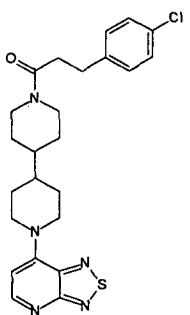
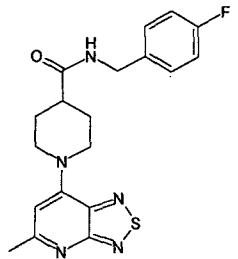
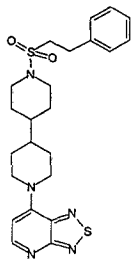
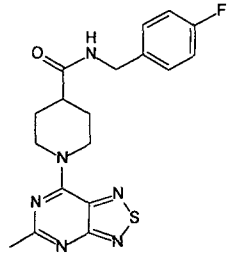
154		E		1,96	1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid 4-fluorobenzamide	
155		E		2,24	1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid (3-fluoro-4-methyl-phenyl)-amide	
156		C		1,56	1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid (5-methyl-pyridin-2-yl)-amide	
157		E		2,23	1-Pyrido[2,3-b]pyrazin-8-yl-piperidine-4-carboxylic acid [2-(4-chlorophenyl)-ethyl]-amide	
158		E		2,32	[4-(4-Chlorophenyl)-piperazin-1-yl]-(1-pyrido[2,3-b]pyrazin-8-yl-piperidin-4-yl)-methanone	
159		E		1,90	1-Pyrido[2,3-b]pyrazin-8-yl-piperidine-4-carboxylic acid (4-methyl-thiazol-2-yl)-amide	

160		D		2,08	1- [1,2,5]Thiadiazol o[3,4-b]pyridin-7- yl-piperidine-4- carboxylic acid methyl-quinolin- 2-yl-amide	
161		E		1,81	1-Pyrido[2,3- b]pyrazin-8-yl- piperidine-4- carboxylic acid thiazol-2-ylamide	
162		E		1,99	1- [1,2,5]Thiadiazol o[3,4-d]pyrimidin- 7-yl-piperidine-4- carboxylic acid (2,4-difluoro- phenyl)-amide	
163		E		1,93	N-(5-Cyano- pyridin-2-yl)-2-(1- [1,2,5]thiadiazolo [3,4-b]pyridin-7- yl-piperidin-4-yl)- acetamide	
164		C		2,23	7-((1S,4S)-5-o- Tolyl-2,5-diaza- bicyclo[2.2.1]hept -2-yl)- [1,2,5]thiadiazolo [3,4-b]pyridine	¹ H NMR (500 MHz, DMSO) ppm = 8.47 (d, J=5.4, 1H), 7.04 (d, J=6.8, 2H), 6.88 (s, 1H), 6.73 (s, 1H), 6.69 - 4.91 (m, 1H), 6.40 - 6.04 (m, 1H), 4.46 (s, 2H), 3.82 - 3.48 (m, 2H), 3.24 (s, 1H), 2.23 - 2.10 (m, 5H).
165		A		2,11	7-((1S,4S)-5-(4- Fluoro-phenyl)- 2,5-diaza- bicyclo[2.2.1]hept -2-yl)- [1,2,5]thiadiazolo [3,4-b]pyridine	¹ H NMR (500 MHz, DMSO) ppm = 8.45 (s, 1H), 7.06 - 6.87 (m, 2H), 6.71 - 6.54 (m, 2H), 6.39 - 6.06 (m, 1H), 6.58 - 4.89 (m, 1H), 4.73 (s, 1H), 4.45 - 3.32 (m, 3H), 3.10 (s, 1H), 2.24 - 2.08 (m, 2H).

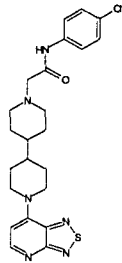
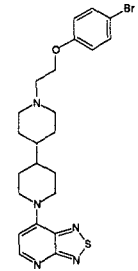
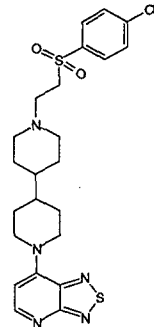
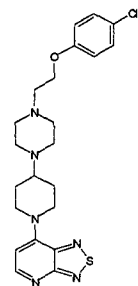
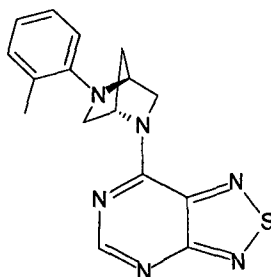
166		A		2,32	7-[(1S,4S)-5-(4-Chloro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo[3,4-b]pyridine	¹ H NMR (500 MHz, DMSO) ppm = 8.52 - 8.40 (m, 1H), 7.14 (d, J=8.8, 2H), 6.64 (d, J=8.9, 2H), 6.35 - 6.09 (m, 1H), 6.61 - 4.90 (m, 1H), 4.76 (s, 1H), 3.73 (s, 2H), 3.36 (s, 1H), 3.13 (s, 1H), 2.17 (s, 2H).
167		C		1,83	7-{4-[4-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethyl)-piperazin-1-ylmethyl]-piperidin-1-yl}-[1,2,5]thiadiazolo[3,4-b]pyridine	¹ H NMR (500 MHz, DMSO-d ₆) ppm = 9.17 - 8.94 (m, 1H), 8.57 (d, J=6.4, 1H), 6.99 - 6.80 (m, 4H), 5.12 - 4.88 (m, 1H), 4.45 - 4.36 (m, 1H), 4.31 (dd, J=11.5, 2.3, 1H), 4.06 - 3.95 (m, 1H), 3.31 - 2.96 (m, 12H), 2.78 - 2.63 (m, 2H), 2.59 - 2.54 (m, 1H), 2.34 - 2.20 (m, 1H), 2.03 - 1.92 (m, 2H), 1.50 - 1.31 (m, 2H).
168		D		1,66	(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-(1-pyrido[2,3-b]pyrazin-8-yl-piperidin-4-yl)-methanone	
169		C		1,85	{4-[2-(4-Fluorophenoxy)-ethyl]-piperazin-1-yl}-(1-pyrido[2,3-b]pyrazin-8-yl-piperidin-4-yl)-methanone	¹ H NMR (500 MHz, DMSO) ppm = 9.00 (d, J=1.8, 1H), 8.84 (d, J=1.8, 1H), 8.68 (d, J=5.6, 1H), 7.13 - 7.05 (m, 3H), 7.00 - 6.93 (m, 2H), 4.56 - 4.45 (m, 2H), 4.14 - 4.08 (m, 2H), 3.64 - 3.46 (m, 4H), 3.26 - 3.21 (m, 2H), 3.07 - 2.98 (m, 1H), 2.88
170		E		1,54	N-Pyridin-2-yl-2-(1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-piperidin-4-yl)-acetamide	

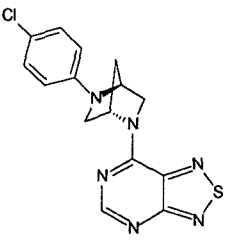
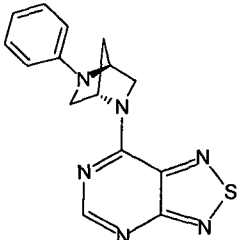
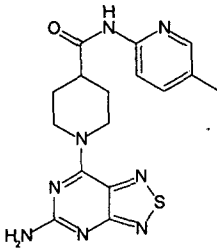
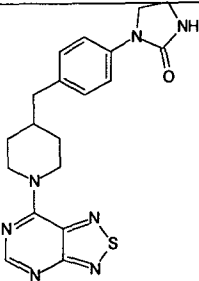
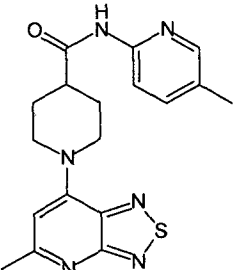
171		E		2,24	2-(1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidin-4-yl)-N-(5-trifluoromethylpyridin-2-yl)-acetamide	
172		D		2,11	N-(5-Bromopyridin-2-yl)-2-(1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-piperidin-4-yl)-acetamide	
173		D		2,49	1'-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-[4,4']bipiperidinyl-1-carboxylic acid benzyl ester	
174		E		1,57	8-[4-(4-Benzylpiperazin-1-ylmethyl)-piperidin-1-yl]-pyrido[2,3-b]pyrazine	
175		D		2,19	N-[5-(3-Fluorophenyl)-pyridin-2-yl]-2-(1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-piperidin-4-yl)-acetamide	
176		E		1,77	4-(1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidin-4-yl)-piperazine-1-carboxylic acid benzyl ester	

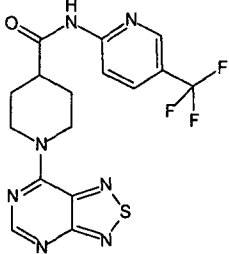
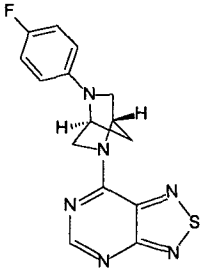
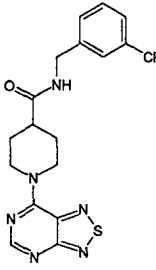
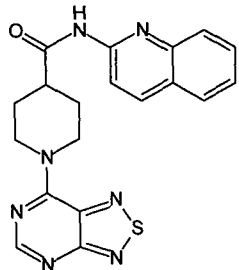
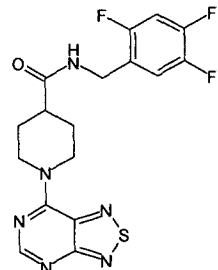
177		A		1,92	3-(4-Chlorophenyl)-1-[4-(1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-piperidin-4-yl)-piperazin-1-yl]propan-1-one	¹ H NMR (500 MHz, DMSO) ppm = 8.63 (d, J=6.3, 1H), 7.37 - 7.30 (m, 2H), 7.30 - 7.23 (m, 2H), 6.95 (d, J=6.4, 1H), 5.15 (s, 2H), 4.62 - 4.10 (m, 2H), 3.75 - 3.59 (m, 3H), 3.49 - 3.34 (m, 4H), 3.13 - 2.87 (m, 2H), 2.86 - 2.78 (m, 2H), 2.75 - 2.61 (m, 2H).
178		E		1,89	2-(4-Chlorophenoxy)-1-[4-(1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-piperidin-4-yl)-piperazin-1-yl]ethanone	
179		D		1,93	N-(4-Chlorophenyl)-2-[4-(1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-methyl)-piperazin-1-yl]acetamide	
180		D		1,86	N-(4-Chlorophenyl)-N-methyl-2-[4-(1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-methyl)-piperazin-1-yl]acetamide	
181		B		1,58	4-Isoquinolin-1-yl-1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-piperidin-4-ol	¹ H NMR (400 MHz, DMSO-d ₆) ppm = 9.13 (d, J=8.8, 1H), 8.53 (d, J=7.5, 1H), 8.40 (d, J=5.6, 1H), 8.01 (d, J=8.1, 1H), 7.84 - 7.76 (m, 2H), 7.71 - 7.64 (m, 1H), 7.12 (d, J=7.5, 1H), 6.28 (s, 1H), 4.20 (s, 2H), 2.65 - 2.55 (m, 2H), 2.52 - 2.51 (m, 2H), 2.44 - 2.35 (m, 2H).

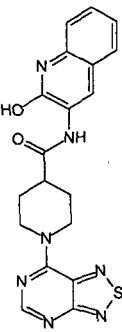
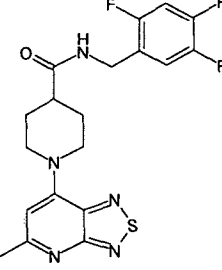
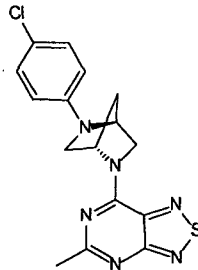
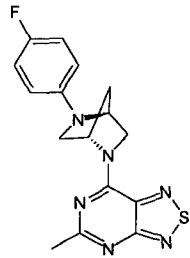
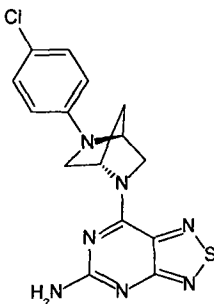
182		A		2,43	2-(4-Chloro-phenoxy)-1-(1'-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-[4,4']bipiperidinyl-1-yl)-ethanone	¹ H NMR (500 MHz, DMSO) ppm = 8.56 (d, J=5.5, 1H), 7.31 (d, J=9.0, 2H), 6.93 (d, J=9.0, 2H), 6.70 (d, J=5.5, 1H), 4.95 - 4.74 (m, 4H), 4.35 (d, J=12.6, 1H), 3.84 (d, J=13.2, 1H), 3.17 - 3.09 (m, 1H), 3.01 - 2.91 (m, 1H), 1.83 (d, J=12.3, 2H), 1.
183		A		2,47	3-(4-Chloro-phenyl)-1-(1'-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-[4,4']bipiperidinyl-1-yl)-propan-1-one	¹ H NMR (500 MHz, DMSO) ppm = 8.55 (d, J=5.5, 1H), 7.34 - 7.29 (m, 2H), 7.28 - 7.22 (m, 2H), 6.69 (d, J=5.5, 1H), 4.92 - 4.80 (m, 2H), 4.43 (d, J=12.8, 1H), 3.85 (d, J=13.8, 1H), 3.18 - 3.08 (m, 1H), 2.91 - 2.82 (m, 1H), 2.79 (t, J=7.5, 2H), 2.6
184		C		2,02	1-(5-Methyl-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidine-4-carboxylic acid 4-fluoro-benzylamide	¹ H NMR (400 MHz, DMSO) ppm = 8.42 - 8.32 (m, 1H), 7.31 - 7.22 (m, 2H), 7.17 - 7.08 (m, 2H), 6.68 (s, 1H), 4.77 (d, J=13.2, 2H), 4.25 (d, J=5.9, 2H), 3.27 - 3.17 (m, 2H), 2.63 - 2.56 (m, 1H), 2.53 (s, 3H), 1.88 (d, J=10.2, 2H), 1.81 - 1.66 (m, 2
185		C		2,47	1'-(2-Phenyl-ethanesulfonyl)-1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-[4,4']bipiperidinyl	
186		E		1,97	1-(5-Methyl-[1,2,5]thiadiazolo[3,4-d]pyrimidin-7-yl)-piperidine-4-carboxylic acid 4-fluoro-benzylamide	

