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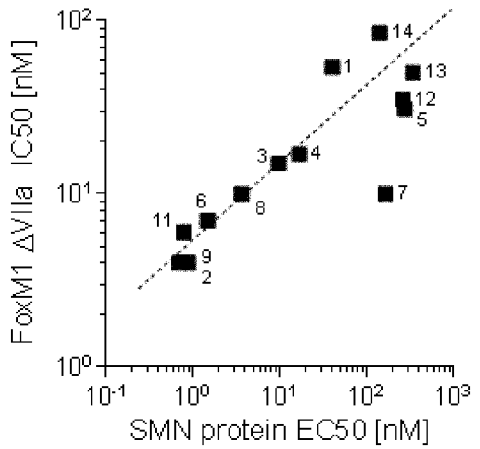
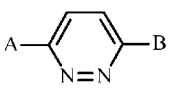
[Continued on next page]

(54) Title: COMPOUNDS FOR THE TREATMENT OF CANCER

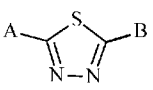
(57) Abstract: The present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I) or of formula (VI), wherein A and B are as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment, prevention and/or delay of progression of cancer.

Fig. 2





(I)



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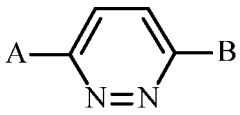
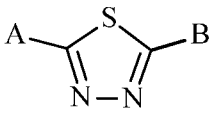
Compounds for the treatment of cancer

FIELD OF THE INVENTION

The present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I) or of formula (VI)



(I)



(VI),

wherein A and B are as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment, prevention and/or delay of progression of cancer.

BACKGROUND

FoxM1 is a transcription factor of the Forkhead family. It is also known in the literature as Trident (in mouse), HFH-11 (in human), WIN or INS-1 (in rat), MPP-2 (partial human cDNA) or FKHL-16. The Forkhead family comprises a large number of transcription factors defined by a conserved DNA binding domain called Forkhead or winged-helix domain. The FoxM1 gene was cloned by screening cDNA libraries with degenerate primers for homologues with a conserved Forkhead DNAbinding domain (W. Korver, J. Roose, H. Clevers, Nucleic Acids Res. 25 (1997) 1715–1719). The FoxM1 gene was revealed to encode a Forkhead transcription factor family member that exhibits 45% identity in the DNA-binding domain with five of its closest related Forkhead members, namely FoxA3 (HNF-3γ, FoxC1 (fkh-1), FoxF2 (FREAC-2), FoxK1 (ILF) and FoxN2 (HTLF). The FoxM1 C-terminal region was found to have homology (76% identity) with a human partial cDNA encoding an open reading-frame of 221 amino acids, termed MPP-2. MPP-2 stands for MPM-2-reactive phosphoprotein-2 and was identified after screening a lymphoblast-derived cDNA library with the MPM-2 monoclonal antibody, which binds specifically to epitopes on mitotic proteins that are phosphorylated in a phosphoserine-proline dependent manner. FoxM1 binds DNA in vitro through the consensus site TAAACA. This motif shares the core sequence recognized by other members of the forkhead family. In particular, repeats of these motifs, in alternating orientation, were often characterized within the selected binding sequences for FoxM1.

The human FoxM1 gene is a 10-exon structure spanning approximately 25 kb on the 12p13-3 chromosomal band (telomeric position) (W. Korver, J. Roose, H. Clevers, Nucleic Acids Res. 25 (1997) 1715–1719). Two exons, named exons Va and VIIa, also referred to as exon A1 (or rat exon 6) and A2 respectively, are alternatively spliced (H. Ye, T.F. Kelly, U. Samadani, L. Lim, S. Rubio, D.G. Overdier, K.A. Roebuck, R.H. Costa, Mol. Cell Biol. 17 (1997) 1626–1641). Exon Va encodes a 15 amino-acidinsertion within the C-terminal part of the DNA binding-domain, and is not seen in any of the other Forkhead transcription factor family members. Exon VIIa represents a 38 amino-acid insertion within the C-terminus of the protein. Differential splicing of exons Va and VIIa in human FoxM1, gives rise to three classes of transcripts, class A containing both alternative exons, class B containing none of the alternative exons, and class C in which exon Va only is retained (H. Ye, T.F. Kelly, U. Samadani, L. Lim, S. Rubio, D.G. Overdier, K.A. Roebuck, R.H. Costa, Mol. Cell Biol. 17 (1997) 1626–1641). Both FoxM1B and FoxM1C are transcriptionally active, whereas FoxM1A is transcriptionally inactive, due to the insertion of exon VIIa in the C-terminal transactivation domain. This disruption of the transactivation domain in FoxM1A not only leads to transcriptional inactivation, it might also cause this variant to act as a dominant-negative variant as it has retained normal DNA binding activity in the absence of a functional transactivation domain (H. Ye, T.F. Kelly, U. Samadani, L. Lim, S. Rubio, D.G. Overdier, K.A. Roebuck, R.H. Costa, Mol. Cell Biol. 17 (1997) 1626–1641).

FoxM1 is overexpressed in a broad range of tumor types, including those of neural, gastrointestinal, and reproductive origin (see Bektas et al., supra; Nakamura et al., 2004, Oncogene 23: 2385-400; Pilarsky et al., 2004, Neoplasia .Q: 744-50; Liu et al., 2006, Cancer Res 66: 3593-602). This expression pattern of FoxM1 is attributed to the ability of FoxM1 to transactivate genes required for cell cycle progression (Wang et al.,2002, Proc Nat. Acad Sci US A 99:16881-6). Increased nuclear staining of FoxM1B found in human basal cell carcinomas suggests that FoxM1 is required for cellular proliferation in human cancers (Teh et al., 2002, Cancer Res. 62: 4773-80). The detailed role of FoxM1 in establishing or facilitating tumor progression and disease management has not been fully elucidated, however.

EP 2 298 896 (A1) discloses siRNA molecules inhibiting expression of FoxM1B protein and the use of the siRNA molecules for inhibiting tumor growth.

WO 2011/127297 (A1) discloses a composition comprising a siRNA FoxM1 inhibitor and Herceptin for the treatment of breast cancer.

WO 2014/028459 (A1) discloses 1,4-disubstituted pyridazine analogs and methods for treating SMN-deficiency related conditions.

WO 2014/116845 (A1) discloses thiadiazole analogs and methods for treating SMN-deficiency related conditions.

WO 2015/017589 (A1) discloses 1,4-disubstituted pyridazine analogs and methods for treating SMN-deficiency related conditions.

The problem to be solved by the present invention was to provide new compounds suitable for modifying splicing of the FoxM1 gene for use in the treatment of cancer.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. Induction of alternative splicing of FoxM1 towards full-length FoxM1 in fibroblasts. Human fibroblasts were incubated with compounds of present invention at different concentrations for 24 hours, and changes in FoxM1_FL (containing exon VIIa) and FoxM1_ΔVIIa (lacking exon VIIa) mRNA expression were assessed by RT-qPCR. **Fig. 1A** Compound 1; **Fig. 1B** Compound 2; **Fig. 1C** Compound 3; **Fig. 1D** Compound 4; **Fig. 1E** Compound 6; **Fig. 1F** Compound 7; **Fig. 1G** Compound 8; **Fig. 1H** Compound 9; **Fig. 1I** Compound 11. Data represent means ± standard error of the mean (SEM) of 3-9 independent observations. Data was generated as described in Example 1.

Figure 2. Correlation of in vitro potency of the compounds of the invention for modulation of the FoxM1 splicing vs. splicing of the survival of motoneuron 2 (SMN2) gene. Half-maximal effects for the FoxM1_ΔVIIa splice variant and for the SMN protein are shown. Data was obtained as described in Example 2.

DETAILED DESCRIPTION OF THE INVENTION

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described below.

All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

The nomenclature used in this Application is based on IUPAC systematic nomenclature, unless indicated otherwise.

Any open valency appearing on a carbon, oxygen, sulfur or nitrogen atom in the structures herein indicates the presence of a hydrogen, unless indicated otherwise.

The definitions described herein apply irrespective of whether the terms in question appear alone or in combination. It is contemplated that the definitions described herein can be appended to form chemically-relevant combinations, such as e.g. "heterocycloalkylaryl", "haloalkylheteroaryl", "arylalkylheterocycloalkyl", or "alkoxyalkyl". The last member of the combination is the radical which is binding to the rest of the molecule. The other members of the combination are attached to the binding radical in reversed order in respect of the literal sequence, e.g. the combination arylalkylheterocycloalkyl refers to a heterocycloalkyl-radical which is substituted by an alkyl which is substituted by an aryl.

When indicating the number of substituents, the term "one or more" refers to the range from one substituent to the highest possible number of substitution, i.e. replacement of one hydrogen up to replacement of all hydrogens by substituents.

The term "optional" or "optionally" denotes that a subsequently described event or circumstance can but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not.

The term "substituent" denotes an atom or a group of atoms replacing a hydrogen atom on the parent molecule.

The term "substituted" denotes that a specified group bears one or more substituents. Where any group can carry multiple substituents and a variety of possible substituents is provided, the substituents are independently selected and need not to be the same. The term "unsubstituted" means that the specified group bears no substituents. The term "optionally substituted" means that the specified group is unsubstituted or substituted by one or more substituents, independently chosen from the group of possible substituents. When indicating the number of substituents, the term "one or more" means from one substituent to the highest possible number of substitution, i.e. replacement of one hydrogen up to replacement of all hydrogens by substituents.

The terms "compound(s) of this invention", "compound(s) of the present invention", "FoxM1 gene splicing modifier", "FoxM1 splicing modifier", and "compounds modifying splicing of the FoxM1 gene" are interchangeably used herein and refer to compounds as disclosed herein and stereoisomers, tautomers, solvates, and salts (e.g., pharmaceutically acceptable salts) thereof.

When the compounds of the invention are solids, it is understood by those skilled in the art that these compounds, and their solvates and salts, may exist in different solid forms, particularly different crystal forms, all of which are intended to be within the scope of the present invention and specified formulas.

The term "pharmaceutically acceptable salts" denotes salts which are not biologically or otherwise undesirable. Pharmaceutically acceptable salts include both acid and base addition salts.

The term "pharmaceutically acceptable acid addition salt" denotes those pharmaceutically acceptable salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid, and organic acids selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, maloneic acid, succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic acid, cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, and salicyclic acid.

The term "pharmaceutically acceptable base addition salt" denotes those pharmaceutically acceptable salts formed with an organic or inorganic base. Examples of acceptable inorganic bases include sodium, potassium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, and aluminum salts. Salts derived from pharmaceutically acceptable organic nontoxic bases includes salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperizine, piperidine, N-ethylpiperidine, and polyamine resins.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., New York, 1994. In describing an optically active compound, the prefixes D and L, or R and S, are used to denote the absolute configuration of the molecule about its chiral center(s). The substituents attached to the chiral center under consideration are ranked in accordance with the Sequence Rule of Cahn, Ingold and Prelog. (Cahn et al. Angew. Chem. Inter. Edit. 1966, 5, 385; errata 511). The prefixes D and L or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or L designating that the compound is levorotatory. A compound prefixed with (+) or D is dextrorotatory.

The term "halo", "halogen", and "halide" are used interchangeably herein and denote fluoro, chloro, bromo, or iodo, most particularly fluoro or chloro.

The term "alkyl" denotes a monovalent linear or branched saturated hydrocarbon group of

1 to 12 carbon atoms. In particular embodiments, alkyl has 1 to 7 carbon atoms, and in more particular embodiments 1 to 4 carbon atoms. Examples of alkyl include methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, or tert-butyl, particularly methyl.

The term "alkenyl" denotes a monovalent linear or branched hydrocarbon group of 2 to 7 carbon atoms with at least one double bond. In particular embodimets, alkenyl has 2 to 4 carbon atoms with at least one double bond. Examples of alkenyl include ethenyl, propenyl, prop-2-enyl, isopropenyl, n-butenyl, and iso-butenyl.

The term "alkynyl" denotes a monovalent linear or branched saturated hydrocarbon group of 2 to 7 carbon atoms comprising one, two or three triple bonds. In particular embodiments alkynyl has from 2 to 4 carbon atoms comprising one or two triple bonds. Examples of alkynyl include ethynyl, propynyl, prop-2-ynyl, isopropynyl, and n-butynyl.

The term "alkoxy" denotes a group of the formula -O-R', wherein R' is an alkyl group. Examples of alkoxy moieties include methoxy, ethoxy, isopropoxy, and tert-butoxy, particularly methoxy.

The term "haloalkyl" denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of haloalkyl include monofluoro-, difluoro- or trifluoro-methyl, -ethyl or -propyl, for example 3,3,3-trifluoropropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, fluoromethyl, or trifluoromethyl. The term "perhaloalkyl" denotes an alkyl group where all hydrogen atoms of the alkyl group have been replaced by the same or different halogen atoms.

The term "haloalkoxy" denotes an alkoxy group wherein at least one of the hydrogen atoms of the alkoxy group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of haloalkoxyl include monofluoro-, difluoro- or trifluoro-methoxy, -ethoxy or -propoxy, for example 3,3,3-trifluoropropoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, fluoromethoxy, or trifluoromethoxy. The term "perhaloalkoxy" denotes an alkoxy group where all hydrogen atoms of the alkoxy group have been replaced by the same or different halogen atoms.

The term "hydroxyalkyl" denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by a hydroxy group. Examples of hydroxyalky include hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 2-hydroxy-1-hydroxymethylethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl or 2-(hydroxymethyl)-3-hydroxypropyl.

The term "bicyclic ring system" denotes two rings which are fused to each other via a common single or double bond (annelated bicyclic ring system), via a sequence of three or more common atoms (bridged bicyclic ring system) or via a common single atom (spiro bicyclic ring system). Bicyclic ring systems can be saturated, partially unsaturated, unsaturated or aromatic. Bicyclic ring systems can comprise heteroatoms selected from N, O and S.

The term "cycloalkyl" denotes a monovalent saturated monocyclic or bicyclic hydrocarbon group of 3 to 10 ring carbon atoms. In particular embodiments cycloalkyl denotes a monovalent saturated monocyclic hydrocarbon group of 3 to 8 ring carbon atoms. Bicyclic means consisting of two saturated carbocycles having one or more carbon atoms in common. Particular cycloalkyl groups are monocyclic. Examples for monocyclic cycloalkyl are cyclopropyl, cyclobutanyl, cyclopentyl, cyclohexyl or cycloheptyl. Examples for bicyclic cycloalkyl are bicyclo[2.2.1]heptanyl, or bicyclo[2.2.2]octanyl.

The term "cycloalkenyl" denotes a monovalent unsaturated non-aromatic monocyclic or bicyclic hydrocarbon group of 3 to 8 ring carbon atoms. Particular cycloalkenyl groups are monocyclic. Examples of cycloalkenyl groups include cyclobuten-1-yl, and cyclopenten-1-yl.

The term "heterocycloalkyl" denotes a monovalent saturated or partly unsaturated mono- or bicyclic ring system of 3 to 9 ring atoms, comprising 1, 2, or 3 ring heteroatoms selected from N, O and S, the remaining ring atoms being carbon. In particular embodiments, heterocycloalkyl is a monovalent saturated monocyclic ring system of 4 to 7 ring atoms, comprising 1, 2, or 3 ring heteroatoms selected from N, O and S, the remaining ring atoms being carbon. Examples for monocyclic saturated heterocycloalkyl are aziridinyl, oxiranyl, azetidinyl, oxetanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydro-thienyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-thiomorpholin-4-yl, azepanyl, diazepanyl, homopiperazinyl, or oxazepanyl. Examples for bicyclic saturated heterocycloalkyl are 8-aza-bicyclo[3.2.1]octyl, quinuclidinyl, 8-oxa-3-aza-bicyclo[3.2.1]octyl, 9-aza-bicyclo[3.3.1]nonyl, 3-oxa-9-aza-bicyclo[3.3.1]nonyl, or 3-thia-9-aza-bicyclo[3.3.1]nonyl. Examples for partly unsaturated heterocycloalkyl are dihydrofuryl, imidazolinyl, dihydro-oxazolyl, tetrahydro-pyridinyl, or dihydropyranyl.

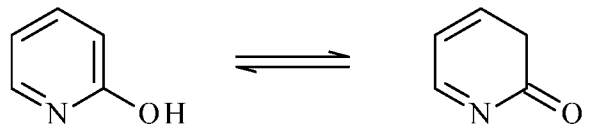
The term "aromatic" denotes the conventional idea of aromaticity as defined in the literature, in particular in IUPAC - Compendium of Chemical Terminology, 2nd, A. D. McNaught & A. Wilkinson (Eds). Blackwell Scientific Publications, Oxford (1997).

The term "aryl" denotes a monovalent aromatic carbocyclic mono- or bicyclic ring system comprising 6 to 10 carbon ring atoms. Examples of aryl moieties include phenyl and naphthyl.

The term “aryloxy” denotes a group of the formula -O-R’, wherein R’ is aryl. An example of aryloxy is phenoxy.

The term “heteroaryl” denotes a monovalent aromatic heterocyclic mono- or bicyclic ring system of 5 to 12 ring atoms, comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, the remaining ring atoms being carbon. Examples of heteroaryl moieties include pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, triazinyl, azepinyl, diazepinyl, isoxazolyl, benzofuranyl, isothiazolyl, benzothienyl, indolyl, isoindolyl, isobenzofuranyl, benzimidazolyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzooxadiazolyl, benzothiadiazolyl, benzotriazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, or quinoxalinyl, most particularly pyrazolyl or pyridinyl.