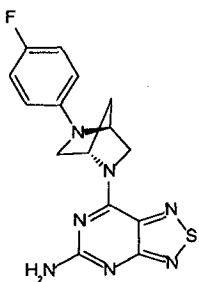
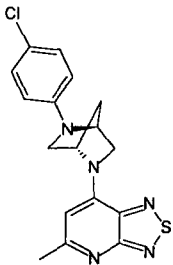
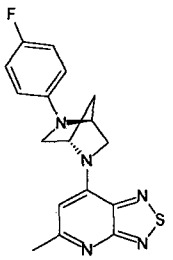
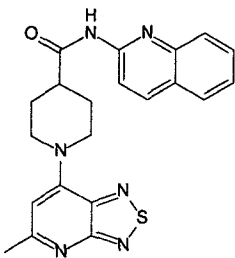
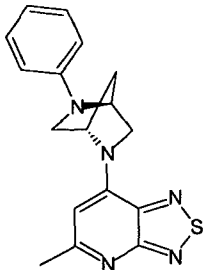
187		A		2,27	1-(5-Methyl-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidine-4-carboxylic acid (3-fluoro-4-methyl-phenyl)-amide	¹ H NMR (500 MHz, DMSO) ppm = 10.04 (s, 1H), 7.58 - 7.50 (m, 1H), 7.25 - 7.14 (m, 2H), 6.71 (s, 1H), 4.81 (d, J=13.1, 2H), 3.28 - 3.22 (m, 2H), 2.76 - 2.65 (m, 1H), 2.54 (s, 3H), 2.16 (s, 3H), 1.96 (d, J=11.0, 2H), 1.85 - 1.73 (m, 2H).
188		C		2,04	1-(5-Methyl-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidine-4-carboxylic acid (2,4-difluorophenyl)-amide	
189		E		1,88	7-{4-[4-(2-Phenylethanesulfonyl)-piperazin-1-yl]-piperidin-1-yl}-[1,2,5]thiadiazolo[3,4-b]pyridine	
190		C		1,90	1'-[2-(4-Methoxyphenoxy)-ethyl]-1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-[4,4']bipiperidiny	¹ H NMR (500 MHz, DMSO) ppm = 8.51 (d, J=7.3, 1H), 7.03 (d, J=7.4, 1H), 6.98 - 6.85 (m, 4H), 5.50 - 4.91 (m, 1H), 4.36 - 4.28 (m, 2H), 3.70 (s, 3H), 3.57 - 3.53 (m, 3H), 3.43 - 3.35 (m, 4H), 3.03 - 2.90 (m, 2H), 2.01 - 1.92 (m, 2H), 1.87 (d, J=1
191		C		1,84	4-[2-(1'-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-[4,4']bipiperidinyl-1-yl)-ethoxy]benzonitrile	

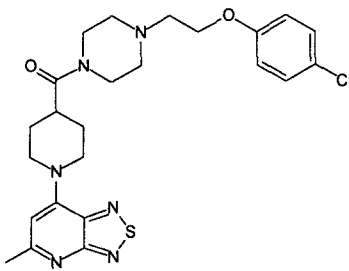
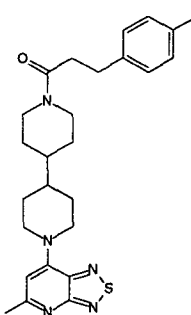
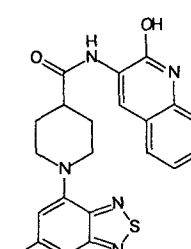
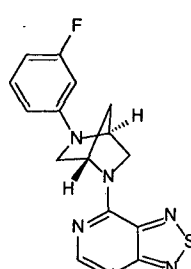
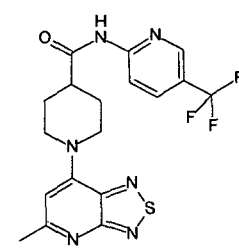
192		D		1,49	N-(4-Chloro-phenyl)-2-(1'-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-[4,4']bipiperidinyl)-acetamide	
193		E		2,12	1'-[2-(4-Bromo-phenoxy)-ethyl]-1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-[4,4']bipiperidinyl	
194		C		1,95	1'-[2-(4-Chloro-benzenesulfonyl)-ethyl]-1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-[4,4']bipiperidinyl	¹ H NMR (500 MHz, DMSO) ppm = 8.55 (d, J=5.5, 1H), 7.94 - 7.87 (m, 2H), 7.71 (d, J=8.1, 2H), 6.68 (d, J=5.5, 1H), 4.91 - 4.80 (m, 2H), 3.73 - 3.39 (m, 2H), 3.28 - 3.24 (m, 2H), 3.15 - 3.06 (m, 2H), 2.86 - 2.52 (m, 3H), 1.82 - 1.65 (m, 3H), 1.56
195		C		1,86	7-(4-{4-[2-(4-Chloro-phenoxy)-ethyl]-piperazin-1-yl}-piperidin-1-yl)-[1,2,5]thiadiazolo[3,4-b]pyridine	¹ H NMR (500 MHz, DMSO) ppm = 8.60 (d, J=7.2, 1H), 7.36 (d, J=8.9, 2H), 7.10 (d, J=7.2, 1H), 7.04 (d, J=9.0, 2H), 5.55 - 5.08 (m, 2H), 4.43 - 4.33 (m, 2H), 3.63 - 3.36 (m, 13H), 2.38 (d, J=10.9, 2H), 2.06 - 1.86 (m, 2H).
196		A		2,23	7-((1S,4S)-5-o-Tolyl-2,5-diazabicyclo[2.2.1]hept-2-yl)-[1,2,5]thiadiazolo[3,4-d]pyrimidine	¹ H NMR (500 MHz, DMSO-d ₆) ppm = 8.47 (d, J=1.7, 1H), 7.09 - 7.01 (m, 2H), 6.95 - 6.87 (m, 1H), 6.79 - 6.70 (m, 1H), 6.13 - 5.18 (m, 1H), 4.49 (d, J=35.4, 1H), 4.43 - 4.20 (m, 1H), 4.00 - 3.79 (m, 1H), 3.79 - 3.70 (m, 1H), 3.36 - 3.32 (m, 1H), 2.21 - 2.17 (m, 4H), 2.15 - 2.05 (m, 1H).

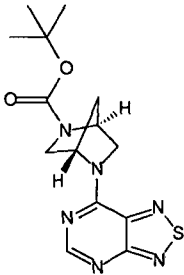
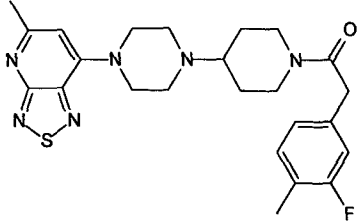
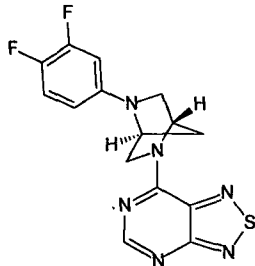
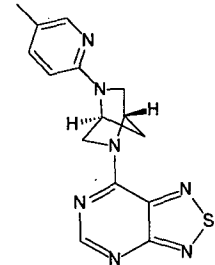
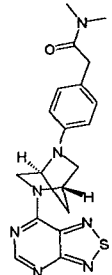
197		A		2,24	7-[(1S,4S)-5-(4-Chloro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo[3,4-d]pyrimidine	¹ H NMR (400 MHz, DMSO) ppm = 8.47 (d, J=16.1, 1H), 7.20 - 7.11 (m, 2H), 6.71 - 6.61 (m, 2H), 6.18 - 5.31 (m, 1H), 4.77 (d, J=23.1, 1H), 4.28 - 4.12 (m, 1H), 3.86 - 3.68 (m, 2H), 3.25 - 3.14 (m, 1H), 2.19 (d, J=33.0, 2H).
198		A		2,12	7-((1S,4S)-5-Phenyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-[1,2,5]thiadiazolo[3,4-d]pyrimidine	¹ H NMR (500 MHz, DMSO-d ₆) ppm = 8.52 (d, J=31.3, 1H), 7.20 - 7.08 (m, 2H), 6.69 - 6.57 (m, 3H), 6.18 - 5.32 (m, 1H), 4.85 - 4.68 (m, 1H), 4.35 - 4.09 (m, 1H), 3.93 - 3.66 (m, 2H), 3.26 - 3.15 (m, 1H), 2.30 - 2.21 (m, 1H), 2.20 - 2.13 (m, 1H).
199		D		1,60	1-(5-Amino-[1,2,5]thiadiazolo[3,4-d]pyrimidin-7-yl)-piperidine-4-carboxylic acid (5-methyl-pyridin-2-yl)-amide	
200		B		2,11	1-[4-(1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidin-4-ylmethyl)-phenyl]-imidazolidin-2-one	¹ H NMR (500 MHz, DMSO) ppm = 8.49 (s, 1H), 7.49 - 7.39 (m, 2H), 7.15 - 7.03 (m, 2H), 6.83 (s, 1H), 5.80 (d, J=12.1, 1H), 5.09 (d, J=11.1, 1H), 3.85 - 3.77 (m, 2H), 3.47 (s, 1H), 3.42 - 3.35 (m, 2H), 3.06 (s, 1H), 2.51 (s, 2H), 2.02 - 1.89 (m,
201		A		0,38	1-(5-Methyl-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidine-4-carboxylic acid (5-methyl-pyridin-2-yl)-amide	¹ H NMR (400 MHz, DMSO) ppm = 10.39 (s, 1H), 8.14 (d, J=2.3, 1H), 7.97 (d, J=8.4, 1H), 7.57 (dd, J=8.5, 2.3, 1H), 6.70 (s, 1H), 4.85 - 4.75 (m, 2H), 3.29 - 3.15 (m, 2H), 2.94 - 2.82 (m, 1H), 2.54 (s, 3H), 2.24 (s, 3H), 2.00 - 1.91 (m, 2H), 1.85

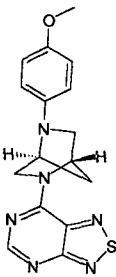
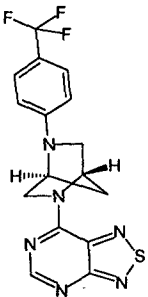
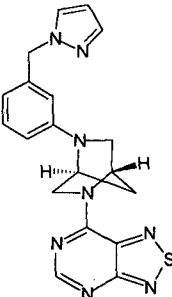
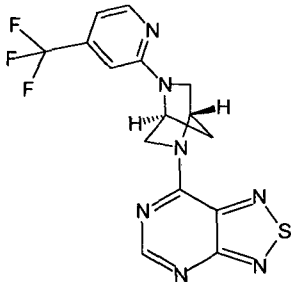
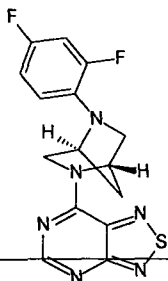
202		A		2,23	1- [1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid (5-trifluoromethylpyridin-2-yl)-amide	
203		A		2,08	7-[(1S,4S)-5-(4-Fluoro-phenyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo[3,4-d]pyrimidine	1H NMR (500 MHz, DMSO) ppm = 8.46 (d, J=21.6, 1H), 7.01 - 6.95 (m, 2H), 6.69 - 6.59 (m, 2H), 6.09 (s, 1H), 4.82 - 4.64 (m, 1H), 4.29 - 4.11 (m, 1H), 3.87 - 3.66 (m, 2H), 3.20 - 3.12 (m, 1H), 2.29 - 2.07 (m, 2H).
204		C		2,12	1- [1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid 3-chlorobenzylamide	1H NMR (500 MHz, DMSO) ppm = 8.57 (s, 1H), 8.48 - 8.41 (m, 1H), 7.39 - 7.26 (m, 3H), 7.23 - 7.16 (m, 1H), 5.77 (s, 1H), 5.08 (s, 1H), 4.27 (d, J=5.9, 2H), 3.74 - 3.65 (m, 1H), 3.24 (s, 1H), 2.75 - 2.65 (m, 1H), 1.99 (d, J=12.4, 2H), 1.79 - 1.7
205		A		1,79	1- [1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid quinolin-2-ylamide	1H NMR (500 MHz, DMSO) ppm = 10.88 (s, 1H), 8.54 (s, 1H), 8.39 - 8.24 (m, 2H), 7.90 (d, J=8.0, 1H), 7.81 (d, J=8.4, 1H), 7.74 - 7.67 (m, 1H), 7.52 - 7.45 (m, 1H), 5.82 (s, 1H), 5.13 (s, 1H), 3.76 - 3.58 (m, 1H), 3.29 - 3.22 (m, 1H), 3.11 - 3.0
206		C		2,06	1- [1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid 2,4,5-trifluorobenzylamide	1H NMR (400 MHz, DMSO) ppm = 8.57 (s, 1H), 8.46 - 8.38 (m, 1H), 7.57 - 7.45 (m, 1H), 7.39 - 7.27 (m, 1H), 5.75 (s, 1H), 5.05 (s, 1H), 4.26 (d, J=5.6, 2H), 3.69 (s, 1H), 3.27 (s, 1H), 2.76 - 2.63 (m, 1H), 1.98 (d, J=12.7, 2H), 1.72 (s, 2H).

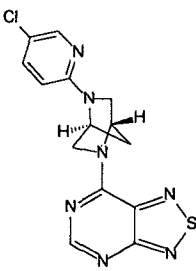
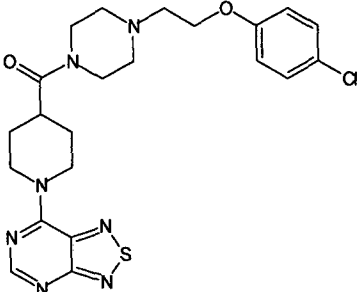
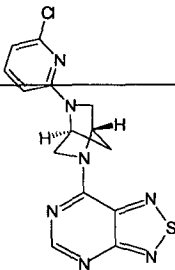
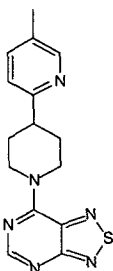
207		A		2,05	1- [1,2,5]Thiadiazolo [3,4-d]pyrimidin- 7-yl-piperidine-4- carboxylic acid (2-hydroxy- quinolin-3-yl)- amide	¹ H NMR (500 MHz, DMSO) ppm = 12.26 (s, 1H), 9.48 (s, 1H), 8.68 (s, 1H), 8.64 (s, 1H), 7.64 - 7.58 (m, 1H), 7.44 - 7.35 (m, 1H), 7.30 (d, J=8.1, 1H), 7.23 - 7.14 (m, 1H), 5.88 - 5.80 (m, 1H), 5.17 (d, J=13.8, 1H), 3.81 - 3.72 (m, 1H), 3.41 - 3.
208		D		2,16	1-(5-Methyl- [1,2,5]thiadiazolo [3,4-b]pyridin-7- yl)-piperidine-4- carboxylic acid 2,4,5-trifluoro- benzylamide	
209		A		2,37	7-[(1S,4S)-5-(4- Chloro-phenyl)- 2,5-diaza- bicyclo[2.2.1]hept -2-yl]-5-methyl- [1,2,5]thiadiazolo [3,4-d]pyrimidine	¹ H NMR (500 MHz, DMSO) ppm = 7.15 (dd, J=9.0, 2.6, 2H), 6.70 - 6.63 (m, 2H), 6.10 - 5.41 (m, 1H), 4.75 (d, J=37.4, 1H), 4.24 - 4.09 (m, 1H), 3.82 - 3.76 (m, 1H), 3.75 - 3.68 (m, 1H), 3.20 - 3.13 (m, 1H), 2.46 (d, J=34.9, 3H), 2.26 - 2.18 (m, 1H)
210		B		2,17	7-[(1S,4S)-5-(4- Fluoro-phenyl)- 2,5-diaza- bicyclo[2.2.1]hept -2-yl]-5-methyl- [1,2,5]thiadiazolo [3,4-d]pyrimidine	¹ H NMR (500 MHz, DMSO) ppm = 7.02 - 6.94 (m, 2H), 6.68 - 6.60 (m, 2H), 6.11 - 5.40 (m, 1H), 4.79 - 4.65 (m, 1H), 4.24 - 4.10 (m, 1H), 3.84 - 3.68 (m, 2H), 3.17 - 3.09 (m, 1H), 2.50 - 2.40 (m, 3H), 2.27 - 2.07 (m, 2H).
211		A		2,38	7-[(1S,4S)-5-(4- Chloro-phenyl)- 2,5-diaza- bicyclo[2.2.1]hept -2-yl]- [1,2,5]thiadiazolo [3,4-d]pyrimidin- 5-ylamine	¹ H NMR (500 MHz, DMSO) ppm = 8.49 - 7.98 (m, 1H), 7.88 - 7.38 (m, 1H), 7.21 - 7.15 (m, 2H), 6.72 - 6.64 (m, 2H), 6.13 - 5.33 (m, 1H), 4.77 (d, J=35.3, 1H), 4.27 - 4.09 (m, 1H), 3.84 - 3.78 (m, 1H), 3.78 - 3.69 (m, 1H), 3.25 - 3.15 (m, 1H), 2.29

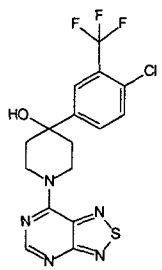
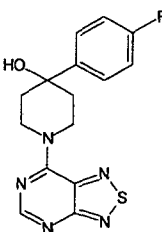
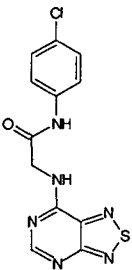
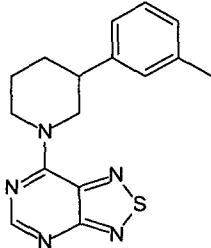
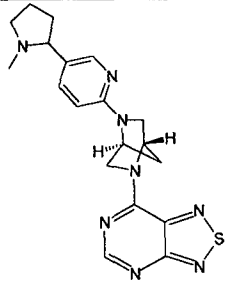
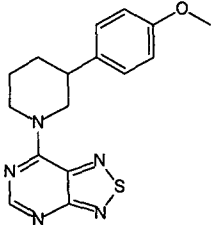
212		A		1,71	7-[(1S,4S)-5-(4-Fluoro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo[3,4-d]pyrimidin-5-ylamine	¹ H NMR (500 MHz, DMSO) ppm = 7.03 - 6.93 (m, 2H), 6.68 (s, 1H), 6.66 - 6.58 (m, 3H), 6.05 (s, 1H), 4.70 (s, 1H), 4.18 - 4.03 (m, 1H), 3.76 (dd, J=9.3, 2.0, 1H), 3.70 (d, J=2.2, 1H), 3.18 - 3.04 (m, 1H), 2.22 - 2.04 (m, 2H).
213		A		2,53	7-[(1S,4S)-5-(4-Chloro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-5-methyl-[1,2,5]thiadiazolo[3,4-b]pyridine	¹ H NMR (400 MHz, DMSO) ppm = 7.18 (d, J=8.1, 2H), 6.72 - 6.64 (m, 2H), 7.03 - 6.52 (m, 1H), 6.34 - 5.28 (m, 1H), 4.91 - 4.80 (m, 1H), 4.45 - 4.20 (m, 1H), 3.96 - 3.62 (m, 2H), 3.24 - 3.18 (m, 1H), 2.62 - 2.53 (m, 3H), 2.35 - 2.19 (m, 2H).
214		A		2,36	7-[(1S,4S)-5-(4-Fluoro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-5-methyl-[1,2,5]thiadiazolo[3,4-b]pyridine	¹ H NMR (500 MHz, DMSO) ppm = 7.07 - 6.53 (m, 3H), 6.70 - 6.62 (m, 2H), 6.32 - 5.29 (m, 1H), 4.86 - 4.79 (m, 1H), 4.46 - 4.22 (m, 1H), 3.95 - 3.72 (m, 2H), 3.69 - 3.13 (m, 1H), 2.64 - 2.53 (m, 3H), 2.34 - 2.18 (m, 2H).
215		A		1,49	1-(5-Methyl-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidine-4-carboxylic acid quinolin-2-ylamide	¹ H NMR (400 MHz, DMSO) ppm = 10.85 (s, 1H), 8.37 - 8.26 (m, 2H), 7.94 - 7.85 (m, 1H), 7.85 - 7.78 (m, 1H), 7.75 - 7.66 (m, 1H), 7.53 - 7.42 (m, 1H), 6.72 (s, 1H), 4.86 - 4.78 (m, 2H), 3.29 - 3.20 (m, 2H), 3.03 - 2.93 (m, 1H), 2.55 (s, 3H), 2.0
216		C		1,59	5-Methyl-7-((1S,4S)-5-phenyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-[1,2,5]thiadiazolo[3,4-b]pyridine	¹ H NMR (500 MHz, DMSO) ppm = 7.19 - 7.03 (m, 2H), 6.70 - 6.51 (m, 3H), 6.17 (s, 1H), 4.74 (s, 1H), 4.28 (s, 1H), 3.73 (s, 2H), 3.43 (s, 1H), 3.18 - 2.99 (m, 1H), 2.48 - 2.40 (m, 3H), 2.23 - 2.11 (m, 2H).

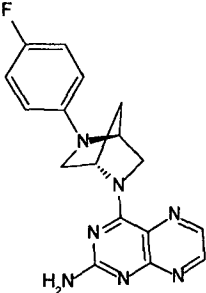
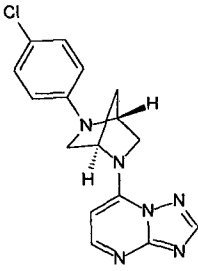
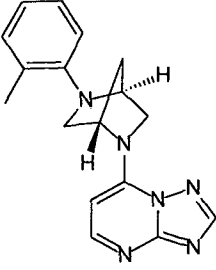
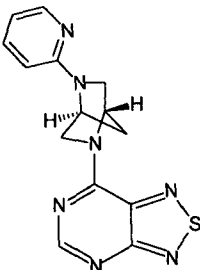
217		C		1,33	{4-[2-(4-Chloro-phenoxy)-ethyl]-piperazin-1-yl}-[1-(5-methyl-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidin-4-yl]-methanone	¹ H NMR (500 MHz, DMSO) ppm = 7.37 - 7.25 (m, 2H), 7.04 - 6.91 (m, 2H), 6.66 (s, 1H), 4.85 - 4.67 (m, 2H), 4.09 (t, J=5.6, 2H), 3.57 (t, J=5.0, 2H), 3.50 - 3.43 (m, 2H), 3.36 (d, J=1.5, 2H), 3.29 - 3.28 (m, 2H), 3.12 - 2.96 (m, 1H), 2.72 (t, J=5
218		A		1,89	3-(4-Fluoro-phenyl)-1-[1'-(5-methyl-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-[4,4']bipiperidinyl-1-yl]-propan-1-one	¹ H NMR (500 MHz, DMSO) ppm = 7.30 - 7.22 (m, 2H), 7.12 - 7.03 (m, 2H), 6.64 (s, 1H), 4.81 (d, J=12.8, 2H), 4.47 - 4.39 (m, 1H), 3.90 - 3.83 (m, 1H), 3.11 - 3.02 (m, 2H), 2.93 - 2.75 (m, 3H), 2.63 - 2.50 (m, 5H), 2.47 - 2.36 (m, 1H), 1.83 - 1.75
219		A		1,72	1-(5-Methyl-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidine-4-carboxylic acid (2-hydroxy-quinolin-3-yl)-amide	
220		A		2,13	7-[(1S,4S)-5-(3-Fluoro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo[3,4-d]pyrimidine	¹ H NMR (400 MHz, DMSO) ppm = 8.47 (d, J=15.5, 1H), 7.20 - 7.08 (m, 1H), 6.54 - 6.32 (m, 3H), 6.11 (s, 1H), 4.86 - 4.74 (m, 1H), 4.28 - 4.13 (m, 1H), 3.86 - 3.68 (m, 2H), 3.27 - 3.17 (m, 1H), 2.23 (s, 1H), 2.15 (s, 1H).
221		C		1,80	1-(5-Methyl-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidine-4-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide	

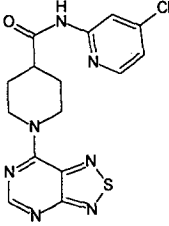
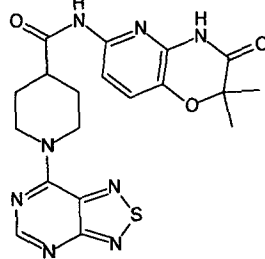
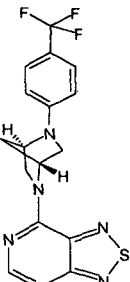
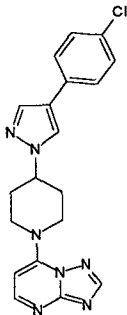
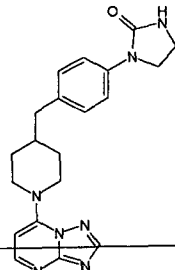
222		E		2,00	(1S,4S)-5-[(1,2,5)thiadiazolo[3,4-d]pyrimidin-7-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester	
223		E		1,48	2-(3-Fluoro-4-methyl-phenyl)-1-{4-[4-(5-methyl-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperazin-1-yl]-piperidin-1-yl}-ethanone	
224		A		2,17	7-[(1S,4S)-5-(3,4-Difluoro-phenyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo[3,4-d]pyrimidine	1H NMR (400 MHz, DMSO) ppm = 8.47 (d, J=13.9, 1H), 7.29 - 7.02 (m, 1H), 6.82 - 6.59 (m, 1H), 6.51 - 6.32 (m, 1H), 6.10 (s, 1H), 4.76 (d, J=22.7, 1H), 4.36 - 4.09 (m, 2H), 3.86 - 3.65 (m, 2H), 2.18 (d, J=33.8, 2H).
225		A		1,09	7-[(1S,4S)-5-(5-Methyl-pyridin-2-yl)-2,5-diazabicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo[3,4-d]pyrimidine	1H NMR (400 MHz, DMSO) ppm = 8.47 (d, J=18.1, 1H), 7.89 (s, 1H), 7.37 - 7.28 (m, 1H), 6.54 - 6.45 (m, 1H), 6.11 (s, 1H), 4.98 (d, J=14.8, 1H), 4.30 - 4.05 (m, 1H), 3.90 - 3.62 (m, 2H), 3.47 - 3.36 (m, 1H), 2.21 (s, 1H), 2.13 (s, 1H), 2.10 (d,
226		C		1,69	N,N-Dimethyl-2-[4-((1S,4S)-5-[(1,2,5)thiadiazolo[3,4-d]pyrimidin-7-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl)-phenyl]-acetamide	