The term “pyridinyl substituted with hydroxy” equally refers to its tautomeric form pyridine-one, such as for example “pyridin-2-ol” and its tautomer “3H-pyridin-2-one”



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The term “alkylene” denotes a linear saturated divalent hydrocarbon group of 1 to 7 carbon atoms or a divalent branched saturated divalent hydrocarbon group of 3 to 7 carbon atoms. Examples of alkylene groups include methylene, ethylene, propylene, 2-methylpropylene, butylene, 2-ethylbutylene, pentylene, hexylene.

The term “alkylamino” denotes a group -NR’R”, wherein R’ is hydrogen and R” is a alkyl. The term “dialkylamino” as used herein denotes a group -NR’R”, wherein R’ and R” are both alkyl. Examples of alkylamino groups include methylamino and ethylamino. Examples of alkylamino groups include dimethylamino, methylethylamino, diethylamino and di(1-methylethyl)amino.

The term “active pharmaceutical ingredient” (or “API”) denotes the compound or molecule in a pharmaceutical composition that has a particular biological activity.

The terms “pharmaceutical composition” and “pharmaceutical formulation” (or “formulation”) are used interchangeably and denote a mixture or solution comprising a therapeutically effective amount of an active pharmaceutical ingredient together with one or more pharmaceutically acceptable excipients to be administered to a mammal, e.g., a human in need thereof.

The term “pharmaceutically acceptable” denotes an attribute of a material which is useful

in preparing a pharmaceutical composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable and is acceptable for veterinary as well as human pharmaceutical use.

The terms "pharmaceutically acceptable excipient", "pharmaceutically acceptable carrier" and "therapeutically inert excipient" can be used interchangeably and denote any pharmaceutically acceptable ingredient in a pharmaceutical composition having no therapeutic activity and being non-toxic to the subject administered, such as disintegrators, binders, fillers, solvents, buffers, tonicity agents, stabilizers, antioxidants, surfactants, carriers, diluents or lubricants used in formulating pharmaceutical products.

A "pharmaceutically acceptable carrier" refers to an ingredient in a pharmaceutical composition, other than an active ingredient, which is nontoxic to a subject. A pharmaceutically acceptable carrier includes, but is not limited to, a buffer, excipient, stabilizer, or preservative.

An "individual" or "subject" is a mammal. Mammals include, but are not limited to, domesticated animals (e.g., cows, sheep, cats, dogs, and horses), primates (e.g., humans and non-human primates such as monkeys), rabbits, and rodents (e.g., mice and rats). In certain embodiments, the individual or subject is a human.

The term "animal" as used herein comprises human beings and non-human animals. In one embodiment, a "non-human animal" is a mammal, for example a rodent such as rat or a mouse. In one embodiment, a non-human animal is a mouse.

The term "treating" or "treatment" of a disease state includes inhibiting the disease state, i.e., arresting the development of the disease state or its clinical symptoms, or relieving the disease state, i.e., causing temporary or permanent regression of the disease state or its clinical symptoms.

The term "preventing" or "prevention" of a disease state denotes causing the clinical symptoms of the disease state not to develop in a subject that can be exposed to or predisposed to the disease state, but does not yet experience or display symptoms of the disease state.

The term "FoxM1 polypeptide" is used herein to refer to native FoxM1 polypeptide from any animal, e.g. mammalian, species, including humans, and FoxM1 variants. The amino acid sequence of human FoxM1A polypeptide is given in Seq. Id. No. 1, the amino acid sequence of human FoxM1B is given in Seq. Id. No. 2 and the amino acid sequence of FoxM1C polypeptide is given in Seq. Id. No. 3.

The nucleotide sequences of the three FoxM1 variants are set forth in Seq. Id. No. 4 (FoxM1A), Seq. Id. No. 5 (FoxM1B) and Seq. Id. No. 6 (FoxM1C).

The term "compound modifying splicing of the FoxM1 gene" is used herein to refer to compounds which lead to the production of transcriptionally inactive forms of the FoxM1 polypeptide, in particular to the production of FoxM1A variant, by modifying the FoxM1 splicing such that transcriptionally inactive forms are generated, in particular FoxM1A, and by suppressing the production of transcriptionally active FoxM1 variants, in particular FoxM1B and FoxM1C.

Methods for detection and/or measurement of polypeptides in biological material are well known in the art and include, but are not limited to, Western-blotting, Flow cytometry, ELISAs or RIAs, or various proteomics techniques. An example for a method to measure a polypeptide is an ELISA. This type of protein quantitation is based on an antibody capable of capturing a specific antigen, and a second antibody capable of detecting the captured antigen. The assays mentioned hereinbefore are described in Harlow, E. and Lane, D. Antibodies: A Laboratory Manual, (1988), Cold Spring Harbor Laboratory Press.

Methods for detection and/or measurement of RNA in biological material are well known in the art and include, but are not limited to, Northern-blotting, RNA protection assay, RT PCR. Suitable methods are described in Molecular Cloning: A Laboratory Manual(Fourth Edition) By Michael R. Green, Joseph Sambrook, Peter MacCallum 2012, 2,028 pp, ISBN 978-1-936113-42-2.

In a first aspect, the present invention provides compounds modifying splicing of the FoxM1 gene for use in the treatment, prevention and/or delay of progression of cancer, wherein the compounds induce a transcriptionally inactive FoxM1 variant. In a particular embodiment of the present invention, the transcriptionally inactive FoxM1 variant is FoxM1A.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier for use in the treatment, prevention and/or delay of progression of cancer, wherein the FoxM1 gene splicing modifier induces a transcriptionally inactive FoxM1 variant.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier for use in the treatment, prevention and/or delay of progression of cancer, wherein the FoxM1 gene splicing modifier induces the transcriptionally inactive FoxM1A variant.

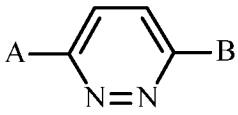
In a particular embodiment of the present invention the FoxM1 gene is the human FoxM1 gene.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier for use in the treatment, prevention and/or delay of progression of cancer, wherein the FoxM1 gene is the human FoxM1 gene.

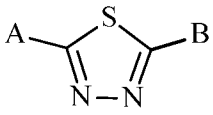
In a particular embodiment of the present invention the cancer is selected from the group consisting of cancer of the liver, prostate, brain, breast, lung, colon, pancreas, skin, cervix, ovary, mouth, blood and nervous system.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier for use in the treatment, prevention and/or delay of progression of cancer, wherein the cancer is selected from the group consisting of cancer of the liver, prostate, brain, breast, lung, colon, pancreas, skin, cervix, ovary, mouth, blood and nervous system.

In more detail, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I) or a compound of formula (VI)



(I)



(VI), wherein

A is 2-hydroxy-phenyl which is substituted with:

0, 1, 2, or 3 substituents independently selected from C_{1-4} alkyl, oxo, oxime, hydroxy, halo-C_{1-4} alkyl, dihalo-C_{1-4} alkyl, trihalo-C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxy-C_{3-7} cycloalkyl, halo-C_{1-4} alkoxy, dihalo-C_{1-4} alkoxy, trihalo-C_{1-4} alkoxy, hydroxy, cyano, halogen, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, heteroaryl, C_{1-4} alkyl substituted with hydroxy, C_{1-4} alkoxy substituted with aryl, amino, -C(O)NH-C_{1-4}alkyl-heteroaryl, -NHC(O)-C_{1-4} alkylheteroaryl, C_{1-4} alkyl-C(O)NH-heteroaryl, C_{1-4}alkyl-NHC(O)-heteroaryl, C_{3-7} cycloalkyl, 5-7 membered cycloalkenyl, or 5, 6 or 9 membered heterocycle containing 1 or 2 heteroatoms independently, selected from S, O and N,
wherein two C_{1-4} alkyl groups can combine with the atoms to which they are bound to form a 5-6 membered ring;
wherein heteroaryl has 5, 6 or 9 ring atoms, 1, 2 or 3 ring heteroatoms selected from N, O and S, and is substituted with 0, 1, or 2 substituents independently selected from oxo, hydroxy, nitro, halogen, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkoxy, C_{3-7} cycloalkyl, C_{1-4} alkyl-OH, trihalo-C_{1-4} alkyl, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, -C(O)NH_2, -NH_2, NO_2, hydroxy-C_{1-4}alkylamino, hydroxy-C_{1-4} alkyl, 4-7 membered heterocycle-C_{1-4} alkyl, amino-C_{1-4} alkyl, mono-C_{1-4}alkylamino-C_{1-4} alkyl, and di-C_{1-4}alkylamino-C_{1-4} alkyl; or

A is 2-naphthyl optionally substituted at the 3 position with hydroxy and additionally substituted with 0, 1, or 2 substituents selected from hydroxy, cyano, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-5} alkoxy, wherein the alkoxy is unsubstituted or substituted with hydroxy, C_{1-4} alkoxy, amino, -NHC(O)-C_{1-4} alkyl, -NHC(O)O-C_{1-4} alkyl, C_{1-4}

alkylene-4-7 membered heterocycle, 4-7 membered heterocycle, mono-C_{1-4} alkylamino, and di- C_{1-4} alkylamino; or

A is 6 membered heteroaryl having 1-3 ring nitrogen atoms and which is substituted by phenyl or a heteroaryl having 5 or 6 ring atoms, 1 or 2 ring heteroatoms independently selected from N, O and S and is substituted with 0, 1, or 2 substituents independently selected from cyano, C_{1-4} alkyl, mono-C_{1-4} alkylamino, di-C_{1-4}alkylamino, hydroxy-C_{1-4} alkylamino, hydroxy-C_{1-4} alkyl, amino-C_{1-4} alkyl and mono-C_{1-4} alkylamino-C_{1-4} alkyl, and di-C_{1-4}alkylamino-C_{1-4} alkyl; or

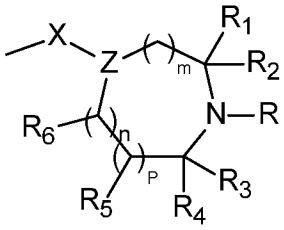
A is bicyclic heteroaryl having 9 to 10 ring atoms, 1, 2, or 3 ring heteroatoms independently selected from N, O or S, and which is substituted with 0, 1, or 2 substituents independently selected from cyano, oxime, halogen, hydroxy, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkoxy substituted with hydroxy, amino, mono-C_{1-4} alkylamino, and di-C_{1-4} alkylamino; or

A is tricyclic heteroaryl having 12 or 13 ring atoms, 1, 2, or 3 ring heteroatoms independently selected from N, O or S, and which is substituted with 0, 1, or 2 substituents independently selected from cyano, halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkoxy substituted with hydroxy, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, and heteroaryl having 5, 6 or 9 ring atoms, 1, 2 or 3 ring heteroatoms selected from N, O and S, and which is substituted with 0, 1, or 2 substituents independently selected from oxo, hydroxy, nitro, halogen, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkoxy, C_{3-7} cycloalkyl, C_{1-4} alkyl-OH, trihalo-C_{1-4} alkyl, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, -C(O)NH_2, -NH_2, -NO_2, hydroxy-C_{1-4} alkylamino, hydroxy-C_{1-4} alkyl, 4-7 membered heterocycle-C_{1-4} alkyl, amino-C_{1-4} alkyl, mono-C_{1-4} alkylamino-C_{1-4} alkyl and di-C_{1-4} alkylamino-C_{1-4} alkyl; or

A is phenyl which is substituted with 0, 1, 2, or 3 substituents independently selected from C_{1-4} alkyl, oxo, oxime, hydroxy, halo-C_{1-4} alkyl, dihalo-C_{1-4} alkyl, trihalo-C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxy-C_{3-7} cycloalkyl, halo-C_{1-4} alkoxy, dihalo-C_{1-4} alkoxy, trihalo-C_{1-4} alkoxy, cyano, halogen, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, heteroaryl, C_{1-4} alkyl substituted with hydroxy, C_{1-4} alkoxy substituted with aryl, -C(O)NH-C_{1-4} alkyl- heteroaryl, -NHC(O)-C_{1-4} alkylheteroaryl, C_{1-4} alkyl-C(O)NH-heteroaryl, C_{1-4} alkyl-NHC(O)-heteroaryl, C_{3-7} cycloalkyl, 5-7 membered cycloalkenyl or 5, 6 or 9 membered heterocycle containing 1 or 2 heteroatoms, independently, selected from S, 0 and N; wherein two C_{1-4} alkyl groups can combine with the atoms to which they are

bound to form a 5-6 membered ring;

wherein heteroaryl has 5, 6 or 9 ring atoms, 1, 2 or 3 ring heteroatoms selected from N, 0 and S and is substituted with 0, 1, or 2 substituents independently selected from oxo, hydroxy, nitro, halogen, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkoxy, C_{3-7} cycloalkyl, C_{1-4} alkyl-OH, trihalo-C_{1-4} alkyl, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, -$C(O)NH_2$, -NH_2,-NO_2, hydroxy-C_{1-4} alkylamino, hydroxy-C_{1-4} alkyl, 4-7 memberered heterocycle-C_{1-4} alkyl, amino-C_{1-4} alkyl, mono-C_{1-4} alkylamino-C_{1-4} alkyl, and di-C_{1-4} alkylamino-C_{1-4} alkyl;

B is a group of the formula  , wherein

m, n and p are independently selected from 0 or 1;

R, R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen and C_{1-4} alkyl, wherein alkyl is optionally substituted with hydroxy, amino, mono-C_{1-4} akylamino or di-C_{1-4} akylamino;

R_5 and R_6 are independently selected from hydrogen and fluorine; or

R and R_3, taken in combination form a fused 5 or 6 membered heterocyclic ring having 0 or 1 additional ring heteroatoms selected from N, O or S; or

R_1 and R_3, taken in combination form a C_{1-3} alkylene group; or

R_1 and R_5, taken in combination form a C_{1-3} alkylene group; or

R_3 and R_4, taken in combination with the carbon atom to which they attach, form a spirocyclic C_{3-6} cycloAlkyl;

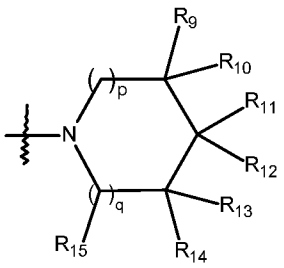
X is CR_AR_B, O, NR_7 or a bond;

R_7 is hydrogen, or C_{1-4} alkyl;

R_A and R_B are independently selected from hydrogen and C_{1-4} alkyl, or R_A and R_B, taken in combination, form a divalent C_{2-5} alkylene group;

Z is CR_8 or N; with the proviso that when Z is N, X is a bond;

R_8 is hydrogen or taken in combination with R_6 form a double bond; or

B is a group of the formula  , wherein

p and q are independently selected from the group consisting of 0, 1, and 2;

R_9 and R_{13} are independently selected from hydrogen and C_{1-4} alkyl;

R_{10} and R_{14} are independently selected from hydrogen, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, and C_{1-4} alkyl optionally substituted with hydroxy, amino, mono-C_{1-4} alkylamino or di-C_{1-4} alkylamino;

R_{11} is hydrogen, C_{1-4} alkyl, amino, mono-C_{1-4} alkylamino, or di-C_{1-4} alkylamino;

R_{12} is hydrogen or C_{1-4} alkyl; or

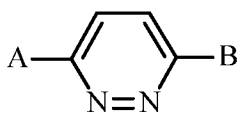
R_9 and R_{11} taken in combination form a saturated azacycle having 4 to 7 ring atoms which is optionally substituted with one to three C_{1-4} alkyl groups; or

R_{11} and R_{12}, taken in combination form a saturated azacycle having 4 to 7 ring atoms which is optionally substituted with one to three C_{1-4} alkyl groups.

or a pharmaceutically acceptable salt thereof;

for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment of the present invention, the FoxM1 gene splicing modifier is selected from a compound of formula (I):

 (I), wherein

A is 2-hydroxy-phenyl which is substituted with:

0, 1, 2, or 3 substituents independently selected from C_{1-4} alkyl, oxo, oxime, hydroxy, halo-C_{1-4} alkyl, dihalo-C_{1-4} alkyl, trihalo-C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxy-C_{3-7} cycloalkyl, halo-C_{1-4} alkoxy, dihalo-C_{1-4} alkoxy, trihalo-C_{1-4} alkoxy, hydroxy, cyano, halogen, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, heteroaryl, C_{1-4} alkyl substituted with hydroxy, C_{1-4} alkoxy substituted with aryl, amino, -C(O)NH-C_{1-4}alkyl-heteroaryl, -NHC(O)-C_{1-4} alkylheteroaryl, C_{1-4} alkyl-C(O)NH-heteroaryl, C_{1-4}alkyl-NHC(O)-heteroaryl, C_{3-7} cycloalkyl, 5-7 membered cycloalkenyl, or 5, 6 or 9 membered heterocycle containing 1 or 2 heteroatoms independently, selected from S, O and N,

wherein two C_{1-4} alkyl groups can combine with the atoms to which they are bound to form a 5-6 membered ring;

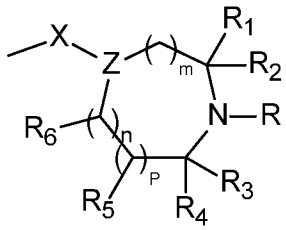
wherein heteroaryl has 5, 6 or 9 ring atoms, 1, 2 or 3 ring heteroatoms selected from N, O and S, and is substituted with 0, 1, or 2 substituents independently selected from oxo, hydroxy, nitro, halogen, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkoxy, C_{3-7} cycloalkyl, C_{1-4} alkyl-OH, trihalo-C_{1-4} alkyl, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, -C(O)NH_2, -NH_2, NO_2, hydroxy-C_{1-4}alkylamino, hydroxy-C_{1-4} alkyl, 4-7 membered heterocycle-C_{1-4} alkyl, amino-C_{1-4} alkyl, mono-C_{1-4}alkylamino-C_{1-4} alkyl, and di-C_{1-4}alkylamino-C_{1-4} alkyl; or