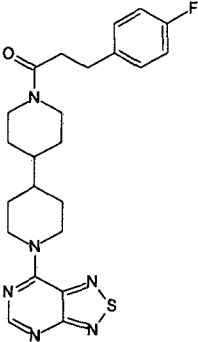
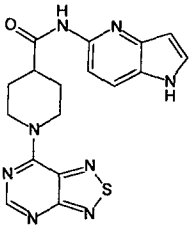
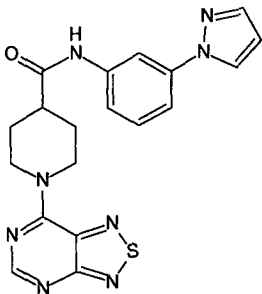
227		A		1,94	7-[(1S,4S)-5-(4-Methoxy-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo [3,4-d]pyrimidine	¹ H NMR (500 MHz, DMSO) ppm = 8.48 (s, 1H), 6.81 - 6.74 (m, 2H), 6.67 - 6.56 (m, 2H), 6.08 (s, 1H), 4.72 (s, 1H), 4.26 - 4.13 (m, 1H), 3.83 - 3.70 (m, 2H), 3.63 (d, J=6.3, 3H), 3.10 (dd, J=16.1, 9.1, 1H), 2.27 - 2.08 (m, 2H).
228		A		2,34	7-[(1S,4S)-5-(4-Trifluoromethyl-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo [3,4-d]pyrimidine	¹ H NMR (500 MHz, DMSO) ppm = 8.47 (d, J=20.5, 1H), 7.43 (dd, J=8.9, 3.1, 2H), 6.81 - 6.74 (m, 2H), 6.15 - 5.43 (m, 1H), 4.94 - 4.81 (m, 1H), 4.28 (dd, J=11.5, 1.8, 1H), 3.91 - 3.81 (m, 1H), 3.80 - 3.70 (m, 1H), 3.29 (d, J=9.3, 1H), 2.26 (s, 1H).
229		A		1,91	7-[(1S,4S)-5-(3-Pyrazol-1-ylmethyl-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo [3,4-d]pyrimidine	¹ H NMR (500 MHz, DMSO) ppm = 8.46 (d, J=23.7, 1H), 7.75 (d, J=2.2, 1H), 7.42 (t, J=1.6, 1H), 7.08 (td, J=7.9, 2.5, 1H), 6.67 - 6.50 (m, 2H), 6.46 - 6.37 (m, 1H), 6.30 - 6.19 (m, 1H), 6.14 - 5.44 (m, 1H), 5.28 - 5.11 (m, 2H), 4.73 (d, J=33.5, 1H).
230		A		2,10	7-[(1S,4S)-5-(4-Trifluoromethyl-pyridin-2-yl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo [3,4-d]pyrimidine	¹ H NMR (500 MHz, DMSO-d ₆) ppm = 8.51 - 8.44 (m, 1H), 8.28 (t, J=5.6, 1H), 6.86 - 6.75 (m, 2H), 6.17 - 5.40 (m, 1H), 5.16 (d, J=12.9, 1H), 4.35 - 4.13 (m, 1H), 3.92 - 3.80 (m, 1H), 3.78 - 3.69 (m, 1H), 3.56 (dd, J=27.3, 9.9, 1H), 2.28 - 2.10 (m, 2H).
231		A		2,17	7-[(1S,4S)-5-(2,4-Difluoro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo [3,4-d]pyrimidine	¹ H NMR (500 MHz, DMSO-d ₆) ppm = 8.47 (d, J=9.0, 1H), 7.14 - 7.04 (m, 1H), 6.97 - 6.84 (m, 2H), 6.08 - 5.39 (m, 1H), 4.73 - 4.59 (m, 1H), 4.33 - 4.23 (m, 1H), 3.95 - 3.79 (m, 2H).

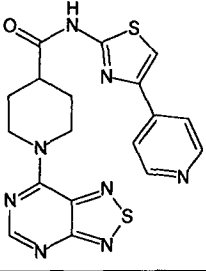
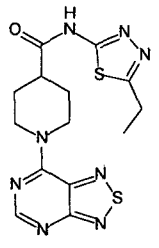
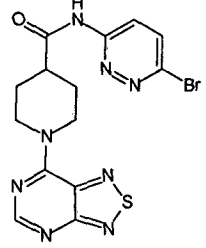
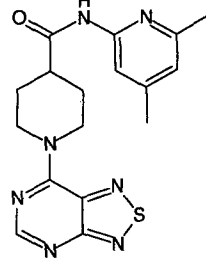
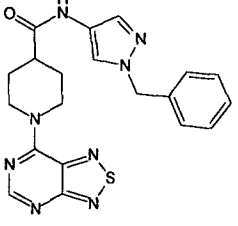
						3.35 - 3.29 (m, 1H), 2.25 - 2.16 (m, 1H), 2.12 (s, 1H).
232		A		1,86	7-[(1S,4S)-5-(5-Chloro-pyridin-2-yl)-2,5-diazabicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo[3,4-d]pyrimidine	
233		A		1,50	4-[2-(4-Chlorophenoxy)-ethyl]-piperazin-1-yl-(1-[1,2,5]thiadiazolo[3,4-d]pyrimidin-7-yl-piperidin-4-yl)-methanone	1H NMR (500 MHz, DMSO-d6) ppm = 8.51 (s, 1H), 7.36 - 7.26 (m, 2H), 7.02 - 6.92 (m, 2H), 5.80 - 5.72 (m, 1H), 5.07 (s, 1H), 4.10 (t, J=5.7, 2H), 3.65 (d, J=20.7, 1H), 3.61 - 3.55 (m, 2H), 3.49 - 3.43 (m, 2H), 3.34 - 3.21 (m, 1H), 3.21 - 3.09 (m, 1H), 2.73 (t, J=5.7, 2H), 2.56 - 2.50 (m, 2H), 2.47 - 2.41 (m, 2H), 1.89 - 1.82 (m, 2H), 1.78 - 1.53 (m, 2H).
234		C		2,12	7-[(1S,4S)-5-(6-Chloro-pyridin-2-yl)-2,5-diazabicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo[3,4-d]pyrimidine	
235		E		1,23	5-Methyl-1'-[1,2,5]thiadiazolo[3,4-d]pyrimidin-7-yl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl	

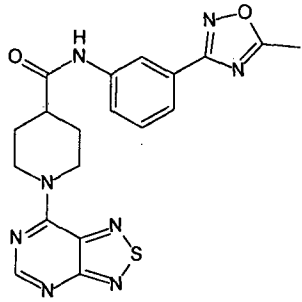
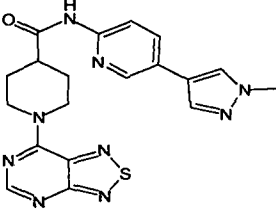
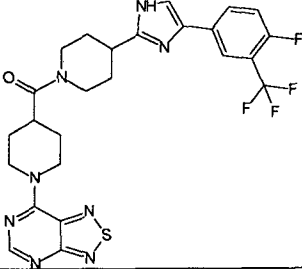
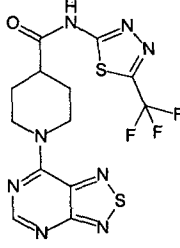
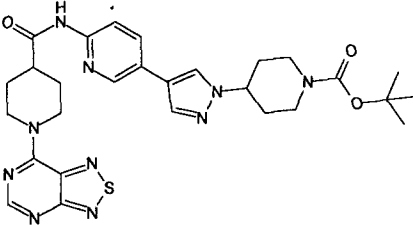
236		E		2,29	4-(4-Chloro-3-trifluoromethyl-phenyl)-1-[1,2,5]thiadiazolo[3,4-d]pyrimidin-7-yl-piperidin-4-ol	
237		E		1,86	4-(4-Fluoro-phenyl)-1-[1,2,5]thiadiazolo[3,4-d]pyrimidin-7-yl-piperidin-4-ol	
238		E		1,84	N-(4-Chloro-phenyl)-2-([1,2,5]thiadiazolo[3,4-d]pyrimidin-7-ylamino)-acetamide	
239		E		2,51	7-(3-m-Tolyl-piperidin-1-yl)-[1,2,5]thiadiazolo[3,4-d]pyrimidine	
240		E		1,08	7-((1S,4S)-5-[5-(1-Methyl-pyrrolidin-2-yl)-pyridin-2-yl]-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-[1,2,5]thiadiazolo[3,4-d]pyrimidine	
241		E		2,32	7-[3-(4-Methoxy-phenyl)-piperidin-1-yl]-[1,2,5]thiadiazolo[3,4-d]pyrimidine	

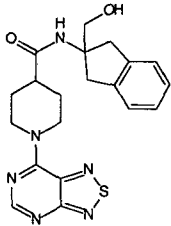
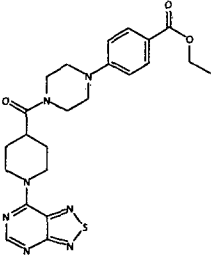
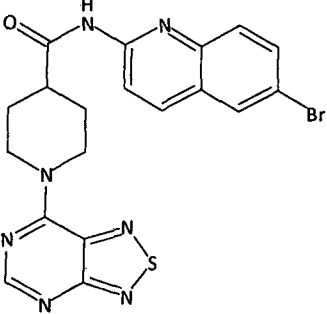
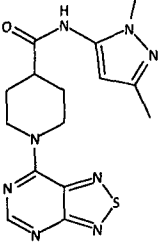
242		A		1,65	4-[(1S,4S)-5-(4-Fluoro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-pteridin-2-ylamine	¹ H NMR (500 MHz, DMSO, rotamers, d-TFA exchanged) ppm = 8.83 (d, J = 2.3 Hz, 0.5H), 8.76 (t, J = 2.0 Hz, 1H), 8.67 (d, J = 2.3 Hz, 0.5H), 7.00 (q, J = 8.5 Hz, 2H), 6.72 – 6.62 (m, 2H), 6.48 (s, 0.5H), 5.54 – 5.48 (m, 0.5H), 4.80 – 4.67 (m, 1H), 4.42 – 4.31 (m, 0.5H), 4.29 – 4.21 (m, 0.5H), 3.94 – 3.73 (m, 2H), 3.28 – 3.18 (m, 1H), 2.30– 2.06 (m, 2H).
243		B		2,09	7-[(1R,4R)-5-(4-Chloro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-[1,2,4]triazolo[1,5-a]pyrimidine	¹ H NMR (400 MHz, DMSO-d ₆) ppm = 8.36 (s, 1H), 8.23 (d, J=5.7, 1H), 7.20 – 7.11 (m, 2H), 6.69 – 6.60 (m, 2H), 6.29 (s, 1H), 4.73 (s, 1H), 4.05 (d, J=5.2, 2H), 3.69 (dd, J=9.4, 2.1, 1H), 3.26 – 3.14 (m, 2H), 2.16 (s, 2H).
244		A		2,04	7-((1S,4S)-5-o-Tolyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-[1,2,4]triazolo[1,5-a]pyrimidine	¹ H NMR (500 MHz, DMSO) ppm = 8.38 (s, 1H), 8.25 (d, J = 5.7 Hz, 1H), 7.05 (t, J = 7.4 Hz, 2H), 6.88 (d, J = 8.0 Hz, 1H), 6.75 (t, J = 7.3 Hz, 1H), 6.30 (s, 1H), 4.44 (s, 1H), 4.06 (dd, J = 10.5, 5.3 Hz, 1H), 3.64 (dd, J = 9.4, 2.3 Hz, 1H), 3.36 (d, J = 9.4 Hz, 1H), 3.17 (d, J = 5.2 Hz, 1H), 2.20 (s, 4H), 2.11 (s, 2H).
245		D		1,03	7-((1S,4S)-5-Pyridin-2-yl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-[1,2,5]thiadiazolo[3,4-d]pyrimidine	¹ H NMR (500 MHz, DMSO-d ₆) ppm = 8.51 – 8.44 (m, 1H), 8.07 – 8.03 (m, 1H), 7.51 – 7.45 (m, 1H), 6.61 – 6.52 (m, 2H), 6.15 – 5.46 (m, 1H), 5.08 – 5.01 (m, 1H), 4.31 – 4.13 (m, 1H), 3.90 – 3.75 (m, 1H), 3.74 – 3.68 (m, 1H), 3.51 – 3.42 (m, 1H), 2.24 – 2.21 (m, 1H).