A is 2-naphthyl optionally substituted at the 3 position with hydroxy and additionally substituted with 0, 1, or 2 substituents selected from hydroxy, cyano, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-5} alkoxy, wherein the alkoxy is unsubstituted or substituted with hydroxy, C_{1-4} alkoxy, amino, -NHC(O)-C_{1-4} alkyl, -NHC(O)O-C_{1-4} alkyl, C_{1-4} alkylene-4-7 membered heterocycle, 4-7 membered heterocycle, mono-C_{1-4} alkylamino, and di- C_{1-4} alkylamino; or

A is 6 membered heteroaryl having 1-3 ring nitrogen atoms and which is substituted by phenyl or a heteroaryl having 5 or 6 ring atoms, 1 or 2 ring heteroatoms independently selected from N, 0 and S and is substituted with 0, 1, or 2 substituents independently selected from cyano, C_{1-4} alkyl, mono-C_{1-4} alkylamino, di-C_{1-4}alkylamino, hydroxy-C_{1-4} alkylamino, hydroxy-C_{1-4} alkyl, amino-C_{1-4} alkyl and mono-C_{1-4} alkylamino-C_{1-4} alkyl, and di-C_{1-4}alkylamino-C_{1-4} alkyl; or

A is bicyclic heteroaryl having 9 to 10 ring atoms, 1, 2, or 3 ring heteroatoms independently selected from N, 0 or S, and which is substituted with 0, 1, or 2 substituents independently selected from cyano, oxime, halogen, hydroxy, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkoxy substituted with hydroxy, amino, mono-C_{1-4} alkylamino, and di-C_{1-4} alkylamino; or

A is tricyclic heteroaryl having 12 or 13 ring atoms, 1, 2, or 3 ring heteroatoms independently selected from N, O or S, and which is substituted with 0, 1, or 2 substituents independently selected from cyano, halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkoxy substituted with hydroxy, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, and heteroaryl having 5, 6 or 9 ring atoms, 1, 2 or 3 ring heteroatoms selected from N, O and S, and which is substituted with 0, 1, or 2 substituents independently selected from oxo, hydroxy, nitro, halogen, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkoxy, C_{3-7} cycloalkyl, C_{1-4} alkyl-OH, trihalo-C_{1-4} alkyl, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, -C(O)NH_2, -NH_2, -NO_2, hydroxy-C_{1-4} alkylamino, hydroxy-C_{1-4} alkyl, 4-7 membered heterocycle-C_{1-4} alkyl, amino-C_{1-4} alkyl, mono-C_{1-4} alkylamino-C_{1-4} alkyl and di-C_{1-4} alkylamino-C_{1-4} alkyl;

B is a group of the formula  , wherein

m, n and p are independently selected from 0 or 1;

R, R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen and C_{1-4} alkyl, wherein alkyl is optionally substituted with hydroxy, amino, mono-C_{1-4} akylamino or di-C_{1-4} akylamino;

R_5 and R_6 are independently selected from hydrogen and fluorine; or

R and R_3, taken in combination form a fused 5 or 6 membered heterocyclic ring having 0 or 1 additional ring heteroatoms selected from N, O or S; or

R_1 and R_3, taken in combination form a C_{1-3} alkylene group; or

R_1 and R_5, taken in combination form a C_{1-3} alkylene group; or

R_3 and R_4, taken in combination with the carbon atom to which they attach, form a spirocyclic C_{3-6} cycloAlkyl;

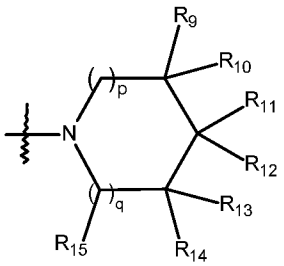
X is CR_AR_B, O, NR_7 or a bond;

R_7 is hydrogen, or C_{1-4} alkyl;

R_A and R_B are independently selected from hydrogen and C_{1-4} alkyl, or R_A and R_B, taken in combination, form a divalent C_{2-5} alkylene group;

Z is CR_8 or N; with the proviso that when Z is N, X is a bond;

R_8 is hydrogen or taken in combination with R_6 form a double bond; or

B is a group of the formula 

, wherein

p and q are independently selected from the group consisting of 0, 1, and 2;

R_9 and R_{13} are independently selected from hydrogen and C_{1-4} alkyl;

R_{10} and R_{14} are independently selected from hydrogen, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, and C_{1-4} alkyl optionally substituted with hydroxy, amino, mono-C_{1-4} alkylamino or di-C_{1-4} alkylamino;

R_{11} is hydrogen, C_{1-4} alkyl, amino, mono-C_{1-4} alkylamino, or di-C_{1-4} alkylamino;

R_{12} is hydrogen or C_{1-4} alkyl; or

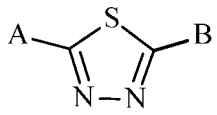
R_9 and R_{11} taken in combination form a saturated azacycle having 4 to 7 ring atoms which is optionally substituted with one to three C_{1-4} alkyl groups; or

R_{11} and R_{12}, taken in combination form a saturated azacycle having 4 to 7 ring atoms which is optionally substituted with one to three C_{1-4} alkyl group;

or a pharmaceutically acceptable salt thereof;

for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment of the present invention, the FoxM1 gene splicing modifier is selected from a compound of formula (VI)

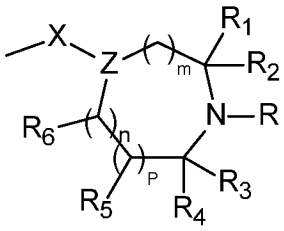


(VI), wherein

A is 6 membered heteroaryl having 1-3 ring nitrogen atoms and which is substituted by phenyl or a heteroaryl having 5 or 6 ring atoms, 1 or 2 ring heteroatoms independently selected from N, O and S and is substituted with 0, 1, or 2 substituents independently selected from cyano, C_{1-4} alkyl, mono-C_{1-4} alkylamino, di-C_{1-4}alkylamino, hydroxy-C_{1-4} alkylamino, hydroxy-C_{1-4} alkyl, amino-C_{1-4} alkyl and mono-C_{1-4} alkylamino-C_{1-4} alkyl, and di-C_{1-4}alkylamino-C_{1-4} alkyl; or

A is bicyclic heteroaryl having 9 to 10 ring atoms, 1, 2, or 3 ring heteroatoms independently selected from N, O or S, and which is substituted with 0, 1, or 2 substituents independently selected from cyano, oxime, halogen, hydroxy, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkoxy substituted with hydroxy, amino, mono-C_{1-4} alkylamino, and di-C_{1-4} alkylamino; or

A is phenyl which is substituted with 0, 1, 2, or 3 substituents independently selected from C_{1-4} alkyl, oxo, oxime, hydroxy, halo-C_{1-4} alkyl, dihalo-C_{1-4} alkyl, trihalo-C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxy-C_{3-7} cycloalkyl, halo-C_{1-4} alkoxy, dihalo-C_{1-4} alkoxy, trihalo-C_{1-4} alkoxy, cyano, halogen, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, heteroaryl, C_{1-4} alkyl substituted with hydroxy, C_{1-4} alkoxy substituted with aryl, -C(O)NH-C_{1-4} alkyl- heteroaryl, -NHC(O)-C_{1-4} alkylheteroaryl, C_{1-4} alkyl-C(O)NH-heteroaryl, C_{1-4} alkyl-NHC(O)-heteroaryl, C_{3-7} cycloalkyl, 5-7 membered cycloalkenyl or 5, 6 or 9 membered heterocycle containing 1 or 2 heteroatoms, independently, selected from S, 0 and N;
wherein two C_{1-4} alkyl groups can combine with the atoms to which they are bound to form a 5-6 membered ring;
wherein heteroaryl has 5, 6 or 9 ring atoms, 1, 2 or 3 ring heteroatoms selected from N, 0 and S and is substituted with 0, 1, or 2 substituents independently selected from oxo, hydroxy, nitro, halogen, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkoxy, C_{3-7} cycloalkyl, C_{1-4} alkyl-OH, trihalo-C_{1-4} alkyl, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, -C(O)NH_2, -NH_2,-NO_2, hydroxy-C_{1-4} alkylamino, hydroxy-C_{1-4} alkyl, 4-7 memberered heterocycle-C_{1-4} alkyl, amino-C_{1-4} alkyl, mono-C_{1-4} alkylamino-C_{1-4} alkyl, and di-C_{1-4} alkylamino-C_{1-4} alkyl;



B is a group of the formula , wherein

m, n and p are independently selected from 0 or 1;

R, R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen and C_{1-4} alkyl, wherein alkyl is optionally substituted with hydroxy, amino, mono-C_{1-4} akylamino or di-C_{1-4} akylamino;

R_5 and R_6 are independently selected from hydrogen and fluorine; or

R and R_3, taken in combination form a fused 5 or 6 membered heterocyclic ring having 0 or 1 additional ring heteroatoms selected from N, O or S; or

R_1 and R_3, taken in combination form a C_{1-3} alkylene group; or

R_1 and R_5, taken in combination form a C_{1-3} alkylene group; or

R_3 and R_4, taken in combination with the carbon atom to which they attach, form a spirocyclic C_{3-6} cycloAlkyl;

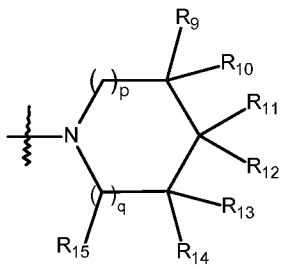
X is CR_AR_B, O, NR_7 or a bond;

R_7 is hydrogen, or C_{1-4} alkyl;

R_A and R_B are independently selected from hydrogen and C_{1-4} alkyl, or R_A and R_B, taken in combination, form a divalent C_{2-5} alkylene group;

Z is CR_8 or N; with the proviso that when Z is N, X is a bond;

R_8 is hydrogen or taken in combination with R_6 form a double bond; or



B is a group of the formula , wherein

p and q are independently selected from the group consisting of 0, 1, and 2;

R_9 and R_{13} are independently selected from hydrogen and C_{1-4} alkyl;

R_{10} and R_{14} are independently selected from hydrogen, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, and C_{1-4} alkyl optionally substituted with hydroxy, amino, mono-C_{1-4} alkylamino or di-C_{1-4} alkylamino;

R_{11} is hydrogen, C_{1-4} alkyl, amino, mono-C_{1-4} alkylamino, or di-C_{1-4} alkylamino;

R_{12} is hydrogen or C_{1-4} alkyl; or

R_9 and R_{11} taken in combination form a saturated azacycle having 4 to 7 ring atoms which is optionally substituted with one to three C_{1-4} alkyl groups; or

R_{11} and R_{12}, taken in combination form a saturated azacycle having 4 to 7 ring atoms which is optionally substituted with one to three C_{1-4} alkyl groups.

or a pharmaceutically acceptable salt thereof;

for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I) or of formula (VI), wherein

A is 2-hydroxy-phenyl which is substituted with:

0, 1, 2, or 3 substituents independently selected from C_{1-4} alkyl, oxo, oxime, hydroxy, halo-C_{1-4} alkyl, dihalo-C_{1-4} alkyl, trihalo-C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxy-C_{3-7} cycloalkyl, halo-C_{1-4} alkoxy, dihalo-C_{1-4} alkoxy, trihalo-C_{1-4} alkoxy, hydroxy, cyano, halogen, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, heteroaryl, C_{1-4} alkyl substituted with hydroxy, C_{1-4} alkoxy substituted with aryl, amino, -C(O)NH-C_{1-4}alkyl-heteroaryl, -NHC(O)-C_{1-4} alkylheteroaryl, C_{1-4} alkyl-C(O)NH-heteroaryl, C_{1-4}alkyl-NHC(O)-heteroaryl, C_{3-7} cycloalkyl, 5-7 membered cycloalkenyl, or 5, 6 or 9 membered heterocycle containing 1 or 2 heteroatoms independently, selected from S, O and N,
wherein two C_{1-4} alkyl groups can combine with the atoms to which they are bound to form a 5-6 membered ring;
wherein heteroaryl has 5, 6 or 9 ring atoms, 1, 2 or 3 ring heteroatoms selected

from N, O and S, and is substituted with 0, 1, or 2 substituents independently selected from oxo, hydroxy, nitro, halogen, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkoxy, C_{3-7} cycloalkyl, C_{1-4} alkyl-OH, trihalo-C_{1-4} alkyl, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, -C(O)NH_2, -NH_2, NO_2, hydroxy-C_{1-4}alkylamino, hydroxy-C_{1-4} alkyl, 4-7 membered heterocycle-C_{1-4} alkyl, amino-C_{1-4} alkyl, mono-C_{1-4}alkylamino-C_{1-4} alkyl, and di-C_{1-4}alkylamino-C_{1-4} alkyl; or

A is 2-naphthyl optionally substituted at the 3 position with hydroxy and additionally substituted with 0, 1, or 2 substituents selected from hydroxy, cyano, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-5} alkoxy, wherein the alkoxy is unsubstituted or substituted with hydroxy, C_{1-4} alkoxy, amino, -NHC(O)-C_{1-4} alkyl, -NHC(O)O-C_{1-4} alkyl, C_{1-4} alkylene-4-7 membered heterocycle, 4-7 membered heterocycle, mono-C_{1-4} alkylamino, and di- C_{1-4} alkylamino; or

A is phenyl which is substituted with 0, 1, 2, or 3 substituents independently selected from C_{1-4} alkyl, oxo, oxime, hydroxy, halo-C_{1-4} alkyl, dihalo-C_{1-4} alkyl, trihalo-C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxy-C_{3-7} cycloalkyl, halo-C_{1-4} alkoxy, dihalo-C_{1-4} alkoxy, trihalo-C_{1-4} alkoxy, cyano, halogen, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, heteroaryl, C_{1-4} alkyl substituted with hydroxy, C_{1-4} alkoxy substituted with aryl, -C(O)NH-C_{1-4} alkyl- heteroaryl, -NHC(O)-C_{1-4} alkylheteroaryl, C_{1-4} alkyl-C(O)NH-heteroaryl, C_{1-4} alkyl-NHC(O)-heteroaryl, C_{3-7} cycloalkyl, 5-7 membered cycloalkenyl or 5, 6 or 9 membered heterocycle containing 1 or 2 heteroatoms, independently, selected from S, 0 and N;
wherein two C_{1-4} alkyl groups can combine with the atoms to which they are bound to form a 5-6 membered ring;
wherein heteroaryl has 5, 6 or 9 ring atoms, 1, 2 or 3 ring heteroatoms selected from N, 0 and S and is substituted with 0, 1, or 2 substituents independently selected from oxo, hydroxy, nitro, halogen, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkoxy, C_{3-7} cycloalkyl, C_{1-4} alkyl-OH, trihalo-C_{1-4} alkyl, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, -C(O)NH_2, -NH_2,-NO_2, hydroxy-C_{1-4} alkylamino, hydroxy-C_{1-4} alkyl, 4-7 memberered heterocycle-C_{1-4} alkyl, amino-C_{1-4} alkyl, mono-C_{1-4} alkylamino-C_{1-4} alkyl, and di-C_{1-4} alkylamino-C_{1-4} alkyl;

or a pharmaceutically acceptable salt thereof;

for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing

modifier selected from a compound of formula (I) or a compound of formula (VI), wherein A is 2-hydroxy-phenyl substituted with 0, 1, 2, or 3 substituents independently selected from C_{1-4} alkyl, halo-C_{1-4} alkyl, C_{1-4} alkoxy, hydroxy, cyano, halogen, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, heteroaryl, and C_{1-4} alkyl substituted with hydroxy or amino, wherein heteroaryl has 5 or 6 ring atoms, 1 or 2 ring heteroatoms selected from N, 0 and S and is substituted with 0, 1, or 2 substituents independently selected from C_{1-4} alkyl, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, hydroxy-C_{1-4} alkylamino, hydroxy-C_{1-4} alkyl, 4-7 membered heterocycle-C_{1-4} alkyl, amino-C_{1-4} alkyl, mono- C_{1-4} alkylamino-C_{1-4} alkyl, and di-C_{1-4} alkylamino-C_{1-4} alkyl; or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I) or a compound of formula (VI), wherein A is 2-naphthyl optionally substituted at the 3 position with hydroxy and additionally substituted with 0, 1, or 2 substituents selected from hydroxy, cyano, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, wherein alkoxy is unsubstituted or substituted with hydroxy, C_{1-4} alkoxy, amino, -N(H)C(O)-C_{1-4} alkyl, -N(H)C(O)O-C_{1-4} alkyl, 4 to 7 membered heterocycle, mono-C_{1-4} alkylamino and di-C_{1-4} alkylamino; or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I) or a compound of formula (VI), wherein A is phenyl substituted with 0, 1, 2, or 3 substituents independently selected from C_{1-4} alkyl, halo-C_{1-4} alkyl, C_{1-4} alkoxy, hydroxy, cyano, halogen, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, heteroaryl, and C_{1-4} alkyl substituted with hydroxy or amino, wherein heteroaryl has 5 or 6 ring atoms, 1 or 2 ring heteroatoms selected from N, 0 and S and is substituted with 0, 1, or 2 substituents independently selected from C_{1-4} alkyl, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, hydroxy-C_{1-4} alkylamino, hydroxy-C_{1-4} alkyl, 4-7 membered heterocycle-C_{1-4} alkyl, amino-C_{1-4} alkyl, mono- C_{1-4} alkylamino-C_{1-4} alkyl, and di-C_{1-4} alkylamino-C_{1-4} alkyl; or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I) or a compound of formula (VI), wherein

A is 2-hydroxy-phenyl substituted with one additional substituent selected from cyano and heteroaryl; or

A is 2-naphthyl optionally substituted at the 3 position with hydroxy and additionally substituted with 0 or 1 substituents selected from hydroxy and C_{1-4} alkoxy; or

A is phenyl which is substituted with two or three substituents independently selected from halogen and heteroaryl;

wherein heteroaryl has 5 or 6 ring atoms of which 1 or 2 are nitrogen and is substituted with 0, 1, or 2 substituents independently selected from C_{1-4} alkyl and hydroxy;
or a pharmaceutically acceptable salt thereof;
for use in the treatment, prevention and/or delay of progression of cancer.