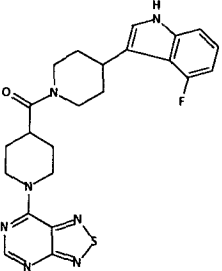
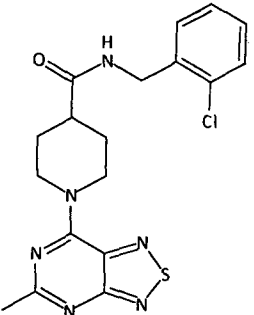
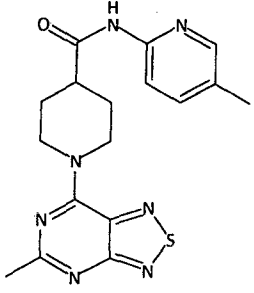
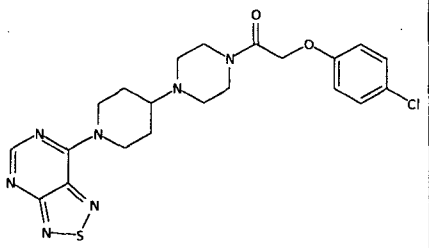
						2.15 (s, 1H).
246		E		1,99	1- [1,2,5]Thiadiazol o[3,4-d]pyrimidin- 7-yl-piperidine-4- carboxylic acid (4-chloro-pyridin- 2-yl)-amide	
247		E		1,81	1- [1,2,5]Thiadiazol o[3,4-d]pyrimidin- 7-yl-piperidine-4- carboxylic acid (2,2-dimethyl-3- oxo-3,4-dihydro- 2H-pyrido[3,2- b][1,4]oxazin-6- yl)-amide	
248		E		2,33	7-[(3R,6R)-5-(4- Trifluoromethyl- phenyl)-2,5- diaz- bicyclo[2.2.1]hept -2-yl]- [1,2,5]thiadiazolo [3,4-d]pyrimidine	
249		C		2,21	7-{4-[4-(4-Chloro- phenyl)-pyrazol- 1-yl]-piperidin-1- yl}- [1,2,4]triazolo[1,5 -a]pyrimidine	¹ H NMR (400 MHz, DMSO-d ₆) ppm = 8.52 (s, 1H), 8.48 (d, J=5.5, 1H), 8.34 (s, 1H), 7.93 (s, 1H), 7.61 (d, J=8.5, 2H), 7.40 (d, J=8.5, 2H), 6.71 (d, J=5.6, 1H), 4.83 - 4.66 (m, 2H), 4.59 (td, J=11.0, 5.4, 1H), 3.51 - 3.36 (m, 2H), 2.30 - 2.08 (m, 4H).
250		D		1,83	1-[4-(1- [1,2,4]Triazolo[1, 5-a]pyrimidin-7- yl-piperidin-4- ylmethyl)- phenyl]- imidazolidin-2- one	

251		A		2,23	3-(4-Fluoro-phenyl)-1-(1'-[1,2,5]thiadiazolo[3,4-d]pyrimidin-7-yl-[4,4']bipiperidin-1-yl)-propan-1-one	¹H NMR (400 MHz, DMSO-d₆) ppm = 8.49 (s, 1H), 7.31 - 7.21 (m, 2H), 7.13 - 7.02 (m, 2H), 5.88 (s, 1H), 5.17 (s, 1H), 4.47 - 4.38 (m, 1H), 3.92 - 3.82 (m, 1H), 3.42 (s, 1H), 3.02 (s, 1H), 2.92 - 2.82 (m, 1H), 2.79 (t, J=7.6, 2H), 2.65 - 2.53 (m, 2H), 2.47 - 2.36 (m, 1H), 1.91 - 1.82 (m, 2H), 1.70 - 1.60 (m, 2H), 1.59 - 1.45 (m, 1H), 1.38 - 1.21 (m, 3H), 1.04 - 0.88 (m, 2H).
252		E		1,31	1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid (1H-pyrrolo[3,2-b]pyridin-5-yl)-amide	
253		A		1,86	1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid (3-pyrazol-1-yl-phenyl)-amide	¹H NMR (400 MHz, DMSO-d₆) ppm = 10.16 (s, 1H), 8.54 (s, 1H), 8.39 (d, J=2.5, 1H), 8.19 (t, J=2.1, 1H), 7.73 (d, J=1.7, 1H), 7.56 - 7.35 (m, 3H), 6.53 (dd, J=2.5, 1.7, 1H), 5.81 (s, 1H), 5.13 (s, 1H), 4.06 (q, J=5.3, 1H), 3.71 (s, 1H), 2.92 - 2.79 (m, 1H), 2.07 (d, J=12.3, 2H), 1.80 (s, 2H).

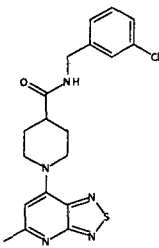
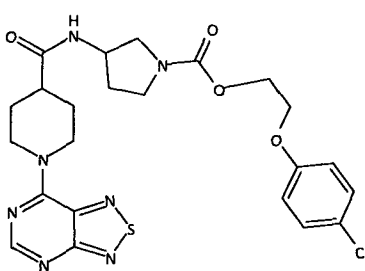
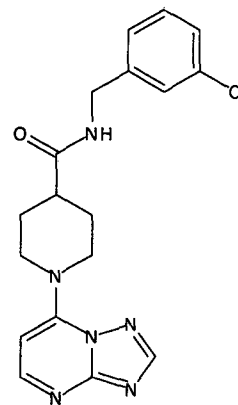
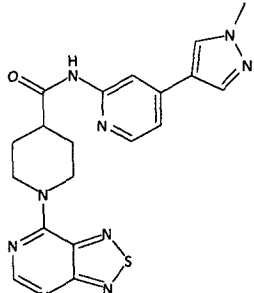
254		B		1,41	1- [1,2,5]Thiadiazol o[3,4-d]pyrimidin- 7-yl-piperidine-4- carboxylic acid (4-pyridin-4-yl- thiazol-2-yl)- amide	¹ H NMR (400 MHz, DMSO-d ₆) ppm = 12.44 (s, 1H), 8.65 - 8.59 (m, 2H), 8.54 (s, 1H), 7.97 (s, 1H), 7.86 - 7.80 (m, 2H), 5.78 (s, 1H), 5.09 (s, 1H), 3.73 (s, 1H), 3.38 (s, 1H), 3.11 - 2.97 (m, 1H), 2.14 - 2.06 (m, 2H), 1.84 - 1.79 (m, 2H).
255		D		1,68	1- [1,2,5]Thiadiazol o[3,4-d]pyrimidin- 7-yl-piperidine-4- carboxylic acid (5-ethyl- [1,3,4]thiadiazol- 2-yl)-amide	¹ H NMR (400 MHz, DMSO-d ₆) ppm = 12.47 (s, 1H), 8.53 (s, 1H), 5.85 - 4.97 (m, 2H), 3.82 - 3.34 (m, 2H), 3.08 - 2.93 (m, 3H), 2.08 (d, J=13.3, 2H), 1.78 (s, 2H), 1.28 (t, J=7.5, 3H).
256		E		1,76	1- [1,2,5]Thiadiazol o[3,4-d]pyrimidin- 7-yl-piperidine-4- carboxylic acid (6-bromo- pyridazin-3-yl)- amide	
257		E		1,46	1- [1,2,5]Thiadiazol o[3,4-d]pyrimidin- 7-yl-piperidine-4- carboxylic acid (4,6-dimethyl- pyridin-2-yl)- amide	
258		E		1,79	1- [1,2,5]Thiadiazol o[3,4-d]pyrimidin- 7-yl-piperidine-4- carboxylic acid (1-benzyl-1H- pyrazol-4-yl)- amide	

259		B		1,89	1- [1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid [3-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-amide	¹ H NMR (400 MHz, DMSO-d ₆) ppm = 10.33 (s, 1H), 8.53 (s, 1H), 8.42 - 8.36 (m, 1H), 7.81 - 7.75 (m, 1H), 7.69 - 7.62 (m, 1H), 7.47 (t, J=7.9, 1H), 5.81 (s, 1H), 5.12 (s, 1H), 3.70 (s, 1H), 3.47 (s, 1H), 2.95 - 2.82 (m, 1H), 2.65 (s, 3H), 2.12 - 2.03 (m, 2H), 1.89 - 1.68 (m, 2H).
260		A		1,63	1- [1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid [5-(1-methyl-1H-pyrazol-4-yl)-pyridin-2-yl]-amide	¹ H NMR (500 MHz, DMSO-d ₆) ppm = 10.53 (s, 1H), 8.59 - 8.50 (m, 2H), 8.16 (s, 1H), 8.06 (d, J=8.6, 1H), 7.93 (dd, J=8.7, 2.4, 1H), 7.89 (s, 1H), 5.89 - 5.74 (m, 1H), 5.19 - 5.05 (m, 1H), 3.86 (s, 3H), 3.72 - 3.60 (m, 1H), 3.26 - 3.17 (m, 1H), 3.03 - 2.94 (m, 1H), 2.10 - 2.00 (m, 2H), 1.87 - 1.69 (m, 2H).
261		E		1,65	{4-[4-(4-Fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-piperidin-1-yl}-(1-[1,2,5]thiadiazolo[3,4-d]pyrimidin-7-yl)piperidin-4-yl)-methanone	
262		E		2,01	1- [1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid (5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-amide	
263		A		2,14	4-(4-{6-[(1-[1,2,5]thiadiazolo[3,4-d]pyrimidin-7-yl)piperidine-4-carboxyl)-amino]pyridin-3-yl}pyrazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester	¹ H NMR (500 MHz, DMSO-d ₆) ppm = 10.54 (s, 1H), 8.58 (dd, J=2.5, 0.8, 1H), 8.53 (s, 1H), 8.32 (s, 1H), 8.09 - 8.03 (m, 1H), 7.98 - 7.89 (m, 2H), 5.80 (s, 1H), 5.12 (s, 1H), 4.41 - 4.31 (m, 1H),

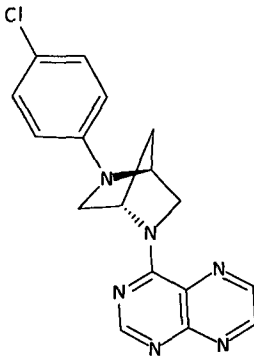
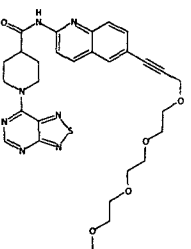
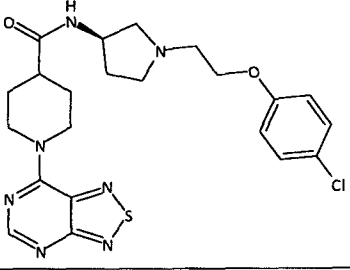
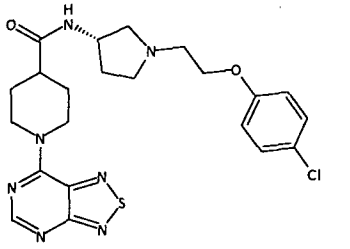
						4.10 - 4.01 (m, 2H), 3.66 (s, 1H), 3.31 - 3.15 (m, 1H), 3.02 - 2.91 (m, 3H), 2.08 - 2.00 (m, 4H), 1.85 - 1.73 (m, 4H), 1.42 (s, 9H).
264		E		1,74	1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid (2-hydroxymethyl-indan-2-yl)-amide	
265			483	2,09	4-[4-(1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carbonyl)-piperazin-1-yl]-benzoic acid ethyl ester	
266		D	470	2,26	1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid (6-bromo-quinolin-2-yl)-amide	1H NMR (400 MHz, DMSO-d6) ppm = 10.94 (s, 1H), 8.53 (s, 1H), 8.32 (s, 2H), 8.19 (d, J=2.3, 1H), 7.82 (dd, J=9.0, 2.3, 1H), 7.74 (d, J=9.0, 1H), 3.24 - 3.17 (m, 1H), 5.96 - 5.64 (m, 1H), 5.28 - 4.98 (m, 1H), 3.81 - 3.53 (m, 1H), 3.08 - 2.97 (m, 1H), 2.19 - 1.99 (m, 2H), 1.94 - 1.66 (m, 2H).
267			359	1,45	1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid (2,5-dimethyl-2H-pyrazol-3-yl)-amide	

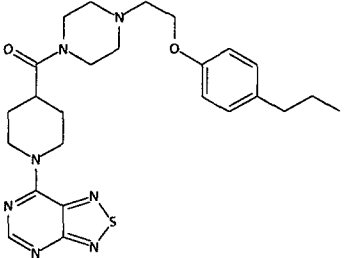
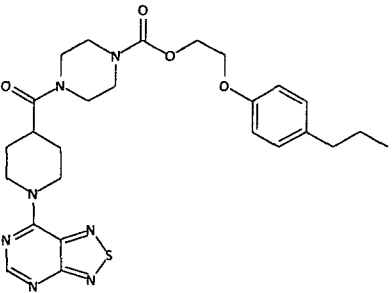
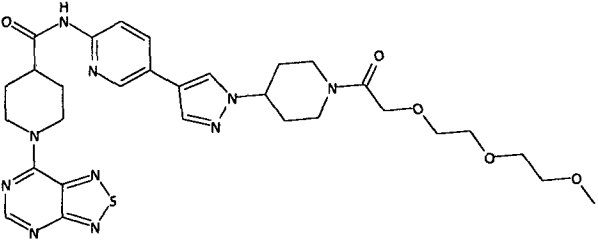
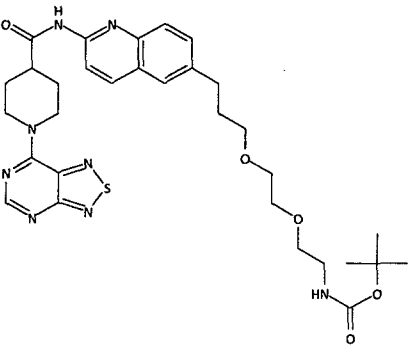
268		B	467	2,12	[4-(4-Fluoro-1H-indol-3-yl)-piperidin-1-yl]-(1-[1,2,5]thiadiazolo[3,4-d]pyrimidin-7-yl)-piperidin-4-yl-methanone	1H NMR (500 MHz, DMSO-d6) ppm = 11.11 (s, 1H), 8.52 (s, 1H), 7.23 - 7.10 (m, 2H), 7.10 - 6.92 (m, 1H), 6.82 - 6.61 (m, 1H), 5.95 - 5.61 (m, 1H), 5.29 - 4.94 (m, 1H), 4.68 - 4.43 (m, 2H), 4.31 - 4.03 (m, 2H), 3.84 - 3.51 (m, 1H), 3.30 - 3.17 (m, 1H), 3.17 - 3.05 (m, 1H), 2.78 - 2.59 (m, 1H), 2.12 - 2.02 (m, 1H), 2.02 - 1.84 (m, 3H), 1.84 - 1.54 (m, 3H), 1.54 - 1.37 (m, 1H).
269		C	404	1,69	1-(5-Methyl-[1,2,5]thiadiazolo[3,4-d]pyrimidin-7-yl)-piperidine-4-carboxylic acid 2-chloro-benzylamide	1H NMR (400 MHz, DMSO-d6) ppm = 8.39 (t, J=5.8, 1H), 7.49 - 7.38 (m, 1H), 7.38 - 7.21 (m, 3H), 6.00 - 5.48 (m, 1H), 5.38 - 4.80 (m, 1H), 4.33 (d, J=5.8, 2H), 3.83 - 3.44 (m, 1H), 3.27 - 3.08 (m, 1H), 2.80 - 2.62 (m, 1H), 2.49 (s, 3H), 2.06 - 1.91 (m, 2H), 1.73 (s, 2H).
270		D	370	1,36	1-(5-Methyl-[1,2,5]thiadiazolo[3,4-d]pyrimidin-7-yl)-piperidine-4-carboxylic acid (5-methyl-pyridin-2-yl)-amide	1H NMR (400 MHz, DMSO-d6) ppm = 10.42 (s, 1H), 8.16 (d, J=2.4, 1H), 7.98 (d, J=8.4, 1H), 7.59 (dd, J=8.5, 2.5, 1H), 6.04 - 5.50 (m, 1H), 5.35 - 4.85 (m, 1H), 3.85 - 3.41 (m, 1H), 3.26 - 3.06 (m, 1H), 3.04 - 2.86 (m, 1H), 2.51 (s, 3H), 2.25 (s, 3H), 2.08 - 1.98 (m, 2H), 1.94 - 1.51 (m, 2H).
271		E	475	1,55	2-(4-Chloro-phenoxy)-1-[4-(1-[1,2,5]thiadiazolo[3,4-d]pyrimidin-7-yl)-piperidin-4-yl]-piperazin-1-yl]-ethanone	

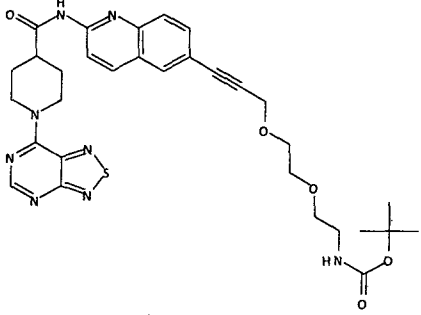
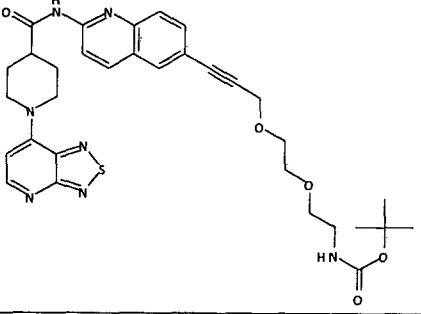
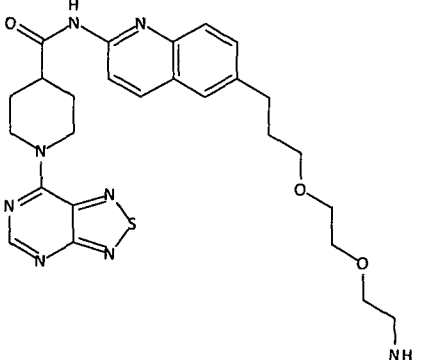
272		C	418	2,24	1- [1,2,5]Thiadiazol o[3,4-d]pyrimidin- 7-yl-piperidine-4- carboxylic acid (6-phenyl-pyridin- 2-yl)-amide	
273		C	388	2,04	1- [1,2,5]Thiadiazol o[3,4-d]pyrimidin- 7-yl-piperidine-4- carboxylic acid (5-tert-butyl- isoxazol-3-yl)- amide	
274		C	422	1,69	1- [1,2,5]Thiadiazol o[3,4-d]pyrimidin- 7-yl-piperidine-4- carboxylic acid [5-(1-methyl-1H- pyrazol-3-yl)- pyridin-2-yl]- amide	1H NMR (500 MHz, DMSO-d6) ppm = 10.60 (s, 1H), 8.80 - 8.65 (m, 1H), 8.53 (s, 1H), 8.10 (d, J=1.6, 2H), 7.74 (d, J=2.2, 1H), 6.72 (d, J=2.3, 1H), 5.98 - 5.41 (m, 1H), 5.28 - 4.74 (m, 1H), 3.88 (s, 3H), 3.75 - 3.59 (m, 1H), 3.25 - 3.17 (m, 1H), 3.07 - 2.91 (m, 1H), 2.16 - 1.97 (m, 2H), 1.91 - 1.60 (m, 2H).
275		A	355	1,76	4-[(1S,4S)-5-(4- Chloro-phenyl)- 2,5-diaza- bicyclo[2.2.1]hept -2-yl]-pteridin-2- ylamine	1H NMR (400 MHz, DMSO-d6) ppm = 8.77 - 8.50 (m, 1H), 8.48 - 8.18 (m, 1H), 7.57 - 7.08 (m, 2H), 7.08 - 6.71 (m, 2H), 6.70 - 6.57 (m, 2H), 6.42 - 5.26 (m, 1H), 4.80 - 4.54 (m, 1H), 4.32 - 2.96 (m, 4H), 2.20 - 2.01 (m, 2H).
276		B	407	1,44	1- [1,2,5]Thiadiazol o[3,4-d]pyrimidin- 7-yl-piperidine-4- carboxylic acid (7-methyl- [1,8]naphthyridin- 2-yl)-amide	1H NMR (500 MHz, DMSO-d6) ppm = 11.03 (s, 1H), 8.54 (s, 1H), 8.35 (d, J=8.8, 1H), 8.31 (d, J=8.8, 1H), 8.24 (d, J=8.2, 1H), 7.40 (d, J=8.2, 1H), 6.14 - 5.46 (m, 1H), 5.40 - 4.66 (m, 1H), 3.85 - 3.59 (m, 1H), 3.33 - 3.12 (m, 1H), 3.12 - 2.99 (m, 1H), 2.66 (s, 3H), 2.20 - 1.98 (m, 2H), 1.96 - 1.61

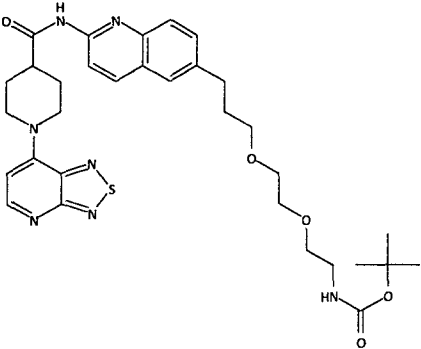
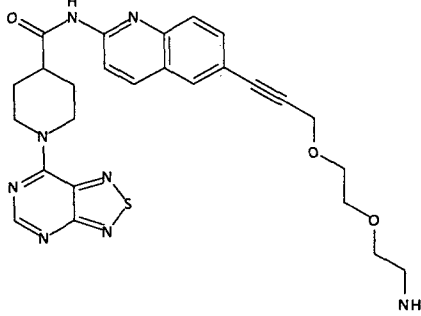
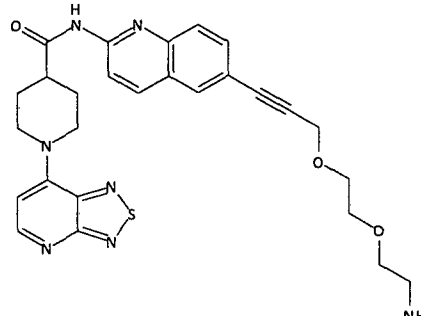
						(m, 2H).
277		A	403	1,61	1-(5-Methyl-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidine-4-carboxylic acid 3-chloro-benzylamide	1H NMR (500 MHz, DMSO-d6) ppm = 8.42 (t, J=6.0, 1H), 7.42 - 7.32 (m, 1H), 7.32 - 7.26 (m, 2H), 7.25 - 7.16 (m, 1H), 6.69 (s, 1H), 4.87 - 4.69 (m, 2H), 4.27 (d, J=6.0, 2H), 3.28 - 3.17 (m, 2H), 2.69 - 2.56 (m, 1H), 2.53 (s, 3H), 1.96 - 1.82 (m, 2H), 1.81 - 1.64 (m, 2H).
278		E	533	2,06	3-[(1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carbonyl)-amino]-pyrrolidine-1-carboxylic acid 2-(4-chlorophenoxy)-ethyl ester	
279		E	372	1,82	1-[1,2,4]Triazolo[1,5-a]pyrimidin-7-yl-piperidine-4-carboxylic acid 3-chloro-benzylamide	1H NMR (500 MHz, DMSO-d6) ppm = 15.70 (s, 1H), 8.82 (s, 1H), 8.52 (d, J=7.0, 1H), 7.38 - 7.26 (m, 3H), 7.26 - 7.18 (m, 1H), 7.05 (d, J=7.1, 1H), 5.16 - 4.85 (m, 2H), 4.34 (s, 2H), 3.79 - 3.57 (m, 2H), 2.90 - 2.74 (m, 1H), 2.14 - 2.02 (m, 2H), 2.02 - 1.88 (m, 2H).
280			422	1,45	1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid [4-(1-methyl-1H-pyrazol-4-yl)-pyridin-2-yl]-amide	

281		D	533	1,58	1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid {1-[2-(4-bromophenoxy)-ethyl]-pyrrolidin-3-yl}-amide
282		E	338	1,39	1-[1,2,4]Triazolo[1,5-a]pyrimidin-7-yl-piperidine-4-carboxylic acid (5-methyl-pyridin-2-yl)-amide
283		C	475	1,63	7-(4-{4-[2-(4-Chloro-phenoxy)-ethyl]-piperazin-1-ylmethyl}-piperidin-1-yl)-[1,2,5]thiadiazolo[3,4-d]pyrimidine
284			501	1,61	4-Amino-3-(4-chloro-phenyl)-1-(1'-[1,2,5]thiadiazolo[3,4-d]pyrimidin-7-yl-[4,4']bipiperidiny-1-yl)-butan-1-one
285		E	655	1,54	(4-{2-[4-(3-{2-[2-(2-Methoxyethoxy)-ethoxy]-ethoxy}-prop-1-ynyl)-phenoxy]-ethyl}-piperazin-1-yl)-(1-[1,2,5]thiadiazolo[3,4-d]pyrimidin-7-yl-piperidin-4-yl)-methanone
286		C	659	1,59	(4-{2-[4-(3-{2-[2-(2-Methoxyethoxy)-ethoxy]-ethoxy}-propyl)-phenoxy]-ethyl}-piperazin-1-yl)-(1-[1,2,5]thiadiazolo[3,4-d]pyrimidin-7-yl-piperidin-4-yl)-methanone

287		A	340	1,98	4-[(1S,4S)-5-(4-Chloro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-pteridine	¹ H NMR (400 MHz, DMSO-d ₆) ppm = 9.14 - 8.92 (m, 1H), 8.92 - 8.68 (m, 1H), 8.68 - 8.43 (m, 1H), 7.24 - 7.04 (m, 2H), 6.77 - 6.55 (m, 2H), 6.43 - 5.39 (m, 1H), 4.77 - 4.65 (m, 1H), 4.38 - 3.65 (m, 3H), 3.21 - 3.14 (m, 1H), 2.22 - 2.02 (m, 2H).
288		A	593	2,21	1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid [6-(3-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-prop-1-ynyl)-quinolin-2-yl]-amide	¹ H NMR (500 MHz, DMSO-d ₆) ppm = 10.98 (s, 1H), 8.57 (s, 1H), 8.32 (s, 2H), 8.07 (d, J=1.8, 1H), 7.78 (d, J=8.7, 1H), 7.70 (dd, J=8.7, 1.9, 1H), 5.92 - 5.73 (m, 1H), 5.22 - 5.05 (m, 1H), 4.45 (s, 2H), 3.76 - 3.69 (m, 1H), 3.69 - 3.65 (m, 2H), 3.61 - 3.58 (m, 2H), 3.55 - 3.50 (m, 6H), 3.44 - 3.41 (m, 2H), 3.33 - 3.25 (m, 1H), 3.23 (s, 3H), 3.12 - 3.02 (m, 1H), 2.16 - 2.05 (m, 2H), 1.92 - 1.69 (m, 2H).
289		D	489	1,48	1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid {(R)-1-[2-(4-chloro-phenoxy)-ethyl]-pyrrolidin-3-yl}-amide	
290		D	489	1,48	1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid {(S)-1-[2-(4-chloro-phenoxy)-ethyl]-pyrrolidin-3-yl}-amide	