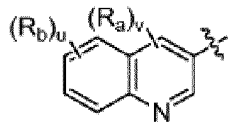
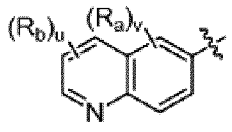
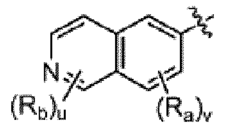
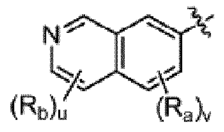
In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I) or a compound of formula (VI), wherein
A is 2-hydroxy-phenyl substituted with one additional substituent selected from cyano and heteroaryl; or
A is 2-naphthyl optionally substituted at the 3 position with hydroxy and additionally substituted with 0 or 1 substituents selected from hydroxy and methoxy; or
A is phenyl which is substituted with two or three substituents independently selected from chloro, fluoro and heteroaryl;
wherein heteroaryl is pyrazolyl or pyridinyl substituted with 0, 1, or 2 substituents independently selected from methyl and hydroxy;
or a pharmaceutically acceptable salt thereof;
for use in the treatment, prevention and/or delay of progression of cancer.

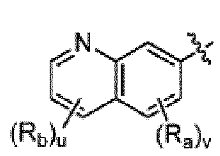
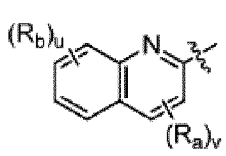
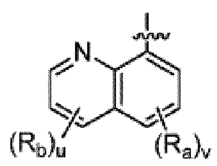
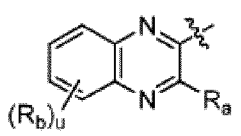
In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I) or a compound of formula (VI) as described herein, wherein A is substituted adjacent to the point of attachment of the pyridazinyl-moiety of formula (I) or the thiadiazolyl-moiety of formula (VI) (i.e. in ortho-position) with halo, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, or hydroxy, and further in another position by 0, 1, or 2 additional substituents as described herein.

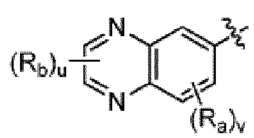
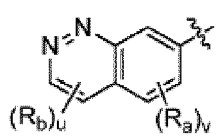
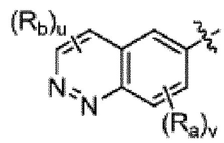
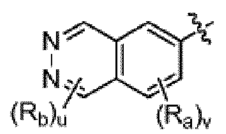
In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I) or a compound of formula (VI) as described herein, wherein A is substituted adjacent to the point of attachment of the pyridazinyl-moiety of formula (I) or the thiadiazolyl-moiety of formula (VI) (i.e. in ortho-position) with fluoro, chloro, or hydroxy, and further in another position by 0, 1, or 2 additional substituents as described herein.

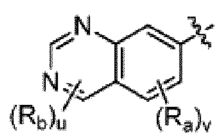
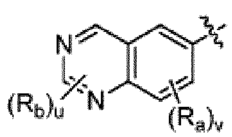
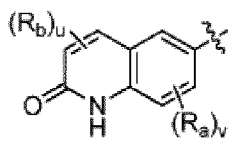
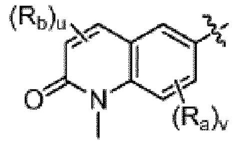
In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I) or a compound of formula (VI) as described herein, wherein A is substituted adjacent to the point of attachment of the pyridazinyl-moiety of formula (I) or the thiadiazolyl-moiety of formula (VI) (i.e. in ortho-position) with fluoro, chloro, or hydroxy.

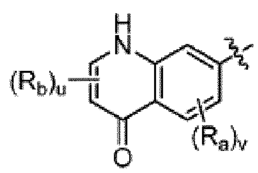
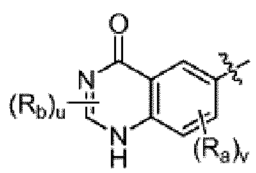
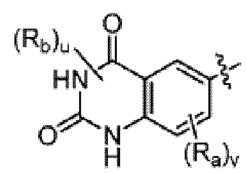
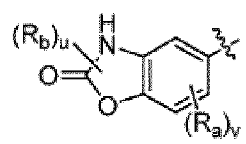
In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I) or of formula (VI), wherein A is selected from:

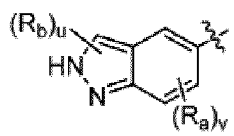
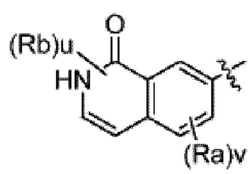
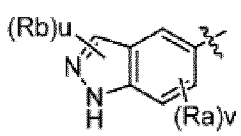
 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

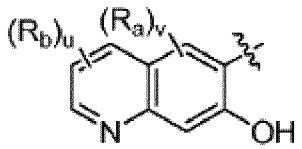
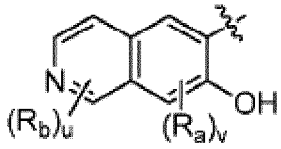
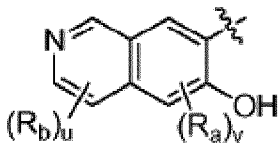
 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  and  ;

wherein u and v are each, independently, 0, 1, 2 or 3; and each R_a and R_b are, independently, selected from cyano, halogen, hydroxy, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{3-7} cycloalkyl, heterocyclyl, heteroaryl, heterocyclyl-C_{1-4} alkyl, C_{1-4} alkyl-aryl, C_{1-4} alkyl-heterocyclyl, C_{1-4} alkyl-heteroaryl, C_{1-4} alkoxy-aryl, C_{1-4} alkoxy-heterocyclyl, C_{1-4} alkoxy-heteroaryl, and C_{1-4} alkoxy substituted with hydroxy, C_{1-4} alkoxy, amino, mono-C_{1-4} alkylamino and di-C_{1-4} alkylamino; or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I) or of formula (VI), wherein A is selected from: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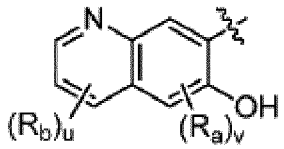
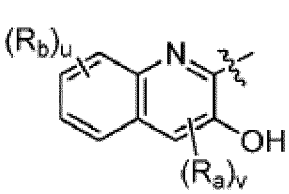
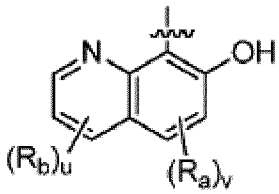
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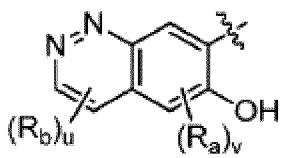
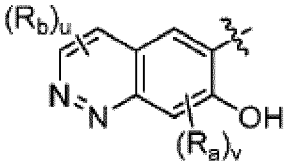
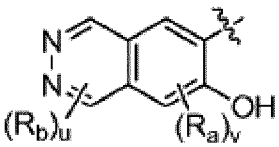
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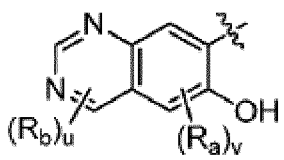
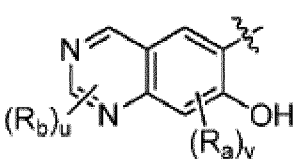
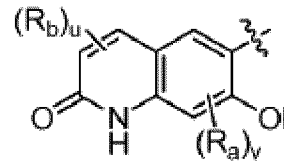
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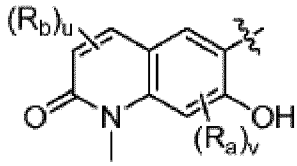

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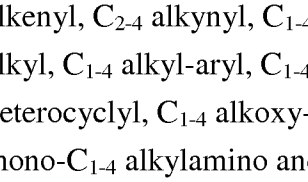


wherein u and v are each, independently, 0, 1, 2 or 3; and

each R_a and R_b are, independently, selected from cyano, halogen, hydroxy, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{3-7} cycloalkyl, heterocyclyl, heteroaryl, heterocyclyl-C_{1-4} alkyl, C_{1-4} alkyl-aryl, C_{1-4} alkyl-heterocyclyl, C_{1-4} alkyl-heteroaryl, C_{1-4} alkoxy-aryl, C_{1-4} alkoxy-heterocyclyl, C_{1-4} alkoxy-heteroaryl, C_{1-4} alkoxy substituted with hydroxy, C_{1-4} alkoxy, amino, mono-C_{1-4} alkylamino and di-C_{1-4} alkylamino; or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I) or a compound of formula (VI), wherein A is

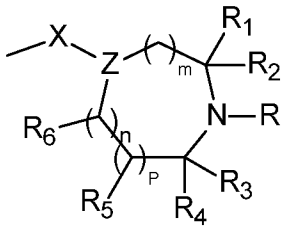
substituted by one or more substituents as described herein, wherein one of the substituents of A is hydroxy in ortho-positon to the pyridazine of formula (I) or to the thiadiazole of formula (VI); or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I) or a compound of formula (VI), wherein A is substituted by one or more substituents as described herein, wherein one of the substituents of A is hydroxy in 2-positon to the pyridazine of formula (I) or to the thiadiazole of formula (VI); or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I), wherein A is substituted by one or more substituents as described herein, wherein one of the substituents of A is hydroxy in ortho-positon to the pyridazine of formula (I); or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (VI), wherein A is substituted by one or more substituents as described herein, wherein one of the substituents of A is hydroxy in ortho-positon to the thiadiazole of formula (VI); or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

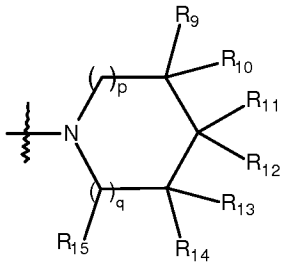
In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I) or a compound of formula (VI), wherein B is



a group of the formula , wherein m, n and p are independently selected from 0 or 1; R, R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, and C_{1-4} alkyl, which alkyl is optionally substituted with hydroxy, amino, mono-C_{1-4} alkylamino or di-C_{1-4} alkylamino; R_5 and R_6 are hydrogen; or R and R_3 taken in combination form a fused 5 or 6 membered heterocyclic ring having 0 or 1 additional ring heteroatoms selected from N, O or S; R_1 and R_3, taken in combination form a C_{1-3} alkylene group; R_1 and R_5 taken in combination form a C_{1-3} alkylene group; R_3 and R_4 taken in combination with the carbon atom to which they attach, form a spirocyclic C_{3-6} cycloalkyl; X is CR_AR_B, O, NR_7 or a

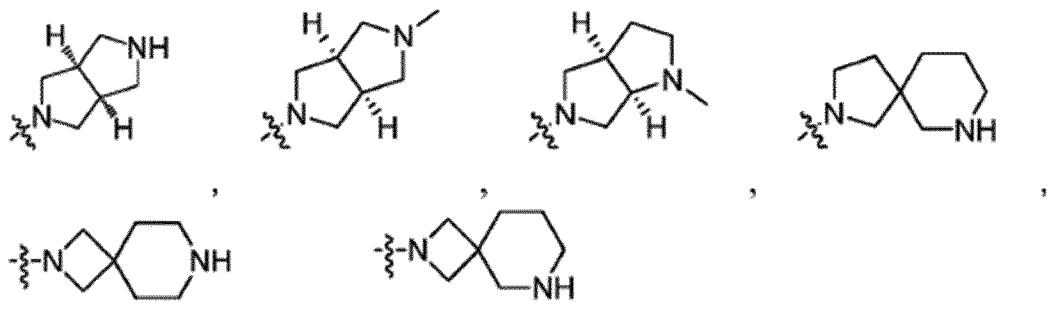
bond; R_A and R_B are independently selected from hydrogen and C_{1-4} alkyl, or R_A and R_B taken in combination, form a divalent C_{2-5} alkylene group; Z is CR_8 or N; when Z is N, X is a bond; R_8 is hydrogen or taken in combination with R_6 form a double bond;
or a pharmaceutically acceptable salt thereof;
for use in the treatment, prevention and/or delay of progression of cancer.

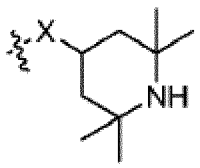
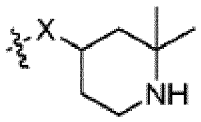
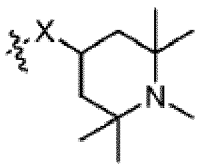
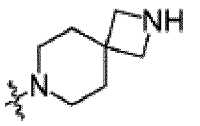
In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I) or a compound of formula (VI), wherein B is



a group of the formula , wherein p and q are independently selected from the group consisting of 0, 1, and 2; R_9 and R_{13} are independently selected from hydrogen and C_{1-4} alkyl; R_{10} and R_{14} are independently selected from hydrogen, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino and C_{1-4} alkyl, which alkyl is optionally substituted with hydroxy, amino, mono-C_{1-4} alkylamino or di-C_{1-4} alkylamino; R_{11} is hydrogen, C_{1-4} alkyl, amino, mono-C_{1-4} alkylamino or di-C_{1-4} alkylamino; R_{12} is hydrogen or C_{1-4} alkyl; or R_9 and R_{11} taken in combination form a saturated azacycle having 4 to 7 ring atoms which is optionally substituted with one to three C_{1-4} alkyl groups; or R_{11} and R_{12} taken in combination form a saturated azacycle having 4 to 7 ring atoms which is optionally substituted with one to three C_{1-4} alkyl groups;
or a pharmaceutically acceptable salt thereof;
for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I) or a compound of formula (VI), wherein B is selected from the group consisting of



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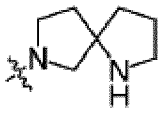
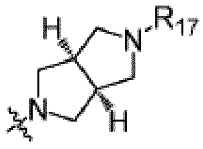
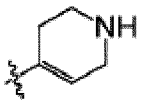
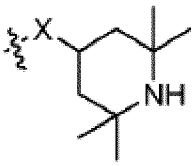



, and



wherein X is O or -N(CH_3)-; and R_{17} is hydrogen or methyl;
or a pharmaceutically acceptable salt thereof;
for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I) or a compound of formula (VI), wherein B is

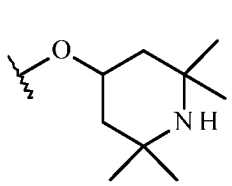
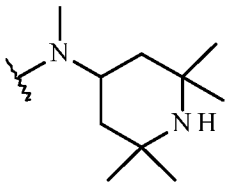


and X is O or -N(CH_3)-; or a pharmaceutically acceptable salt thereof;
for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I) or a compound of formula (VI), wherein X is O; or a pharmaceutically acceptable salt thereof;
for use in the treatment, prevention and/or delay of progression of cancer.

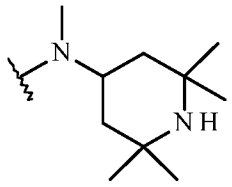
In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I) or a compound of formula (VI), wherein X is -N(CH_3)-; or a pharmaceutically acceptable salt thereof;
for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I) or a compound of formula (VI), wherein B is

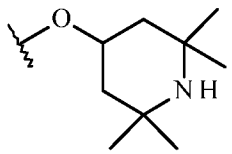
or ; or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I) or a compound of formula (VI), wherein B is



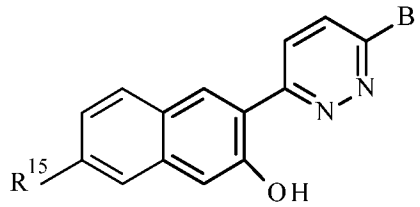
; or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (I) or a compound of formula (VI), wherein B is



; or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (II):

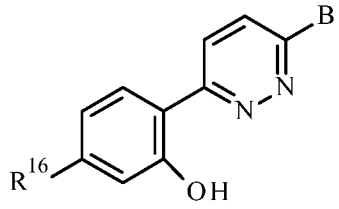


(II), wherein R^{15} is hydrogen, hydroxy, or C_{1-4} alkoxy, wherein alkoxy is optionally substituted with hydroxy, methoxy, amino, mono-methylamino, di-methylamino or morpholine; or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (II), wherein R^{15} is hydrogen, hydroxy or methoxy; or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

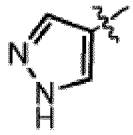
In a particular embodiment, the present invention relates to a FoxM1 gene splicing

modifier selected from a compound of formula (III):

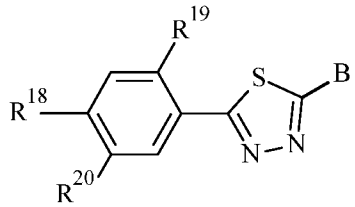


(III), wherein R^{16} is cyano, 5-membered heteroaryl having two ring nitrogen atoms, or 6-membered heteroaryl having one ring nitrogen atom; wherein the 5-membered heteroaryl is optionally substituted with C_{1-4} alkyl; wherein the 6-membered heteroaryl is optionally substituted with one or two substituents selected from C_{1-4} alkyl and hydroxy; or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (III), wherein R^{16} is cyano, pyrazolyl or pyridinyl, wherein pyrazolyl is optionally substituted with methyl and wherein pyridinyl is optionally substituted with one or two substituents selected from methyl and hydroxy; or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (III), wherein R^{16} is  ; or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

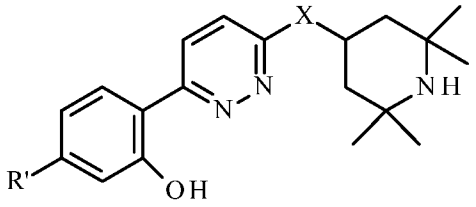
In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (VII):



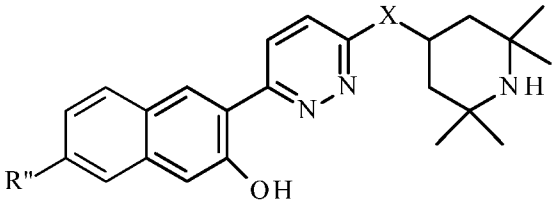
(VII), wherein R^{18} is 5-membered heteroaryl having two ring nitrogen atoms or 6-membered heteroaryl having one ring nitrogen atom; wherein the 5-membered heteroaryl is optionally substituted with C_{1-4} alkyl; wherein the 6-membered heteroaryl is optionally substituted with one or two substituents selected from C_{1-4} alkyl and hydroxy; R^{19} is hydrogen or halogen; and R^{20} is hydrogen or halogen; or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (VII), wherein R^{18} is pyrazolyl optionally substituted with methyl, or pyridinyl substituted with methyl and hydroxy; R^{19} is hydrogen, chloro or fluoro; and R^{20} is hydrogen, chloro or fluoro; or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

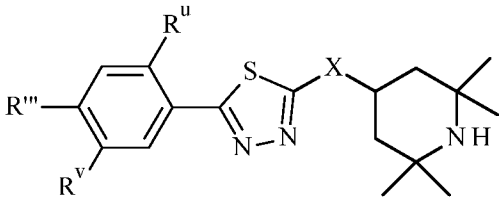
In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (IV) or of formula (V) or of formula (VIII):



(IV)



(V)



(VIII), wherein

X is -O- or -N(CH_3)-; R' is cyano, pyrazolyl optionally substituted with methyl, or pyridinyl substituted with methyl and hydroxy; R" is hydrogen, methyl or methoxy; R'" is pyrazolyl optionally substituted with methyl, or pyridinyl substituted with methyl and hydroxy; R^u is hydrogen, chloro or fluoro; R^v is hydrogen, chloro or fluoro; or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

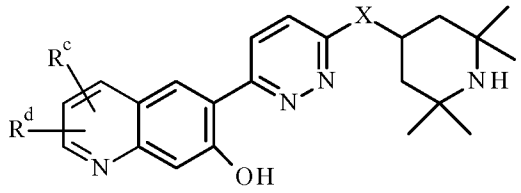
In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (IV), wherein X is -O- or -N(CH_3)-; R' is cyano, pyrazolyl optionally substituted with methyl, or pyridinyl substituted with methyl and hydroxy; or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (V), wherein X is -O- or -N(CH_3)-; R" is hydrogen, methyl or methoxy; or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

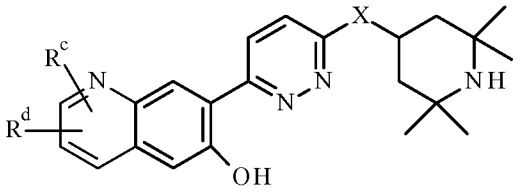
In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (VIII), wherein X is -O- or -N(CH_3)-; R'" is pyrazolyl optionally substituted with methyl, or pyridinyl substituted with methyl and hydroxy; R^u is hydrogen, chloro or fluoro; R^v is hydrogen, chloro or fluoro; or a pharmaceutically

acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

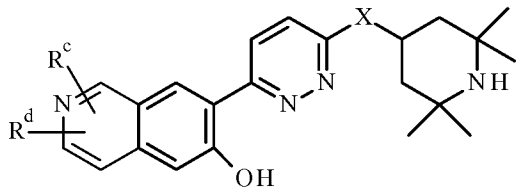
In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from a compound of formula (IX) or of formula (X) or of formula (XI) or of formula (XII) or of formula (XIII) or of formula (XIV) or of formula (XV):



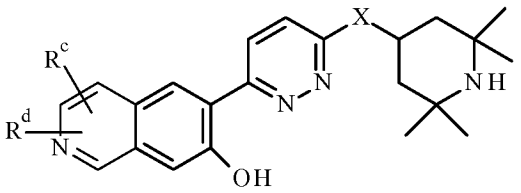
(IX),



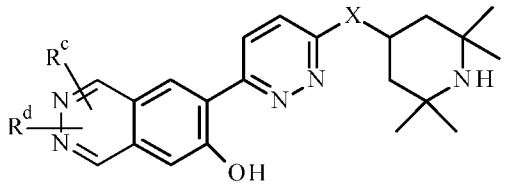
(X),



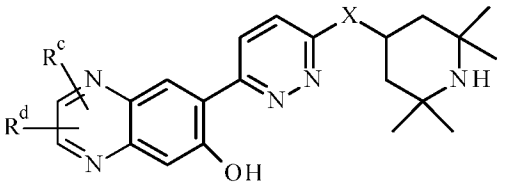
(XI),



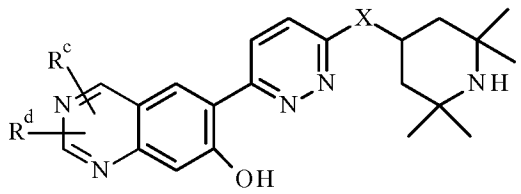
(XII),



(XIII),



(XIV),



(XV),

wherein X is -O- or -N(CH_3)-; and each R^C and R^d are, independently, selected from hydrogen, cyano, halogen, hydroxy, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{3-7} cycloalkyl, heterocyclyl, heteroaryl, heterocyclyl-C_{1-4} alkyl, C_{1-4} alkyl-aryl, C_{1-4} alkyl-heterocyclyl, C_{1-4} alkyl-heteroaryl, C_{1-4} alkoxy-aryl, C_{1-4} alkoxy-heterocyclyl, C_{1-4} alkoxy-heteroaryl, C_{1-4} alkoxy substituted with hydroxy, C_{1-4} alkoxy, amino, mono-C_{1-4} alkylamino and di-C_{1-4} alkylamino; or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier as described herein selected from the group consisting of:
6-(naphthalen-2-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
6-(benzo[b]thio-phen-2-yl)-N-methyl-N-(2,2,6,6-tetra-methylpiperidin-4-yl)pyridazin-3-amine;
2-(6-(2,2,6,6-tetra methylpiperidin-4-ylamino)-pyridazin-3-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetra-methylpiperidin-4-yl)amino)pyridazin-3-yl)benzo[b]-thiophene-5-carbonitrile;

6-(quinolin-3-yl)-N-(2,2,6,6-tetramethyl-piperidin-4-yl)pyridazin-3-amine;
3-(benzo[b]-thiophen-2-yl)-6-(2,2,6,6-tetra-methylpiperidin-4-yloxy)pyridazine;
2-(6-(methyl-(2,2,6,6-tetra-methylpiperidin-4-yl)amino)-pyridazin-3-yl)phenol;
6-(6-(methyl-(2,2,6,6-tetra-methylpiperidin-4-yl)amino)-pyridazin-3-yl)naphthalen-2-ol;
6-(benzo[b]-thiophen-2-yl)-N-(2,2,6,6-tetra-methylpiperidin-4-yl)pyridazin-3-amine;
7-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoquinoline;
6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoquinoline;
N-methyl-6-(quinolin-7-yl)-N-(2,2,6,6-tetramethyl-piperidin-4-yl)pyridazin-3-amine;
N-methyl-6-(quinolin-6-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
6-(isoquinolin-7-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
6-(isoquinolin-6-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
6-(imidazo[1,2-a]pyridin-6-yl-pyridazin-3-yl)-methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amine
methyl-[6-(6-phenyl-pyridin-3-yl)-pyridazin-3-yl]-(2,2,6,6-tetramethyl-piperidin-4-yl)-amine;
methyl-[6-(6-pyrrol-1-yl-pyridin-3-yl)-pyridazin-3-yl]-(2,2,6,6-tetra methyl-piperidin-4-yl)-amine;
methyl-(6-quinoxalin-2-yl-pyridazin-3-yl)-(2,2,6,6-tetramethyl-piperidin-4-yl)-amine;
methyl-(6-quinolin-3-yl-pyridazin-3-yl)-(2,2,6,6-tetramethyl-piperidin-4-yl)-amine;
N-methyl-6-(phthalazin-6-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
6-(benzo[c][1,2,5]oxa-diazol-5-yl)-N-(2,2,6,6-tetramethyl-piperidin-4-yl)pyridazin-3-amine;
6-(benzo[d]thiazol-5-yl)-N-(2,2,6,6-tetramethyl-piperidin-4-yl)pyridazin-3-amine;
6-(2-methylbenzo-[d]oxazol-6-yl)-N-(2,2,6,6-tetramethyl-piperidin-4-yl)pyridazin-3-amine;
3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
5-chloro-2-(6-(methyl(1 ,2,2,6,6-pentamethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
3-(6-(2,2,6,6-tetramethylpiperidin-4-ylamino)pyridazin-3-yl)naphthalen-2-ol;
5-chloro-2-(6-(1 ,2,2,6,6-pentamethylpiperidin-4-ylamino)pyridazin-3-yl)phenol;
4-hydroxy-3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)benzonitrile;
3-[6-(2,2,6,6-tetramethyl-piperidin-4-yloxy)-pyridazin-3-yl]-naphthalen-2-ol;
2-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-4-trifluoromethylphenol;
2-fluoro-6-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-phenol;
3,5-dimethoxy-2-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-phenol;
4,5-dimethoxy-2-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-phenol;
5-methoxy-2-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-phenol;
4,5-difluoro-2-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-phenol;
5-fluoro-2-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-phenol;
3-hydroxy-4-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)benzonitrile;
1-allyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
6-(benzo[b]thiophen-2-yl)-N-(1 ,2,2,6,6-pentamethylpiperidin-4-yl)pyridazin-3-amine;

N-allyl-3-hydroxy-4-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)benzamide;
2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
5-(5-methyl-oxazol-2-yl)-2-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-phenol;
5-(4-hydroxymethyl)-1H-pyrazole-1-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4 yl)amino)pyridazin-3-yl)phenol;
5-(1 H-imidazole-1-yl)-2-(6-(methyl(2,2,6,6-tetramethyl-piperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(4-amino-1H-pyrazole-1-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(4-amino-1H-pyrazol-1-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(3-amino-pyrazol-1-yl)-2 -{6-[methyl-(2,2,6,6-tetra methyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenol;
5-(5-amino-1H-pyrazol-1-yl)-2-(6-(methyl-(2,2,6,6-tetramethyl-piperidin-4-yl) amino)pyridazin-3-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(1H-pyrazol-1-yl)phenol;
2-{6-[(2-hydroxy-ethyl)-(2,2,6,6-tetra methyl-piperidn-4-yl)-amino]-pyridazin-3-yl}-5-pyrazol-1-yl-phenol;
2-(6-(piperidin-4-yloxy)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
2-(6-(((2S,4R, 6 R)-2,6-dimethylpiperidin-4-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
5 2-(6-((2, 6-di-methylpiperidin-4-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
2-(6-((2, 6-di-methylpiperidin-4-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
5-(1H-pyrazol-1-yl)-2-(6-(pyrrolidin-3-yloxy)pyridazin-3-yl)phenol;
2-(6-((-2-methylpiperidin-4-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
(S)-5-(1H-pyrazol-1-yl)-2-(6-(pyrrolidin-3-ylmethoxy)pyridazin-3-yl)phenol;
(R)-5-(1H-pyrazol-1-yl)-2-(6-(pyrrolidin-3-yl methoxy)pyridazin-3-yl)phenol;
2-(6-((3-fluoropiperidin-4-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)-phenol;
2-[6-(1,2,2,6,6-pentamethyl-piperidin-4-yloxy)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
5-pyrazol-1-yl-2-[6-((2,2,6,6-tetramethylpiperidin-4-yloxy)-pyridazin-3-yl]-phenol;
5-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)phenol;
2-(6-piperazin-1-yl-pyridazin-3-yl)-5-pyrazol-1-yl-phenol;

3-[6-(azetidin-3-yl-amino)-pyridazin-3-yl]-naphthalen-2-ol;
2-[6-(azetidin-3-ylamino)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(3, 5-di methyl-piperazin-1-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(7-methyl-2,7-diaza-spiro[4.4]non-2-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-(6-[1,4]diazepan-1-yl-pyridazin-3-yl)-5-pyrazol-1-yl-phenol;
2-{6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-pyridazin-3-yl}-5-pyrazol-1-yl-phenol;
2-[6-(3, 6-diaza-bicyclo[3.2.1]oct-3-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(2, 7-diaza-spiro[3.5]non-7-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(3-hydroxy-methyl-piperazin-1-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(1, 7-diaza-spiro[4.4]non-7-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(4-am in o-4-methyl-piperidin-1-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(3-dimethyl-amino-piperidin-1-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(1 ,2,2,6,6-pentamethyl-piperidin-4-ylamino)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(3, 3-di methyl-piperazin-1-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-(6-(7-(2-hydroxyethyl)-2,7-diazaspiro[4.4]-nonan-2-yl)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
2-(6-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
3-(6-(piperazin-1-yl)pyridazin-3-yl)naphthalene-2,7-diol;
5-pyrazol-1-yl-2-[6-(1,2,3,6-tetrahydro-pyridin-4-yl)-pyridazin-3-yl]-phenol;
2-(6-piperidin-4-yl-pyridazin-3-yl)-5-pyrazol-1-yl-phenol;
3-(6-(1 ,2,3,6-tetra-hydropyridin-4-yl)pyridazin-3-yl)naphthalen-2-ol;
3-(6-(1 ,2, 3, 6-tetrahydropyridin-4-yl)pyridazin-3-yl)naphthalene-2,7-diol;
3-(6-(2,2,6,6-tetramethyl-1 ,2,3, 6-tetrahydropyridin-4-yl)pyridazin-3-yl)naphthalene-2,7-diol;
3-(6-(1-methyl-1 ,2,3,6-tetrahydropyridin-4-yl)pyridazin-3-yl)naphthalene-2,7-diol;
3-(6-(piperidin-4-yl)pyridazin-3-yl)naphthalene-2,7-diol;
3-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)naphthalene-2,7-diol;
3-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalene-2,7-diol;
3-(6-((2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalene-2,7-diol;
[3-(7-hydroxy-6-{6-[methyl-(2,2,6,6-tetra methyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-naphthalen-2-yloxy)-propyl]-carbamic acid tert-butyl ester;
7-(3-amino-propoxy)-3-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}naphthalen-2-ol;
N-[3-(7-hydroxy-6-{6-[methyl-(2,2,6,6-tetra methyl-piperidin-4-yl)-amino]-pyridazin-3-yl}naphthalen-2-yloxy)-propyl]-acetamide;
7-(3-hydroxypropoxy)-3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
7-(3-methoxypropoxy)-3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-

yl)naphthalen-2-ol;
7-(2-morpholinoethoxy)-3-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)naphthalen-2-ol;
3-(6-(piperidin-4-ylmethyl)pyridazin-3-yl)naphthalen-2-ol;
5-(1H-pyrazol-1-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)methyl)pyridazin-3-yl)phenol;
3-methoxy-2-(6-(methyl(2,2,6-trimethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(5-methyloxazol-2-yl)phenol;
2-(6-((6S)-6-((S)-1-hydroxyethyl)-2,2-d imethylpiperidin-4-yloxy)pyridazin-3-yl)-5-(1H pyrazol-1-yl)phenol;
7-hydroxy-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2-naphthonitrile;
3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-7-(piperidin-1-ylmethyl)naphthalen-2-ol;
3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-7-(pyrrolidin-1-ylmethyl)naphthalen-2-ol;
1-bromo-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalene-2,7-diol;
1-chloro-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalene- 2,7-diol;
7-methoxy-3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
7-methoxy-3-(6-(methyl(1,2,2,6,6-pentamethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
7-(3,6-dihydro-2H-pyran-4-yl)-3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
3-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-7-(tetrahydro-2H-pyran-4-yl)naphthalen-2-ol;
7-(difluoromethyl)-3-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
7-((4-hydroxy-2 -methyl butan-2-yl)oxy)-3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
7-(3-hydroxy-3-methylbutoxy)-3-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)benzene-1,3-diol;
3-methoxy-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1 H pyrazol-4-yl)phenol;
5-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-(trifluoromethoxy)phenol;