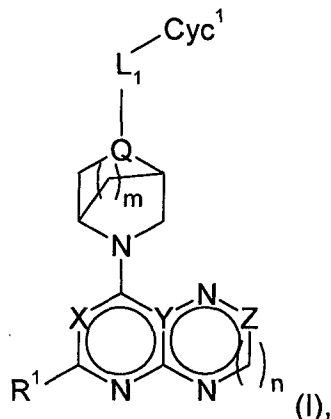
291		D	497	1,78	{4-[2-(4-Propylphenoxy)-ethyl]-piperazin-1-yl}-(1-[1,2,5]thiadiazolo[3,4-d]pyrimidin-7-yl-piperidin-4-yl)-methanone	
292		D	541	2,37	4-(1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carbonyl)-piperazine-1-carboxylic acid 2-(4-propylphenoxy)-ethyl ester	
293			652	1,70	1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid {5-[1-(1-{2-[2-(2-methoxy-ethoxy)-ethoxy]-acetyl}-piperidin-4-yl)-1H-pyrazol-4-yl]-pyridin-2-yl]-amide	
294		C	638	2,35	{2-[2-(3-{2-[(1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carbonyl)-amino]-quinolin-6-yl}-propoxy)-ethoxy]-ethyl}-carbamic acid tert-butyl ester	¹ H NMR (500 MHz, DMSO-d ₆) ppm = 10.82 (s, 1H), 8.54 (s, 1H), 8.24 (s, 2H), 7.73 (d, J=8.6, 1H), 7.70 - 7.66 (m, 1H), 7.58 (dd, J=8.6, 2.0, 1H), 6.75 - 6.67 (m, 1H), 5.89 - 5.76 (m, 1H), 5.20 - 5.05 (m, 1H), 3.74 - 3.61 (m, 1H), 3.54 - 3.47 (m, 4H), 3.45 - 3.37 (m, 4H), 3.28 - 3.17 (m, 1H), 3.10 - 2.99 (m, 3H), 2.79 (t, J=7.7, 2H), 2.13 - 2.04 (m, 2H), 1.93 - 1.69 (m, 4H), 1.35 (s, 9H).

295		A	634	2,48	{2-[2-(3-{2-[(1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl)-piperidine-4-carbonyl]-amino}-quinolin-6-yl)-prop-2-ynoxy]-ethoxy]-ethyl}-carbamic acid tert-butyl ester	¹ H NMR (500 MHz, DMSO-d ₆) ppm = 10.97 (s, 1H), 8.54 (s, 1H), 8.32 (s, 2H), 8.06 (d, J=1.8, 1H), 7.78 (d, J=8.7, 1H), 7.70 (dd, J=8.7, 1.9, 1H), 6.77 - 6.71 (m, 1H), 5.88 - 5.76 (m, 1H), 5.20 - 5.06 (m, 1H), 4.45 (s, 2H), 3.68 - 3.64 (m, 2H), 3.60 - 3.55 (m, 2H), 3.41 (t, J=6.1, 2H), 3.31 - 3.23 (m, 2H), 3.12 - 3.03 (m, 3H), 2.13 - 2.05 (m, 2H), 1.89 - 1.72 (m, 2H), 1.37 (s, 9H).
296		A	633	2,43	{2-[2-(3-{2-[(1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl)-piperidine-4-carbonyl]-amino}-quinolin-6-yl)-prop-2-ynoxy]-ethoxy]-ethyl}-carbamic acid tert-butyl ester	¹ H NMR (500 MHz, DMSO-d ₆) ppm = 10.96 (s, 1H), 8.59 (d, J=5.4, 1H), 8.32 (s, 2H), 8.06 (d, J=1.8, 1H), 7.78 (d, J=8.7, 1H), 7.70 (dd, J=8.7, 1.9, 1H), 6.78 - 6.72 (m, 2H), 4.90 - 4.82 (m, 2H), 4.45 (s, 2H), 3.68 - 3.64 (m, 2H), 3.59 - 3.55 (m, 2H), 3.41 (t, J=6.1, 2H), 3.35 - 3.26 (m, 2H), 3.08 (q, J=6.0, 2H), 3.04 - 2.96 (m, 1H), 2.06 - 2.00 (m, 2H), 1.87 - 1.77 (m, 2H), 1.37 (s, 9H).
297		E	538	1,83	1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid (6-{3-[2-(2-amino-ethoxy)-ethoxy]-propyl}-quinolin-2-yl)-amide	¹ H NMR (500 MHz, DMSO-d ₆) ppm = 10.82 (s, 1H), 8.54 (s, 1H), 8.34 - 8.16 (m, 2H), 7.74 (d, J=8.6, 1H), 7.71 - 7.64 (m, 1H), 7.58 (d, J=8.7, 1H), 5.97 - 5.68 (m, 1H), 5.26 - 4.96 (m, 1H), 3.79 - 3.32 (m, 10H), 3.12 - 2.99 (m, 1H), 2.84 - 2.74 (m, 2H), 2.73 - 2.61 (m, 2H), 2.40 - 2.13 (m, 2H), 2.13 - 2.01 (m, 2H), 1.94 - 1.69 (m, 4H).

298		B	637	2,30	{2-[2-(3-{2-[(1-[1,2,5]Thiadiazol-4-yl)-piperidin-4-carbonyl]-amino}-propoxy)-ethoxy]-ethyl}-carbamic acid tert-butyl ester	¹ H NMR (500 MHz, DMSO-d ₆) ppm = 10.80 (s, 1H), 8.59 (d, J=5.4, 1H), 8.28 - 8.22 (m, 2H), 7.73 (d, J=8.6, 1H), 7.69 - 7.67 (m, 1H), 7.58 (dd, J=8.6, 2.0, 1H), 6.77 (d, J=5.5, 1H), 6.72 - 6.68 (m, 1H), 4.91 - 4.83 (m, 2H), 3.54 - 3.47 (m, 4H), 3.45 - 3.37 (m, 4H), 3.35 - 3.24 (m, 2H), 3.10 - 3.03 (m, 2H), 3.02 - 2.95 (m, 1H), 2.79 (t, J=7.7, 2H), 2.06 - 1.99 (m, 2H), 1.92 - 1.78 (m, 4H), 1.36 (s, 9H).
299		E	534	1,89	1-[1,2,5]Thiadiazol-4-yl-piperidine-4-carboxylic acid (6-{3-[2-(2-amino-ethoxy)-ethoxy]-prop-1-ynyl}-quinolin-2-yl)-amide	¹ H NMR (500 MHz, DMSO-d ₆) ppm = 10.97 (s, 1H), 8.55 (s, 1H), 8.37 - 8.30 (m, 2H), 8.05 (d, J=1.9, 1H), 7.85 - 7.66 (m, 5H), 5.93 - 5.73 (m, 1H), 5.25 - 5.04 (m, 1H), 4.47 (s, 2H), 3.74 - 3.59 (m, 8H), 3.11 - 3.03 (m, 1H), 3.00 (h, J=5.7, 2H), 2.14 - 2.05 (m, 2H), 1.90 - 1.71 (m, 2H).
300		D	533	1,87	1-[1,2,5]Thiadiazol-4-yl-piperidine-4-carboxylic acid (6-{3-[2-(2-amino-ethoxy)-ethoxy]-prop-1-ynyl}-quinolin-2-yl)-amide	¹ H NMR (500 MHz, DMSO-d ₆) ppm = 11.00 (s, 1H), 8.57 (d, J=6.8, 1H), 8.37 - 8.30 (m, 2H), 8.06 (d, J=1.8, 1H), 7.90 - 7.66 (m, 5H), 6.99 (d, J=6.9, 1H), 5.22 - 5.00 (m, 2H), 4.47 (s, 2H), 3.73 - 3.58 (m, 8H), 3.15 - 3.05 (m, 1H), 3.00 (h, J=5.6, 2H), 2.20 - 2.08 (m, 2H), 1.96 - 1.84 (m, 2H).

Claims

5 1. A compound of Formula (I)



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

X is CH or N,

10 Y is C, CH or N,

Z is CH or S,

provided that, if Z is S then Y is not N,

Q is N or $\mathbb{C}R^2$,

n is 0 or 1,

15 m is 0, 1 or 2,

R^1 is H, LA, NH_2 , $NH(LA)$ or $N(LA)_2$,

R^2 is H, OH, Hal or NH_2 ,

L₁, L₂ are independently CO, NH, -CONH, -HNCO, -CO(LA), -(LA)CO, -N(LA), LA, or a bond,

20 Cyc¹ is a mono- or binuclear, aliphatic or aromatic, 4, 5, 6, 7, 8, 9 or 10 membered homo- or heterocycle, having 0, 1, 2, 3 or 4 N, O and/or S atoms, which may be mono- or independently di- or trisubstituted by Hal, OH, CN, LA, O(LA), and/or monosubstituted by an oxo group or L₂-Cyc²,

25 Cyc² is a mono- or binuclear, aliphatic or aromatic, 4, 5, 6, 7, 8, 9 or 10 membered homo- or heterocycle, having 0, 1, 2, 3 or 4 N, O and/or S atoms, which may be mono- or independently di- or trisubstituted

by Hal, OH, CN, LA, O(LA), CO(LA), and/or monosubstituted by an oxo group or L₂-Cyc³,

Cyc³

is a mononuclear, aliphatic or aromatic, 5 or 6 membered homo- or heterocycle, having 0, 1 or 2 N, O and/or S atoms, which may be mono- or independently di- or trisubstituted by Hal, OH, CN, LA, O(LA), CON(LA), COO(LA), or monosubstituted by an oxo group,

LA

is unbranched or branched alkyl, having 1, 2, 3, 4 or 5 carbon atoms, which may be saturated or partially unsaturated, wherein 1, 2 or 3 H atoms may be replaced by Hal, and/or

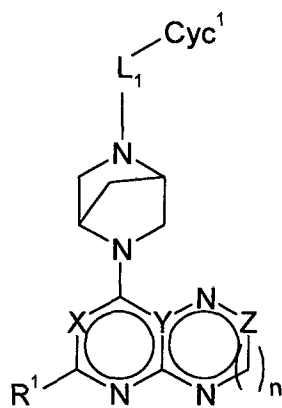
Hal

1 CH₂ group may be replaced by -O-, -SO₂-, -NH-, or -N(CH₃)-

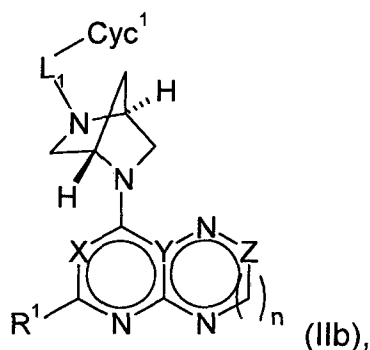
is F, Cl, Br or I,

and wherein a circle in a ring system indicates that the said ring system is aromatic.

2. The compound according to Claim 1, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, which conforms to Formulae (IIa), (IIb),

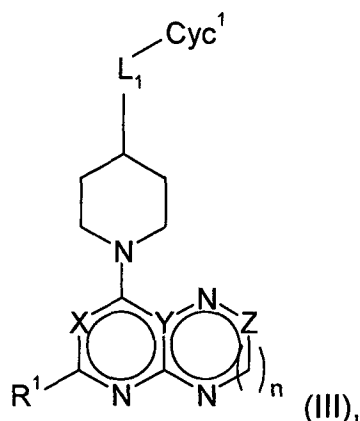


(IIa),



(IIb),

- wherein Q is N, m is 1, and the remaining residues have the meaning indicated for Formula (I),
or which conforms to Formula (III)



wherein Q is CH, m is 0, and the remaining residues have the meaning indicated for Formula (I).

5

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

10

in Subformula 1

R¹ is H, methyl or NH₂,

X is N,

Y is C,

15 Z is CH,

n is 1,

in Subformula 2

R¹ is H, methyl or NH₂,

20 X is CH,

Y is N,

Z is CH,

n is 0,

25 in Subformula 3

R¹ is H, methyl or NH₂,

X is CH,

Y is C,

Z is S,
n is 0,

in Subformula 4

5 R¹ is H, methyl or NH₂,
X is CH,
Y is C,
Z is CH,
n is 1,

10

in Subformula 5

R¹ is H, methyl or NH₂,
X is N,
Y is C,
15 Z is S,
n is 0,

and the remaining residues have the meaning as indicated for Formula (I).

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

25 Subformula 6 of Formula (IIb)

R¹, X, Y, Z, n have the meanings indicated for either of Subformulae 1 to 5 according to Claim 3,

L₁ is a bond,

Cyc¹ is phenyl or pyridyl, which may be mono- or independently
30 disubstituted by Hal, methyl, methoxy,
or which may be monosubstituted by pyrazol-1-ylmethyl,

Hal is F, Cl or Br,

and the remaining residues have the meaning as indicated for Formula (I).