2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)-3-(trifluoromethoxy)phenol;
2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)-3-(trifluoromethoxy)phenol;
4-(3-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(trifluoromethoxy)phenyl)-1-methylpyridin-2(1H)-one;
3-methoxy-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenol;
3-methoxy-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(5,6,7,8-tetrahydroimidazo[1 ,2-a]pyridin-3-yl)phenol;
3-methoxy-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino) pyridazn-3-yl)-5-(pyridin-3-yl)phenol;
5-(1-cyclopentyl-1 H -pyrazol-4-yl)-3-meth oxy-2 -(6-(methyl(2,2,6,6-tetra methylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
3' 5-dimethoxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-[1,1'-biphenyl]-3-ol;
3-(benzyloxy)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(5-methyloxazol-2-yl)phenol;
3-ethoxy-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(5-methyloxazol-2-yl)phenol;
5 3-(cyclopropylmethoxy)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)-pyridazin-3-yl)-5-(5-methyloxazol-2-yl)phenol;
2-methyl-5-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-1 H benzo[d]imidazol-6-ol;
5-chloro-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(1H-pyrazol-1-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
3-hydroxy-4-(6-((2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)benzonitrile;
2-(6-((2,2-dimethylpiperidin-4-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(1H-pyrazol-4-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(4,5,6, 7-tetrahydropyrazolo[1,5-a]pyridin-3-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(4,5,6,7-tetrahydropyrazolo[1,5-a] pyrazin-3-yl)phenol;
4-(1 H-indol-2-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
4-(cyclopent-1-en-1-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(1H-pyrazol-3-

yl)phenol;
4-(4-hydroxy-3-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3 yl)phenyl)pyridin-2-ol;
4-(4-hyd roxy-3-(6-((2,2,6,6-tetra methylpiperidin-4-yl)oxy)pyridazin-3-yl)phenyl)-1-methylpyridin-2-(1H)-one;
4-(4-hydroxy-3-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)phenyl)pyridin-2-ol;
5-(1 H-indazol-7-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
4-chloro-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;
4-fluoro-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;
5-fluoro-4-(1 H-imidazol-4-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-fluoro-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(1H-pyrazol-4-yl)phenol;
5-fluoro-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(1H-pyrazol-5-yl)phenol;
5,6-hydroxy-5-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2,3-dihydro-1H-inden-1-one;
6-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-1 ,4-dihydroindeno[1 ,2-c]pyrazol-7-ol;
6-hydroxy-5-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2,3-dihydro-1H-inden-1-one oxime hydrochloride salt;
5-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2,3-dihydro-1H-indene-1,6-diol;
2-amino-6-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-8H-indeno[1 ,2-d]thiazol-5-ol hydrochloride salt;
15 9-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-8-ol hydrochloride salt;
4-hydroxy-3-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-N-((1-methyl-1H-pyrazol-4-yl)methyl)benzamide;
4-(4-(hydroxymethyl)-1H-pyrazol-1-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)methyl)pyridazin-3-yl)phenol;
6-(3-(benzyloxy)isoquinolin-6-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
6-(1-(benzyloxy)isoquinolin-7-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-

amine;
3-fluoro-5-(2-methoxypyridin-4-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol hydrochloride salt;
4-(3-fluoro-5-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)pyridin-2(1H)-one hydrochloride salt;
4-(3-fluoro-5-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one hydrochloride salt;
5-(3-fluoro-5-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one hydrochloride salt;
3-fluoro-5-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)phenol hydrochloride salt;
5-chloro-3-fluoro-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol hydrochloride salt;
3-fluoro-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol hydrochloride salt;
3-fluoro-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-methyl-1 H pyrazol-4-yl)phenol hydrochloride salt;
5-(5-methoxypyridin-3-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(3-hydroxy-4-(6-methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl) phenyl)pyridin-2-ol;
4-(3-hydroxy-4-(6-methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)pyridin-2-ol;
5-(6-methoxypyridin-3-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
15 5-(3-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)-3-(trifluoromethyl)pyridin-2-ol;
5-(3-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one;
4-(3-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one;
5-(2-methoxypyridin-4-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
4-(3-hydroxy-4-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)phenyl)pyridin-2-ol;
5-(6-(dimethylamino)pyridin-3-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
4-(3-hyd roxy-4-(6-((2,2,6,6-tetra methylpiperidin-4-yl)oxy)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one;

2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(pyrimidin-5-yl)phenol;
5-(3-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl) phenyl)pyridin-3-ol;
1-cyclopropyl-4-(3-hyd roxy-4-(6-(methyl(2,2,6,6-tetra methylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)pyridin-2(1H)-one;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1,2,3,6-tetrahydropyridin-4-yl)phenol;
5-(cyclopent-1-en-1-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(3,6-dihydro-2H-pyran-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(imidazo[1 ,5-a]pyridin-7-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(imidazo[1 ,2-a]pyridin-7-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(2-methylpyridin-4-yl)phenol;
5-(1 H-imidazol-2-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(1 H-imidazol-4-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3 -yl)phenol;
5-(imidazo[1 ,2-a]pyrazin-3-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(5,6,7,8-tetrahydroimidazo[1 ,2-a]pyrazin-3-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(4-methyl-1H-imidazol-2-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-methyl-1H-imidazol-4-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-methyl-1H imidazol-5-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(4-nitro-1H-imidazol-2-yl)phenol;
25 2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(2-methyl-1H imidazol-4-yl)phenol;
5-(1,2-dimethyl-1H-imidazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
1-(3-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)-1H-

pyrazole-4-carboxamide;
2-(6-((3aR,6aS)-5-(2-hydroxyethyl)hexahydropyrrolo[3,4-c]pyrrol-2 (1H)-yl)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol ;
2-(6-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;
2-(6-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)-5-(1 Hpyrazol-4-yl)phenol;
4-(3-hydroxy-4-(6-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one;
4-(3-hydroxy-4-(6-((3aR, 6aR)-1-methylhexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one;
2-(6-(2, 7-diazaspiro[4.5]decan-2-yl)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol; and
4-(4-(6-(2,7-diazaspiro[4.5]decan-2-yl)pyridazin-3-yl)-3-hydroxyphenyl)-1-methylpyridin-2(1H)-one;
5-(2-Methoxy-4-(1H-pyrazol-1-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
6-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)naphthalen-2-ol;
5-(2-Methoxyquinolin-3-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(3-Methoxynaphthalen-2-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-Methoxy-4-(1H-pyrazol-1-yl)phenyl)-N-(1,2,2,6,6-pentamethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-Methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-Methoxy-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
4-(3-Methoxy-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)-1-methylpyridin-2(1H)-one;
5-(3-Methoxy-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)pyridin-2-ol;
5-(3-Methoxy-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)-1-methylpyridin-2(1H)-one;
N-Methyl-5-(2-methyl-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
1-Methyl-4-(4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-3-(trifluoromethoxy)phenyl)pyridin-2(1H)-one;
5-(4-(3,5-Dimethyl-1H-pyrazol-4-yl)-2-methoxyphenyl)-N-methyl-N-(2,2,6,6-

tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-Methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
2-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenol;
2-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-5-(1H-pyrazol-1-yl)phenol;
5-(3-Hydroxy-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)-1-methylpyridin-2(1H)-one;
4-(3-Hydroxy-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)-1-methylpyridin-2(1H)-one;
5-(3-Hydroxy-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)pyridin-2-ol;
3-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)naphthalene-2,7-diol;
3-(5-((3aR,6aS)-Hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,4-thiadiazol-2-yl)naphthalene-2,7-diol;
3-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)naphthalen-2-ol hydrobromide salt;
3-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)quinolin-2-ol;
2-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-4-(1H-pyrazol-1-yl)phenol;
5-(2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
3-Chloro-2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenol;
5-(2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
3-Methoxy-2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-5-(5-methyloxazol-2-yl)phenol;
2-(2-Methoxy-4-(1H-pyrazol-1-yl)phenyl)-5-(1 ,2,3,6-tetrahydropyridin-4-yl)-1,3,4-thiadiazole;
2-(5-(piperazin-1-yl)-1,3,4-thiadiazol-2-yl)-5-(1H-pyrazol-1-yl)phenol;
5-(7-Methoxyquinolin-6-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
6-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)quinolin-7-ol;
3-methoxy-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)benzonitrile;
3-fluoro-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-

yl)benzonitrile;
methyl 3-fluoro-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)benzoate;
5-(2-methoxy-4-(3-(methylamino)-1H-pyrazol-1-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
7-methoxy-6-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)quinoline-2-carbonitrile;
4-(3-methoxy-4-(5-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)-1,3,4-thiadiazol-2-yl)phenyl)-1-methylpyridin-2(1H)-one;
4-(3-chloro-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)-1-methylpyridin-2(1H)-one;
5-(2-Chloro-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-Chloro-4-(4,5, 6, 7-tetrahydropyrazolo[1, 5-a]pyridin-3-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
N-methyl-5-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine Hydrochloride salt;
2-(2-chloro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-5-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)-1,3,4-thiadiazole;
5-(2-chloro-4-(6-methoxypyridin-3-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(4-(6-aminopyridin-3-yl)-2-fluorophenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-fluoro-4-(3-methyl-1H-pyrazol-5-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-fluoro-4-(1H-pyrazol-5-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2,3-difluoro-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2,3-difluoro-4-(1H-pyrazol-5-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2,5-difluoro-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2,5-difluoro-4-(1H-pyrazol-5-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2,6-difluoro-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
2-(2,5-difluoro-4-(1H-pyrazol-4-yl)phenyl)-5-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-

yl)-1,3,4-thiadiazole;
5-(2-chloro-5-fluoro-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(3-fluoro-5-(1H-pyrazol-4-yl)pyridin-2-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(4-(2-aminopyrimidin-4-yl)-2-chlorophenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(5-(2-aminopyrimidin-4-yl)-2-chlorophenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(4-(2,4-dimethylthiazol-5-yl)-2,5-difluorophenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(4-(2,4-dimethylthiazol-5-yl)-2,3-difluorophenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
4-(3-hydroxy-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)am ino)-1,3,4-thiadiazol-2-yl)-5-(trifluoromethoxy)phenyl)-1-methylpyridin-2(1H)-one;
5-(2-fluoro-6-methoxy-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
2-(2-fluoro-6-methoxy-4-(1H-pyrazol-4-yl)phenyl)-5-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,4-thiadiazole;
5-(2,3-difluoro-6-methoxy-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
6-methoxy-2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-3,4-dihydroisoquinolin-1(2H)-one;
5-(2-Chloro-4-(1H-pyrazol-1-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-Chloro-4-(1H-1,2,3-triazol-1-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-chloro-4-(2H-1,2,3-triazol-2-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-chloro-4-(1 H-1 ,2,4-triazol-1-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(4-(3-amino-1H-pyrazol-1-yl)-2-chlorophenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
2-(2-chloro-4-(1 H-imidazol-1-yl)phenyl)-5-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,4-thiadiazole;
5-(2-Chloro-4-(1H-imidazol-1-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-fluoro-4-(1 H-imidazol-1-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-

thiadiazol-2-amine;
5-(2-methoxy-4-(1H-pyrazol-5-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(4-(2,4-dimethylthiazol-5-yl)-2-methoxyphenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-methoxy-4-(pyridin-3-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-fluoro-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-methoxy-4-(2-methoxypyridin-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-methoxy-4-(6-methoxypyridin-3-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
2-(2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-5-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,4-thiadiazole;
2-(2-chloro-4-(1H-pyrazol-4-yl)phenyl)-5-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,4-thiadiazole;
2-(2-Chloro-4-(1H-pyrazol-4-yl)phenyl)-5-((3aR, 6a R)-1-methylhexahyd ropyrrolo[3,4-b]pyrrol-5(1H)-yl)-1,3,4-thiadiazole;
1-(4-(5-(2-chloro-4-(1H-pyrazol-4-yl)phenyl)-1,3,4-thiadiazol-2-yl)morpholin-2-yl)-N,N-dimethylmethanamine;
2-(2-chloro-4-(1H-pyrazol-4-yl)phenyl)-5-(2-methyl-2,7-diazaspiro[4.5]decan-7-yl)-1,3,4-thiadiazole;
2-(2-fluoro-4-(1H-pyrazol-4-yl)phenyl)-5-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,4-thiadiazole;
2-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-5-(2,6-diazaspiro[3.5]nonan-2-yl)-1,3,4-thiadiazole;
2-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-5-(2, 7-diazaspiro[3.5]nonan-2-yl)-1,3,4-thiadiazole;
2-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-5-(1H-pyrazol-1-yl)phenol;
5-(3-chloro-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)pyridin-2(1H)-one;
2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-5-(3-(methylamino)-1H-pyrazol-1-yl)phenol;
3-fluoro-2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)am ino)-1,3,4-thiadiazol-2-yl)-5-(1H-pyrazol-4-yl)phenol;
3,4-d ifluoro-2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-5-

(1H-pyrazol-4-yl)phenol;
6-hydroxy-5-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-2,3-dihydro-1H-inden-1-one;
2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-5-(1H-pyrazol-4-yl)phenol;
2-(5-(2,6-diazaspiro[3.5]nonan-2-yl)-1,3,4-thiadiazol-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenol;
2-(5-(2,7-diazaspiro[3.5]nonan-2-yl)-1,3,4-thiadiazol-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenol;
3-fluoro-2-(5-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,4-thiadiazol-2-yl)-5-(1H-pyrazol-4-yl)phenol Di-hydrochloride salt;
3-Chloro-2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)am ino)-1,3,4-thiadiazol-2-yl)-5-(1H-pyrazol-4-yl)phenol;
2-(2-methoxy-4-(1H-pyrazol-1-yl)phenyl)-5-((2,2,6,6-tetramethylpiperidin-4-yl)methyl)-1,3,4-thiadiazole;
2-(2,3-difluoro-4-(1H-pyrazol-4-yl)phenyl)-5-(2, 7-diazaspiro[3.5]nonan-2-yl)-1,3,4-thiadiazole;
2-(5-(2,7-diazaspiro[3.5]nonan-2-yl)-1,3,4-thiadiazol-2-yl)-3-fluoro-5-(1H-pyrazol-4-yl)phenol;
4-methoxy-1-methyl-3-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)quinolin-2(1H)-one;
4-hydroxy-1-methyl-3-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)quinolin-2(1H)-one;
3-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)quinolin-2(1H)-one;
1-methyl-3-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)quinolin-2(1H)-one;
2-(2-Chloro-4-(1H-pyrazol-4-yl)phenyl)-5-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)yl)-1,3,4-thiadiazole Hydrochloride Salt;
2-(2-Chloro-4-(1H-pyrazol-4-yl)phenyl)-5-(2, 7-diazaspiro[4 .5]decan-2-yl)-1,3,4-thiadiazole Hydrochloride Salt;
(R)-(4-(5-(2-chloro-4-(1H-pyrazol-4-yl)phenyl)-1,3,4-thiadiazol-2-yl)piperazi n-2-yl)methanol Hydrochloride Salt;
2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)benzo[b]thiophene-5-carbonitrile; and
5-(3-chlorobenzo[b]thiophen-2-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
7-hydroxy-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-2(1H)-one;
6-(6-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)quinolin-7-ol;
7-hydroxy-1-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-2(1H)-one;
6-(6-(methyl(1,2,2,6,6-pentamethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;

2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-morpholinoquinolin-7-ol;
4-chloro-2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
3-bromo-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
3-ethyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
3-(1H-imidazol-1-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-(1-methyl-1H-imidazol-4-yl)quinolin-7-ol;
3-isopropyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoline-3,7-diol;
7-hydroxy-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoline-3-carbonitrile;
6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
4-(dimethylamino)-2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
3-chloro-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
4-methoxy-2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
6-(3-(benzyloxy)isoquinolin-6-yi)-N-methyi-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
8-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinoline-1,6-diol;
7-(6-(methyl(1,2,2,6,6-pentamethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
1-cyclopropyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
6-(1-(benzyloxy)isoquinolin-7-yi)-N-methyi-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-6-ol;
2-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-6-ol;
2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(1-methyl-1Hpyrazol-4-yl)quinoIin-7-ol;
2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
4-ethoxy-2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
4-chloro-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-6-ol;

6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-(tetrahydro-2H-pyran-4-yl)quinolin-7-ol;
3-chloro-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-6-ol;
3-bromo-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-6-ol;
3-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-6-ol;
5-bromo-3-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-6-ol;
6-hydroxy-1-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-4(1H)-one;
2,3-dimethyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoxalin-6-ol;
2-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoxaIin-6-ol;
3-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoxaIin-6-ol;
4-methoxy-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
4-(azetidin-1-yl)-2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
7-hydroxy-2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoline-4-carbonitrile;
4-cyclopropyl-2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
4-(3,6-dihydro-2H-pyran-4-yl)-2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(tetrahydro-2Hpyran-4-yl)quinolin-7-ol;
2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(oxetan-3-yl)quinolin-7-ol;
4-(dimethylamino)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
7-hydroxy-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinazolin-4(1H)-one;
6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinazolin-7-ol;
7-hydroxy-1-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3,4-dihydroquinolin-2(1H)-one;
7-hydroxy-1-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3,4-dihydroquinolin-2(1H)-one;
7-hydroxy-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinoline-1-carbonitrile;
7-hydroxy-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoline-2-

carbonitrile;
6-hydroxy-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoline-2-carbonitrile;
6-hydroxy-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinoline-1-carboxamide;
7-hydroxy-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoline-2-carboxamide;
6-hydroxy-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoline-2-carboxamide;
methyl6-hydroxy-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoline-2-carboxylate;
6-hydroxy-7-(6-(piperazin-1-yl)pyridazin-3-yl)quinoline-2-carbonitrile;
7-hydroxy-6-(6-(piperazin-1-yl)pyridazin-3-yl)quinoline-2-carbonitrile;
7-(6-(piperazin-1-yl)pyridazin-3-yl)isoquinolin-6-ol;
7-(6-(1,2,3,6-tetrahydropyridin-4-yl)pyridazin-3-yl)quinolin-6-ol;
1-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-7-ol;
1-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
1,3-dimethyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
7-hydroxy-3-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinoline-1-carbonitrile;
1-amino-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
7-hydroxy-1,3-dimethyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinazoline-2,4(1H,3H)-dione;
6-hydroxy-5-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)benzo[d]oxazoi-2(3H)-one;
2-methyl-5-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2H-indazol-6-ol;
1-methyl-5-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-1H-indazol-6-ol;
6-hydroxy-2-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-1(2H)-one;
2-ethyl-6-hydroxy-7-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoquinolin-1(2H)-one;
1-ethoxy-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
7-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoquinoline-1,6-diol;
7-(6-(methyl(2,2,6,6-tetramethyl-piperidin-4-yl)amino)-pyridazin-3-yl)-3-phenylisoquinolin-6-ol;
3-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
3-cyclopropyl-7-(6-(methyl(2,2,6,6-tetramethyl-piperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;

3-isopropyl-7-(6-(methyl(2,2,6,6-tetramethyl-piperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
3-propyl-7-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)-pyridazin-3-yl)isoquinolin-6-ol;
3-isopropyl-7-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)-pyridazin-3-yl)isoquinolin-6-ol; and
3-methyl-7-(6-(piperazin-1-yl)pyridazin-3-yl)isoquinolin-6-ol;
or a pharmaceutically acceptable salt thereof;
for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier as described herein selected from the group consisting of:
6-(naphthalen-2-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
6-(benzo[b]thio-phen-2-yl)-N-methyl-N-(2,2,6,6-tetra-methylpiperidin-4-yl)pyridazin-3-amine;
2-(6-(2,2,6,6-tetra methylpiperidin-4-ylamino)-pyridazin-3-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetra-methylpiperidin-4-yl)amino)pyridazin-3-yl)benzo[b]-thiophene-5-carbonitrile;
6-(quinolin-3-yl)-N-(2,2,6,6-tetramethyl-piperidin-4-yl)pyridazin-3-amine;
3-(benzo[b]-thiophen-2-yl)-6-(2,2,6,6-tetra-methylpiperidin-4-yloxy)pyridazine;
2-(6-(methyl-(2,2,6,6-tetra-methylpiperidin-4-yl)amino)-pyridazin-3-yl)phenol;
6-(6-(methyl-(2,2,6,6-tetra-methylpiperidin-4-yl)amino)-pyridazin-3-yl)naphthalen-2-ol;
6-(benzo[b]-thiophen-2-yl)-N-(2,2,6,6-tetra-methylpiperidin-4-yl)pyridazin-3-amine;
7-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoquinoline;
6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoquinoline;
N-methyl-6-(quinolin-7-yl)-N-(2,2,6,6-tetramethyl-piperidin-4-yl)pyridazin-3-amine;
N-methyl-6-(quinolin-6-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
6-(isoquinolin-7-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
6-(isoquinolin-6-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
6-(imidazo[1,2-a]pyridin-6-yl-pyridazin-3-yl)-methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amine
methyl-[6-(6-phenyl-pyridin-3-yl)-pyridazin-3-yl]-(2,2,6,6-tetramethyl-piperidin-4-yl)-amine;
methyl-[6-(6-pyrrol-1-yl-pyridin-3-yl)-pyridazin-3-yl]-(2,2,6,6-tetra methyl-piperidin-4-yl)-amine;
methyl-(6-quinoxalin-2-yl-pyridazin-3-yl)-(2,2,6,6-tetramethyl-piperidin-4-yl)-amine;
methyl-(6-quinolin-3-yl-pyridazin-3-yl)-(2,2,6,6-tetramethyl-piperidin-4-yl)-amine;
N-methyl-6-(phthalazin-6-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
6-(benzo[c][1,2,5]oxa-diazol-5-yl)-N-(2,2,6,6-tetramethyl-piperidin-4-yl)pyridazin-3-amine;
6-(benzo[d]thiazol-5-yl)-N-(2,2,6,6-tetramethyl-piperidin-4-yl)pyridazin-3-amine;
6-(2-methylbenzo-[d]oxazol-6-yl)-N-(2,2,6,6-tetramethyl-piperidin-4-yl)pyridazin-3-amine;
3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
5-chloro-2-(6-(methyl(1 ,2,2,6,6-pentamethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;

3-(6-(2,2,6,6-tetramethylpiperidin-4-ylamino)pyridazin-3-yl)naphthalen-2-ol;
5-chloro-2-(6-(1 ,2,2,6,6-pentamethylpiperidin-4-ylamino)pyridazin-3-yl)phenol;
4-hydroxy-3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)benzonitrile;
3-[6-(2,2,6,6-tetramethyl-piperidin-4-yloxy)-pyridazin-3-yl]-naphthalen-2-ol;
2-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-4-trifluoromethylphenol;
2-fluoro-6-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-phenol;
3,5-dimethoxy-2-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-phenol;
4,5-dimethoxy-2-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-phenol;
5-methoxy-2-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-phenol;
4,5-difluoro-2-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-phenol;
5-fluoro-2-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-phenol;
3-hydroxy-4-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)benzonitrile;
1-allyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
6-(benzo[b]thiophen-2-yl)-N-(1,2,2,6,6-pentamethylpiperidin-4-yl)pyridazin-3-amine;
N-allyl-3-hydroxy-4-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)benzamide;
2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
5-(5-methyl-oxazol-2-yl)-2-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-phenol;
5-(4-hydroxymethyl)-1H-pyrazole-1-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4 yl)amino)pyridazin-3-yl)phenol;
5-(1 H-imidazole-1-yl)-2-(6-(methyl(2,2,6,6-tetramethyl-piperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(4-amino-1H-pyrazole-1-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(4-amino-1H-pyrazol-1-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(3-amino-pyrazol-1-yl)-2 -{6-[methyl-(2,2,6,6-tetra methyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenol;
5-(5-amino-1H-pyrazol-1-yl)-2-(6-(methyl-(2,2,6,6-tetramethyl-piperidin-4-yl) amino)pyridazin-3-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(1H-pyrazol-1-yl)phenol;

2-{6-[(2-hydroxy-ethyl)-(2,2,6,6-tetra methyl-piperidn-4-yl)-amino]-pyridazin-3-yl}-5-pyrazol-1-yl-phenol;
2-(6-(piperidin-4-yloxy)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
2-(6-(((2S,4R, 6 R)-2,6-dimethylpiperidin-4-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
5 2-(6-((2, 6-di-methylpiperidin-4-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
2-(6-((2, 6-di-methylpiperidin-4-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
5-(1H-pyrazol-1-yl)-2-(6-(pyrrolidin-3-yloxy)pyridazin-3-yl)phenol;
2-(6-((-2-methylpiperidin-4-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
(S)-5-(1H-pyrazol-1-yl)-2-(6-(pyrrolidin-3-ylmethoxy)pyridazin-3-yl)phenol;
10 (R)-5-(1H-pyrazol-1-yl)-2-(6-(pyrrolidin-3-yl methoxy)pyridazin-3-yl)phenol;
2-(6-((3-fluoropiperidin-4-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)-phenol;
2-[6-(1,2,2,6,6-pentamethyl-piperidin-4-yloxy)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
5-pyrazol-1-yl-2-[6-((2,2,6,6-tetramethylpiperidin-4-yloxy)-pyridazin-3-yl]-phenol;
5-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)phenol;
15 2-(6-piperazin-1-yl-pyridazin-3-yl)-5-pyrazol-1-yl-phenol;
3-[6-(azetidin-3-yl-amino)-pyridazin-3-yl]-naphthalen-2-ol;
2-[6-(azetidin-3-ylamino)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(3, 5-di methyl-piperazin-1-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(7-methyl-2,7-diaza-spiro[4.4]non-2-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
20 2-(6-[1,4]diazepan-1-yl-pyridazin-3-yl)-5-pyrazol-1-yl-phenol;
2-{6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-pyridazin-3-yl}-5-pyrazol-1-yl-phenol;
2-[6-(3, 6-diaza-bicyclo[3.2.1]oct-3-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(2, 7-diaza-spiro[3.5]non-7-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(3-hydroxy-methyl-piperazin-1-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
25 2-[6-(1, 7-diaza-spiro[4.4]non-7-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(4-am in o-4-methyl-piperidin-1-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(3-dimethyl-amino-piperidin-1-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(1 ,2,2,6,6-pentamethyl-piperidin-4-ylamino)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(3, 3-di methyl-piperazin-1-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
30 2-(6-(7-(2-hydroxyethyl)-2,7-diazaspiro[4.4]-nonan-2-yl)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
2-(6-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
3-(6-(piperazin-1-yl)pyridazin-3-yl)naphthalene-2,7-diol;
35 5-pyrazol-1-yl-2-[6-(1,2,3,6-tetrahydro-pyridin-4-yl)-pyridazin-3-yl]-phenol;
2-(6-piperidin-4-yl-pyridazin-3-yl)-5-pyrazol-1-yl-phenol;
3-(6-(1 ,2,3,6-tetra-hydropyridin-4-yl)pyridazin-3-yl)naphthalen-2-ol;
3-(6-(1 ,2, 3, 6-tetrahydropyridin-4-yl)pyridazin-3-yl)naphthalene-2,7-diol;

3-(6-(2,2,6,6-tetramethyl-1 ,2,3, 6-tetrahydropyridin-4-yl)pyridazin-3-yl)naphthalene-2,7-diol;
3-(6-(1-methyl-1 ,2,3,6-tetrahydropyridin-4-yl)pyridazin-3-yl)naphthalene-2,7-diol;
3-(6-(piperidin-4-yl)pyridazin-3-yl)naphthalene-2,7-diol;
3-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)naphthalene-2,7-diol;
3-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalene-2,7-diol;
3-(6-((2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalene-2,7-diol;
[3-(7-hydroxy-6-{6-[methyl-(2,2,6,6-tetra methyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-naphthalen-2-yloxy)-propyl]-carbamic acid tert-butyl ester;
7-(3-amino-propoxy)-3-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}naphthalen-2-ol;
N-[3-(7-hydroxy-6-{6-[methyl-(2,2,6,6-tetra methyl-piperidin-4-yl)-amino]-pyridazin-3-yl}naphthalen-2-yloxy)-propyl]-acetamide;
7-(3-hydroxypropoxy)-3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
7-(3-methoxypropoxy)-3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
7-(2-morpholinoethoxy)-3-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)naphthalen-2-ol;
3-(6-(piperidin-4-ylmethyl)pyridazin-3-yl)naphthalen-2-ol;
5-(1H-pyrazol-1-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)methyl)pyridazin-3-yl)phenol;
3-methoxy-2-(6-(methyl(2,2,6-trimethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(5-methyloxazol-2-yl)phenol;
2-(6-((6S)-6-((S)-1-hydroxyethyl)-2,2-d imethylpiperidin-4-yloxy)pyridazin-3-yl)-5-(1H pyrazol-1-yl)phenol;
7-hydroxy-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2-naphthonitrile;
3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-7-(piperidin-1-ylmethyl)naphthalen-2-ol;
3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-7-(pyrrolidin-1-ylmethyl)naphthalen-2-ol;
1-bromo-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalene-2,7-diol;
1-chloro-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalene- 2,7-diol;
7-methoxy-3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
7-methoxy-3-(6-(methyl(1,2,2,6,6-pentamethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
7-(3,6-dihydro-2H-pyran-4-yl)-3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-

3-yl)naphthalen-2-ol;
3-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-7-(tetrahydro-2H-pyran-4-yl)naphthalen-2-ol;
7-(difluoromethyl)-3-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
7-((4-hyd roxy-2 -methyl butan-2-yl)oxy)-3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
7-(3-hydroxy-3-methylbutoxy)-3-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)benzene-1,3-diol;
3-methoxy-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1 H pyrazol-4-yl)phenol;
5-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-(trifluoromethoxy)phenol;
2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)-3-(trifluoromethoxy)phenol;
2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)-3-(trifluoromethoxy)phenol;
4-(3-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(trifluoromethoxy)phenyl)-1-methylpyridin-2(1H)-one;
3-methoxy-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenol;
3-methoxy-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(5,6,7,8-tetrahydroimidazo[1 ,2-a]pyridin-3-yl)phenol;
3-methoxy-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino) pyridazn-3-yl)-5-(pyridin-3-yl)phenol;
5-(1-cyclopentyl-1 H -pyrazol-4-yl)-3-meth oxy-2 -(6-(methyl(2,2,6,6-tetra methylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
3' 5-dimethoxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-[1,1'-biphenyl]-3-ol;
3-(benzyloxy)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(5-methyloxazol-2-yl)phenol;
3-ethoxy-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(5-methyloxazol-2-yl)phenol;
5 3-(cyclopropylmethoxy)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)-pyridazin-3-yl)-5-(5-methyloxazol-2-yl)phenol;
2-methyl-5-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-1 H

benzo[d]imidazol-6-ol;
5-chloro-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(1H-pyrazol-1-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
3-hydroxy-4-(6-((2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)benzonitrile;
2-(6-((2,2-dimethylpiperidin-4-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(1H-pyrazol-4-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(4,5,6, 7-tetrahydropyrazolo[1,5-a]pyridin-3-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(4,5,6,7-tetrahydropyrazolo[1,5-a] pyrazin-3-yl)phenol;
4-(1 H-indol-2-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
4-(cyclopent-1-en-1-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(1H-pyrazol-3-yl)phenol;
4-(4-hydroxy-3-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3 yl)phenyl)pyridin-2-ol;
4-(4-hyd roxy-3-(6-((2,2,6,6-tetra methylpiperidin-4-yl)oxy)pyridazin-3-yl)phenyl)-1-methylpyridin-2-(1H)-one;
4-(4-hydroxy-3-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)phenyl)pyridin-2-ol;
5-(1 H-indazol-7-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
4-chloro-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;
4-fluoro-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;
5-fluoro-4-(1 H-imidazol-4-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-fluoro-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(1H-pyrazol-4-yl)phenol;
5-fluoro-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(1H-pyrazol-5-yl)phenol;
5,6-hydroxy-5-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2,3-dihydro-1H-inden-1-one;
6-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-1 ,4-dihydroindeno[1 ,2-c]pyrazol-7-ol;
6-hydroxy-5-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2,3-dihydro-

1H-inden-1-one oxime hydrochloride salt;
5-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2,3-dihydro-1H-indene-1,6-diol;
2-amino-6-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-8H-indeno[1 ,2-d]thiazol-5-ol hydrochloride salt;
15 9-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-8-ol hydrochloride salt;
4-hydroxy-3-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-N-((1-methyl-1H-pyrazol-4-yl)methyl)benzamide;
4-(4-(hydroxymethyl)-1H-pyrazol-1-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)methyl)pyridazin-3-yl)phenol;
6-(3-(benzyloxy)isoquinolin-6-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
6-(1-(benzyloxy)isoquinolin-7-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
3-fluoro-5-(2-methoxypyridin-4-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol hydrochloride salt;
4-(3-fluoro-5-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)pyridin-2(1H)-one hydrochloride salt;
30 4-(3-fluoro-5-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one hydrochloride salt;
5-(3-fluoro-5-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one hydrochloride salt;
3-fluoro-5-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)phenol hydrochloride salt;
5-chloro-3-fluoro-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol hydrochloride salt;
3-fluoro-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol hydrochloride salt;
3-fluoro-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-methyl-1 H pyrazol-4-yl)phenol hydrochloride salt;
5-(5-methoxypyridin-3-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(3-hydroxy-4-(6-methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl) phenyl)pyridin-2-ol;
4-(3-hydroxy-4-(6-methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)pyridin-2-ol;

5-(6-methoxypyridin-3-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(3-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)-3-(trifluoromethyl)pyridin-2-ol;
5-(3-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one;
4-(3-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one;
5-(2-methoxypyridin-4-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
4-(3-hydroxy-4-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)phenyl)pyridin-2-ol;
5-(6-(dimethylamino)pyridin-3-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
4-(3-hyd roxy-4-(6-((2,2,6,6-tetra methylpiperidin-4-yl)oxy)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(pyrimidin-5-yl)phenol;
5-(3-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl) phenyl)pyridin-3-ol;
1-cyclopropyl-4-(3-hyd roxy-4-(6-(methyl(2,2,6,6-tetra methylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)pyridin-2(1H)-one;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1,2,3,6-tetrahydropyridin-4-yl)phenol;
5-(cyclopent-1-en-1-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(3,6-dihydro-2H-pyran-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(imidazo[1 ,5-a]pyridin-7-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(imidazo[1 ,2-a]pyridin-7-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(2-methylpyridin-4-yl)phenol;
5-(1 H-imidazol-2-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(1 H-imidazol-4-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3 -yl)phenol;
5-(imidazo[1 ,2-a]pyrazin-3-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;