35

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

5

in Subformula 7 of Formula (III)

R^1 , X, Y, Z, n have the meanings indicated for either of Subformulae 1 to 5,

R^2 is H or OH,

L_1 is a bond, CO, -CONH, CH_2 , - CH_2CH_2O , -CONH CH_2 ,

10 Cyc^1 is phenyl, pyridyl, piperidine, piperazine, quinoline, thiazole, which may be mono- or independently di- or trisubstituted by Hal, LA, OH, CN,

Hal is F, Cl or Br,

15 in Subformula 8 of Formula (III)

R^1 , X, Y, Z, n have the meanings indicated for either of Subformulae 1 to 5,

R^2 is H or OH,

L_1 is a bond, CO, -CONH, CH_2 , - CH_2CH_2O , -CONH CH_2 ,

20 Cyc^1 is phenyl, pyridyl, piperidine, piperazine, quinoline, thiazole, [1,2,4]oxadiazol, which is monosubstituted by L_2-Cyc^2 ,

L_2 is a bond, - CH_2CH_2O , -CONH CH_2 , -CO CH_2CH_2 , -CO CH_2O , -CO CH_2 , CO, -CONH CH_2CH_2 , - CH_2CONH , -CON(CH_3) CH_2 , - $CH_2CH_2OCH_2$, CH_2 , - $CH_2CON(CH_3)CH_2$, -CON(CH_3), -SO $_2CH_2CH_2$, - $CH_2CH_2SO_2$,

25 Cyc^2 is phenyl, pyridyl, pyrazole, imidazolin-2-one, oxadiazole, furan, 2,3-Dihydro-benzo[1,4]dioxin, Benzo[1,3]dioxol, naphthalen, isoxazol, benzofuran, [1,3,4]thiadiazol, thiazole, which may be monosubstituted by Hal, LA, CO(LA), O(LA), CN,

30 in Subformula 9 of Formula (III)

R^1 , X, Y, Z, n have the meanings indicated for either of Subformulae 1 to 5,

R^2 is H or OH,

L_1 is a bond, CO, -CONH, CH_2 , - CH_2CH_2O , -CONH CH_2 ,

35 Cyc^1 is phenyl, pyridyl, piperidine, piperazine, quinoline, thiazole, which is monosubstituted by L_2-Cyc^2 ,

- L₂ is a bond, -CH₂CH₂O, -CONHCH₂, -COCH₂CH₂, -COCH₂O, -COCH₂,
 Cyc² is phenyl, pyridyl, pyrazole, imidazolin-2-one, oxadiazole, which may be monosubstituted by Hal, LA,
 5 Hal is F, Cl or Br,

in Subformula 10 of Formula (III)

- R¹, X, Y, Z, n have the meanings indicated for either of Subformulae 1 to 5,
 R² is H or OH,
 10 L₁ is a bond, CO, -CONH, CH₂, -CH₂CH₂O, -CONHCH₂,
 Cyc¹ is phenyl, pyridyl, piperidine, piperazine, quinoline, thiazole, which is monosubstituted by L₂-Cyc²,
 L₂ is a bond, -CH₂CH₂O, -CONHCH₂, -COCH₂CH₂, -COCH₂O, -COCH₂,
 15 Cyc² is phenyl, pyridyl, pyrazole, imidazolin-2-one, oxadiazole, which is monosubstituted by L₂-Cyc³,
 Cyc³ is phenyl, pyridyl, piperidine which may be mono- or disubstituted by Hal, or LA,
 Hal is F, Cl or Br,

20

and the remaining residues have the meaning as indicated for Formula (I).

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

- 25 4-[(1S,4S)-5-(4-Fluoro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-pteridin-2-ylamine,
 3-(4-Fluoro-phenyl)-1-[1'-(5-methyl-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-[4,4']bipiperidinyl-1-yl]-propan-1-one,
 {4-[2-(4-Chloro-phenoxy)-ethyl]-piperazin-1-yl}-(1-[1,2,5]thiadiazolo[3,4-d]pyrimidin-7-yl)-piperidin-4-yl)-methanone,
 30 7-((1S,4S)-5-o-Tolyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-[1,2,5]thiadiazolo[3,4-d]pyrimidine,
 7-[(1S,4S)-5-(3-Fluoro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo[3,4-d]pyrimidine,
 7-[(1S,4S)-5-(4-Trifluoromethyl-pyridin-2-yl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo[3,4-d]pyrimidine,
 35 7-((1S,4S)-5-Phenyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-[1,2,5]thiadiazolo[3,4-d]pyrimidine,

- 7-[(1S,4S)-5-(5-Chloro-pyridin-2-yl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-
[1,2,5]thiadiazolo[3,4-d]pyrimidine,
7-[(1S,4S)-5-(4-Fluoro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo[3,4-
b]pyridine,
- 5 7-[(1S,4S)-5-(3-Pyrazol-1-ylmethyl-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-
[1,2,5]thiadiazolo[3,4-d]pyrimidine,
7-[(1S,4S)-5-(4-Chloro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo[3,4-
d]pyrimidine,
1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid quinolin-2-ylamide,
- 10 1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid quinolin-2-ylamide,
2-(4-Chloro-phenoxy)-1-(1'-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-[4,4']bipiperidiny-1-yl)-
ethanone,
3-(4-Fluoro-phenyl)-1-(1'-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-[4,4']bipiperidiny-1-yl)-
propan-1-one,
- 15 7-[(1S,4S)-5-(2,4-Difluoro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-
[1,2,5]thiadiazolo[3,4-d]pyrimidine,
{4-[2-(4-Chloro-phenoxy)-ethyl]-piperazin-1-yl}-(1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-
piperidin-4-yl)-methanone,
1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (5-trifluoromethyl-
pyridin-2-yl)-amide,
- 20 7-[(1S,4S)-5-(4-Chloro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo[3,4-
d]pyrimidin-5-ylamine,
7-[(1S,4S)-5-(4-Trifluoromethyl-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-
[1,2,5]thiadiazolo[3,4-d]pyrimidine,
- 25 4-(4-{6-[(1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carbonyl)-amino]-pyridin-3-
yl}-pyrazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester,
3-(4-Chloro-phenyl)-1-[4-(1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-piperidin-4-yl)-piperazin-
1-yl]-propan-1-one,
7-[(1S,4S)-5-(5-Methyl-pyridin-2-yl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-
- 30 [1,2,5]thiadiazolo[3,4-d]pyrimidine,
7-[(1S,4S)-5-(4-Fluoro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo[3,4-
d]pyrimidin-5-ylamine,
7-[(1S,4S)-5-(3,4-Difluoro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-
[1,2,5]thiadiazolo[3,4-d]pyrimidine,
- 35 7-((1S,4S)-5-o-Tolyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-[1,2,4]triazolo[1,5-a]pyrimidine,

- 7-[(1S,4S)-5-(4-Chloro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo[3,4-b]pyridine,
 3-(4-Chloro-phenyl)-1-(1'-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-[4,4']bipiperidiny-1-yl)-propan-1-one,
- 5 1-(5-Methyl-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidine-4-carboxylic acid quinolin-2-ylamide,
 1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide,
 7-((1S,4S)-5-Phenyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-[1,2,5]thiadiazolo[3,4-b]pyridine,
- 10 1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid 3-chloro-benzylamide,
 1-Pyrido[2,3-b]pyrazin-8-yl-piperidine-4-carboxylic acid quinolin-2-ylamide,
 {4-[2-(4-Bromo-phenoxy)-ethyl]-piperazin-1-yl}-(1-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-piperidin-4-yl)-methanone,
 7-[(1S,4S)-5-(4-Chloro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-5-methyl-
- 15 [1,2,5]thiadiazolo[3,4-d]pyrimidine,
 1-(5-Methyl-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidine-4-carboxylic acid (3-fluoro-4-methyl-phenyl)-amide,
 7-[(1S,4S)-5-(4-Fluoro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-5-methyl-
- 20 [1,2,5]thiadiazolo[3,4-b]pyridine,
 1-[4-(1-Pyrido[2,3-b]pyrazin-8-yl-piperidin-4-ylmethyl)-phenyl]-imidazolidin-2-one,
 1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid (2-hydroxy-quinolin-3-yl)-amide,
 1-[1,2,5]Thiadiazolo[3,4-d]pyrimidin-7-yl-piperidine-4-carboxylic acid (3-pyrazol-1-yl-phenyl)-amide,
- 25 {4-[2-(4-Chloro-phenoxy)-ethyl]-piperazin-1-yl}-[1-(5-methyl-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidin-4-yl]-methanone,
 7-[(1S,4S)-5-(4-Fluoro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo[3,4-d]pyrimidine,
 7-[(1S,4S)-5-(4-Methoxy-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-[1,2,5]thiadiazolo[3,4-
- 30 d]pyrimidine,
 1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (2-hydroxy-quinolin-3-yl)-amide,
 1-(5-Methyl-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidine-4-carboxylic acid (5-methyl-pyridin-2-yl)-amide,

2-(3-Fluoro-4-methyl-phenyl)-1-(1'-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl-[4,4']bipiperidiny-1-yl)-ethanone,

3-(4-Fluoro-phenyl)-1-(1'-[1,2,5]thiadiazolo[3,4-d]pyrimidin-7-yl-[4,4']bipiperidiny-1-yl)-propan-1-one,

5 1-[1,2,5]Thiadiazolo[3,4-b]pyridin-7-yl-piperidine-4-carboxylic acid (5-bromo-pyridin-2-yl)-amide,

1-(5-Methyl-[1,2,5]thiadiazolo[3,4-b]pyridin-7-yl)-piperidine-4-carboxylic acid (2-hydroxy-quinolin-3-yl)-amide,

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

7. A pharmaceutical composition comprising a compound according to one or more of Claims 1 to 6, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, as active ingredient,
15 together with a pharmaceutically acceptable carrier.

8. A compound according to one or more of Claims 1 to 6, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, for use in the treatment of a hyperproliferative, inflammatory
20 or degenerative disease.

9. The compound for use according to Claim 8, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, wherein the hyperproliferative disease is cancer.

25 10. The compound for use according to Claim 9, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, wherein the cancer is selected from the group consisting of brain, lung, colon, epidermoid, squamous cell, bladder, gastric, pancreatic, breast, head & neck, renal,
30 kidney, liver, ovarian, prostate, uterine, oesophageal, testicular, gynecological, thyroid cancer, melanoma, acute myelogenous leukemia, multiple myeloma, chronic myelogenous leukemia, myeloid cell leukemia, Kaposi's sarcoma.

11. The compound for use according to Claim 8, or its stereoisomers or tautomers, or
35 pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in

all ratios, wherein the inflammatory disease is selected from multiple sclerosis, rheumatoid arthritis, systemic lupus or inflammatory bowel disease.

12. The compound for use according to Claim 8, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, wherein the degenerative disease is selected from osteoarthritis or Alzheimer's disease.

13. Use of a compound of one or more of Claims 1 to 6, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, for the preparation of a medicament for the treatment of a hyperproliferative, inflammatory or degenerative disease.

14. Use according to claim 13 wherein the disease is cancer.

15. Use according to claim 14 wherein the cancer is selected from the group consisting of brain, lung, colon, epidermoid, squamous cell, bladder, gastric, pancreatic, breast, head & neck, renal, kidney, liver, ovarian, prostate, uterine, oesophageal, testicular, gynecological, thyroid cancer, melanoma, acute myelogenous leukemia, multiple myeloma, chronic myelogenous leukemia, myeloid cell leukemia, Kaposi's sarcoma.

16. A method for treating a hyperproliferative, inflammatory or degenerative disease, comprising administering to a subject a compound of any of claims 1 to 6, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios.

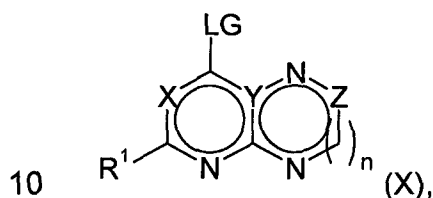
17. The method of claim 16, wherein the cancer is selected from the group consisting of brain, lung, colon, epidermoid, squamous cell, bladder, gastric, pancreatic, breast, head & neck, renal, kidney, liver, ovarian, prostate, uterine, oesophageal, testicular, gynecological, thyroid cancer, melanoma, acute myelogenous leukemia, multiple myeloma, chronic myelogenous leukemia, myeloid cell leukemia, Kaposi's sarcoma.

18. Set (kit) consisting of separate packs of

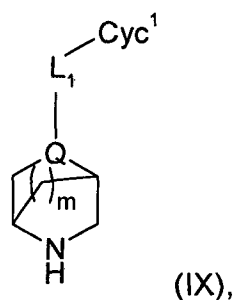
a) an effective amount of a compound according to one or more of Claims 1 to 6, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, and

5 b) an effective amount of a further medicament active ingredient.

19. Process for the manufacture of compounds of Formula (I), wherein a compound of Formula (X)



is reacted with a compound of Formula (IX)



wherein

15 LG is a leaving group suitable for nucleophilic aromatic substitutions, and the remaining substituents have the meaning as indicated for Formula (I), to yield a compound of Formula (I).

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/003356

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07D471/04 C07D487/04 C07D513/04
 ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

3 December 2013

Date of mailing of the international search report

10/12/2013

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/003356

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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Information on patent family members

International application No

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