2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(5,6,7,8-tetrahydroimidazo[1 ,2-a]pyrazin-3-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(4-methyl-1H-imidazol-2-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-methyl-1H-imidazol-4-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-methyl-1H imidazol-5-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(4-nitro-1H-imidazol-2-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(2-methyl-1H imidazol-4-yl)phenol;
5-(1,2-dimethyl-1H-imidazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
1-(3-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)-1H-pyrazole-4-carboxamide;
2-(6-((3aR,6aS)-5-(2-hydroxyethyl)hexahydropyrrolo[3,4-c]pyrrol-2 (1H)-yl)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol ;
2-(6-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;
2-(6-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)-5-(1 Hpyrazol-4-yl)phenol;
4-(3-hydroxy-4-(6-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one;
4-(3-hydroxy-4-(6-((3aR, 6aR)-1-methylhexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one;
2-(6-(2, 7-diazaspiro[4.5]decan-2-yl)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol; and
4-(4-(6-(2,7-diazaspiro[4.5]decan-2-yl)pyridazin-3-yl)-3-hydroxyphenyl)-1-methylpyridin-2(1H)-one;
or a pharmaceutically acceptable salt thereof;
for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier as described herein selected from the group consisting of:
5-(2-Methoxy-4-(1H-pyrazol-1-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
6-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)naphthalen-2-ol;
5-(2-Methoxyquinolin-3-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-

amine;
5-(3-Methoxynaphthalen-2-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-Methoxy-4-(1H-pyrazol-1-yl)phenyl)-N-(1,2,2,6,6-pentamethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-Methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-Methoxy-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
4-(3-Methoxy-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)-1-methylpyridin-2(1H)-one;
5-(3-Methoxy-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)pyridin-2-ol;
5-(3-Methoxy-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)-1-methylpyridin-2(1H)-one;
N-Methyl-5-(2-methyl-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
1-Methyl-4-(4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-3-(trifluoromethoxy)phenyl)pyridin-2(1H)-one;
5-(4-(3,5-Dimethyl-1H-pyrazol-4-yl)-2-methoxyphenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-Methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
2-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenol;
2-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-5-(1H-pyrazol-1-yl)phenol;
5-(3-Hydroxy-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)-1-methylpyridin-2(1H)-one;
4-(3-Hydroxy-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)-1-methylpyridin-2(1H)-one;
5-(3-Hydroxy-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)pyridin-2-ol;
3-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)naphthalene-2,7-diol;
3-(5-((3aR,6aS)-Hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,4-thiadiazol-2-yl)naphthalene-2,7-diol;
3-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)naphthalen-2-ol

hydrobromide salt;
3-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)quinolin-2-ol;
2-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-4-(1H-pyrazol-1-yl)phenol;
5-(2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
3-Chloro-2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenol;
5-(2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
3-Methoxy-2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-5-(5-methyloxazol-2-yl)phenol;
2-(2-Methoxy-4-(1H-pyrazol-1-yl)phenyl)-5-(1 ,2,3,6-tetrahydropyridin-4-yl)-1,3,4-thiadiazole;
2-(5-(piperazin-1-yl)-1,3,4-thiadiazol-2-yl)-5-(1H-pyrazol-1-yl)phenol;
5-(7-Methoxyquinolin-6-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
6-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)quinolin-7-ol;
3-methoxy-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)benzonitrile;
3-fluoro-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)benzonitrile;
methyl 3-fluoro-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)benzoate;
5-(2-methoxy-4-(3-(methylamino)-1H-pyrazol-1-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
7-methoxy-6-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)quinoline-2-carbonitrile;
4-(3-methoxy-4-(5-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)-1,3,4-thiadiazol-2-yl)phenyl)-1-methylpyridin-2(1H)-one;
4-(3-chloro-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)-1-methylpyridin-2(1H)-one;
5-(2-Chloro-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-Chloro-4-(4,5, 6, 7-tetrahydropyrazolo[1, 5-a]pyridin-3-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
N-methyl-5-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine Hydrochloride salt;
2-(2-chloro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-5-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)-

1,3,4-thiadiazole;
5-(2-chloro-4-(6-methoxypyridin-3-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(4-(6-aminopyridin-3-yl)-2-fluorophenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-fluoro-4-(3-methyl-1H-pyrazol-5-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-fluoro-4-(1H-pyrazol-5-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2,3-difluoro-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2,3-difluoro-4-(1H-pyrazol-5-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2,5-difluoro-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2,5-difluoro-4-(1H-pyrazol-5-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2,6-difluoro-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
2-(2,5-difluoro-4-(1H-pyrazol-4-yl)phenyl)-5-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,4-thiadiazole;
5-(2-chloro-5-fluoro-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(3-fluoro-5-(1H-pyrazol-4-yl)pyridin-2-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(4-(2-aminopyrimidin-4-yl)-2-chlorophenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(5-(2-aminopyrimidin-4-yl)-2-chlorophenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(4-(2,4-dimethylthiazol-5-yl)-2,5-difluorophenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(4-(2,4-dimethylthiazol-5-yl)-2,3-difluorophenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
4-(3-hydroxy-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)am ino)-1,3,4-thiadiazol-2-yl)-5-(trifluoromethoxy)phenyl)-1-methylpyridin-2(1H)-one;
5-(2-fluoro-6-methoxy-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
2-(2-fluoro-6-methoxy-4-(1H-pyrazol-4-yl)phenyl)-5-((3aR,6aS)-5-

methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,4-thiadiazole;
5-(2,3-difluoro-6-methoxy-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
6-methoxy-2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-3,4-dihydroisoquinolin-1(2H)-one;
5-(2-Chloro-4-(1H-pyrazol-1-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-Chloro-4-(1H-1,2,3-triazol-1-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-chloro-4-(2H-1,2,3-triazol-2-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-chloro-4-(1 H-1 ,2,4-triazol-1-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(4-(3-amino-1H-pyrazol-1-yl)-2-chlorophenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
2-(2-chloro-4-(1 H-imidazol-1-yl)phenyl)-5-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,4-thiadiazole;
5-(2-Chloro-4-(1H-imidazol-1-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-fluoro-4-(1 H-imidazol-1-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-methoxy-4-(1H-pyrazol-5-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(4-(2,4-dimethylthiazol-5-yl)-2-methoxyphenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-methoxy-4-(pyridin-3-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-fluoro-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-methoxy-4-(2-methoxypyridin-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-methoxy-4-(6-methoxypyridin-3-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
2-(2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-5-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,4-thiadiazole;
2-(2-chloro-4-(1H-pyrazol-4-yl)phenyl)-5-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,4-thiadiazole;
2-(2-Chloro-4-(1H-pyrazol-4-yl)phenyl)-5-((3aR, 6a R)-1-methylhexahyd ropyrrolo[3,4-

b]pyrrol-5(1H)-yl)-1,3,4-thiadiazole;
1-(4-(5-(2-chloro-4-(1H-pyrazol-4-yl)phenyl)-1,3,4-thiadiazol-2-yl)morpholin-2-yl)-N,N-dimethylmethanamine;
2-(2-chloro-4-(1H-pyrazol-4-yl)phenyl)-5-(2-methyl-2,7-diazaspiro[4.5]decan-7-yl)-1,3,4-thiadiazole;
2-(2-fluoro-4-(1H-pyrazol-4-yl)phenyl)-5-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,4-thiadiazole;
2-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-5-(2,6-diazaspiro[3.5]nonan-2-yl)-1,3,4-thiadiazole;
2-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-5-(2, 7-diazaspiro[3.5]nonan-2-yl)-1,3,4-thiadiazole;
2-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-5-(1H-pyrazol-1-yl)phenol;
5-(3-chloro-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)pyridin-2(1H)-one;
2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-5-(3-(methylamino)-1H-pyrazol-1-yl)phenol;
3-fluoro-2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)am ino)-1,3,4-thiadiazol-2-yl)-5-(1H-pyrazol-4-yl)phenol;
3,4-d ifluoro-2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-5-(1H-pyrazol-4-yl)phenol;
6-hydroxy-5-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-2,3-dihydro-1H-inden-1-one;
2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-5-(1H-pyrazol-4-yl)phenol;
2-(5-(2,6-diazaspiro[3.5]nonan-2-yl)-1,3,4-thiadiazol-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenol;
2-(5-(2,7-diazaspiro[3.5]nonan-2-yl)-1,3,4-thiadiazol-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenol;
3-fluoro-2-(5-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,4-thiadiazol-2-yl)-5-(1H-pyrazol-4-yl)phenol Di-hydrochloride salt;
3-Chloro-2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)am ino)-1,3,4-thiadiazol-2-yl)-5-(1H-pyrazol-4-yl)phenol;
2-(2-methoxy-4-(1H-pyrazol-1-yl)phenyl)-5-((2,2,6,6-tetramethylpiperidin-4-yl)methyl)-1,3,4-thiadiazole;
2-(2,3-difluoro-4-(1H-pyrazol-4-yl)phenyl)-5-(2, 7-diazaspiro[3.5]nonan-2-yl)-1,3,4-thiadiazole;
2-(5-(2,7-diazaspiro[3.5]nonan-2-yl)-1,3,4-thiadiazol-2-yl)-3-fluoro-5-(1H-pyrazol-4-yl)phenol;
4-methoxy-1-methyl-3-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)quinolin-2(1H)-one;
4-hydroxy-1-methyl-3-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-

yl)quinolin-2(1H)-one;
3-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)quinolin-2(1H)-one;
1-methyl-3-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)quinolin-2(1H)-one;
2-(2-Chloro-4-(1H-pyrazol-4-yl)phenyl)-5-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)yl)-1,3,4-thiadiazole Hydrochloride Salt;
2-(2-Chloro-4-(1H-pyrazol-4-yl)phenyl)-5-(2, 7-diazaspiro[4 .5]decan-2-yl)-1,3,4-thiadiazole Hydrochloride Salt;
(R)-(4-(5-(2-chloro-4-(1H-pyrazol-4-yl)phenyl)-1,3,4-thiadiazol-2-yl)piperazi n-2-yl)methanol Hydrochloride Salt;
2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)benzo[b]thiophene-5-carbonitrile; and
5-(3-chlorobenzo[b]thiophen-2-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
or a pharmaceutically acceptable salt thereof;
for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from the group consisting of:
7-hydroxy-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-2(1H)-one;
6-(6-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)quinolin-7-ol;
7-hydroxy-1-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-2(1H)-one;
6-(6-(methyl(1,2,2,6,6-pentamethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-morpholinoquinolin-7-ol;
4-chloro-2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
3-bromo-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
3-ethyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
3-(1H-imidazol-1-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-(1-methyl-1H-imidazol-4-yl)quinolin-7-ol;
3-isopropyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoline-3,7-diol;
7-hydroxy-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoline-3-

carbonitrile;
6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
4-(dimethylamino)-2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
3-chloro-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
4-methoxy-2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
6-(3-(benzyloxy)isoquinolin-6-yi)-N-methyi-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
8-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinoline-1,6-diol;
7-(6-(methyl(1,2,2,6,6-pentamethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
1-cyclopropyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
6-(1-(benzyloxy)isoquinolin-7-yi)-N-methyi-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-6-ol;
2-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-6-ol;
2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(1-methyl-1Hpyrazol-4-yl)quinoIin-7-ol;
2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
4-ethoxy-2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
4-chloro-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-6-ol;
6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-(tetrahydro-2H-pyran-4-yl)quinolin-7-ol;
3-chloro-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-6-ol;
3-bromo-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-6-ol;
3-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-6-ol;
5-bromo-3-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-6-ol;
6-hydroxy-1-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-4(1H)-one;
2,3-dimethyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoxalin-6-ol;
2-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoxaIin-6-ol;
3-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoxaIin-6-ol;

4-methoxy-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
4-(azetidin-1-yl)-2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
7-hydroxy-2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoline-4-carbonitrile;
4-cyclopropyl-2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
4-(3,6-dihydro-2H-pyran-4-yl)-2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(tetrahydro-2Hpyran-4-yl)quinolin-7-ol;
2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(oxetan-3-yl)quinolin-7-ol;
4-(dimethylamino)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
7-hydroxy-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinazolin-4(1H)-one;
6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinazolin-7-ol;
7-hydroxy-1-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3,4-dihydroquinolin-2(1H)-one;
7-hydroxy-1-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3,4-dihydroquinolin-2(1H)-one;
7-hydroxy-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinoline-1-carbonitrile;
7-hydroxy-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoline-2-carbonitrile;
6-hydroxy-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoline-2-carbonitrile;
6-hydroxy-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinoline-1-carboxamide;
7-hydroxy-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoline-2-carboxamide;
6-hydroxy-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoline-2-carboxamide;
methyl6-hydroxy-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoline-2-carboxylate;
6-hydroxy-7-(6-(piperazin-1-yl)pyridazin-3-yl)quinoline-2-carbonitrile;
7-hydroxy-6-(6-(piperazin-1-yl)pyridazin-3-yl)quinoline-2-carbonitrile;

7-(6-(piperazin-1-yl)pyridazin-3-yl)isoquinolin-6-ol;
7-(6-(1,2,3,6-tetrahydropyridin-4-yl)pyridazin-3-yl)quinolin-6-ol;
1-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-7-ol;
1-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
1,3-dimethyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
7-hydroxy-3-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinoline-1-carbonitrile;
1-amino-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
7-hydroxy-1,3-dimethyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinazoline-2,4(1H,3H)-dione;
6-hydroxy-5-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)benzo[d]oxazoi-2(3H)-one;
2-methyl-5-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2H-indazol-6-ol;
1-methyl-5-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-1H-indazol-6-ol;
6-hydroxy-2-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-1(2H)-one;
2-ethyl-6-hydroxy-7-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoquinolin-1(2H)-one;
1-ethoxy-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
7-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoquinoline-1,6-diol;
7-(6-(methyl(2,2,6,6-tetramethyl-piperidin-4-yl)amino)-pyridazin-3-yl)-3-phenylisoquinolin-6-ol;
3-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
3-cyclopropyl-7-(6-(methyl(2,2,6,6-tetramethyl-piperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
3-isopropyl-7-(6-(methyl(2,2,6,6-tetramethyl-piperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
3-propyl-7-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)-pyridazin-3-yl)isoquinolin-6-ol;
3-isopropyl-7-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)-pyridazin-3-yl)isoquinolin-6-ol; and
3-methyl-7-(6-(piperazin-1-yl)pyridazin-3-yl)isoquinolin-6-ol;
or a pharmaceutically acceptable salt thereof;
for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a FoxM1 gene splicing modifier selected from the group consisting of:
3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
3-hydroxy-4-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)benzonitrile;

5-(1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenol;
5-pyrazol-1-yl-2-[6-((2,2,6,6-tetramethylpiperidin-4-yloxy)-pyridazin-3-yl]-phenol;
5-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)phenol;
3-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)naphthalene-2,7-diol;
3-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalene-2,7-diol;
7-methoxy-3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
5-(3-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one;
4-(3-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one;
4-(3-chloro-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)-1-methylpyridin-2(1H)-one;
5-(2-Chloro-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2,5-difluoro-4-(1H-pyrazol-5-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
or a pharmaceutically acceptable salt thereof;
for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to the use of a FoxM1 gene splicing modifier as described herein for the preparation of a medicament for the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to the use of a FoxM1 gene splicing modifier as described herein for the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a method for the treatment, prevention and/or delay of progression of cancer comprising administering an effective amount of a FoxM1 gene splicing modifier as described herein to a subject, in particular to a mammal.

In a particular embodiment, the present invention relates to a pharmaceutical composition comprising a FoxM1 gene splicing modifier as described herein for use in the treatment, prevention and/or delay of progression of cancer.

In a particular embodiment, the present invention relates to a combination comprising a

therapeutically effective amount of a FoxM1 gene splicing modifier as described herein or a pharmaceutically acceptable salt thereof and one or more therapeutically active co-agents.

MANUFACTURING PROCESSES

Compounds of formula (I) can be prepared according to methods as disclosed in WO 2014/028459 (A1) or WO 2015/017589 (A1), which are herewith incorporated by reference. General synthetic processes are described in WO 2014/028459 (A1) on pages 34 to 37 and specific preparations of working examples on pages 37 to 188.

Compounds of formula (VI) can be prepared according to methods as disclosed in WO 2014/116845 (A1), which is herewith incorporated by reference. General synthetic processes are described therein on pages 38 to 41 and specific preparations of working examples on pages 41 to 123.

PHARMACEUTICAL COMPOSITIONS, ADMINISTRATION AND USES

Another embodiment provides pharmaceutical compositions or medicaments containing the compounds of the invention and a therapeutically inert carrier, diluent or excipient, as well as methods of using the compounds of the invention to prepare such compositions and medicaments. In one example, compounds of formula I may be formulated by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed into a galenical administration form. The pH of the formulation depends mainly on the particular use and the concentration of compound, but preferably ranges anywhere from about 3 to about 8. In one example, a compound of formula I is formulated in an acetate buffer, at pH 5. In another embodiment, the compounds of formula I are sterile. The compound may be stored, for example, as a solid or amorphous composition, as a lyophilized composition or as an aqueous solution.

Compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The “effective amount” of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to modify FoxM1 gene splicing. For example, such amount may be

below the amount that is toxic to normal cells, or the mammal as a whole.

The compounds of the invention may be administered by any suitable means, including oral, topical(including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal and epidural and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration.

The compounds of the present invention may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents.

A typical composition is prepared by mixing a compound of the present invention and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art and are described in detail in, e.g., Ansel, Howard C., et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lippincott, Williams & Wilkins, 2004; Gennaro, Alfonso R., et al. Remington: The Science and Practice of Pharmacy. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Raymond C. Handbook of Pharmaceutical Excipients. Chicago, Pharmaceutical Press, 2005. The compositions may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aidin the manufacturing of the pharmaceutical product (i.e., medicament).

An example of a suitable oral dosage form is a tablet containing about 25mg, 50mg, 100mg, 250mg, or 500mg of the compound of the invention compounded with about 90-30 mg anhydrous lactose, about 5-40 mg sodium croscarmellose, about 5-30mg polyvinylpyrrolidone (PVP) K30, and about 1-10 mg magnesium stearate. The powdered ingredients are first mixed together and then mixed with a solution of the PVP. The resulting composition can be dried, granulated, mixed with the magnesium stearate and compressed to tablet form using conventional equipment. An example of an aerosol composition can be prepared by dissolving the compound, for example 5-400 mg, of the invention in a suitable buffer solution, e.g. a phosphate buffer, adding a tonicifier, e.g. a salt such sodium chloride, if desired. The solution may be filtered, e.g., using a 0.2 micron filter, to remove impurities and contaminants.

In a particular embodiment, the present invention relates to a pharmaceutical composition

comprising a FoxM1 gene splicing modifier as described herein or pharmaceutically acceptable salt thereof.

In a particular embodiment, the present invention relates to a pharmaceutical composition comprising a FoxM1 gene splicing modifier as described herein or pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable excipients.

In a particular embodiment, the present invention relates to a pharmaceutical composition comprising a therapeutically effective amount of a FoxM1 gene splicing modifier as described herein or pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable excipients.

In a particular embodiment, the present invention relates to a combination comprising a therapeutically effective amount of a FoxM1 gene splicing modifier as described herein or pharmaceutically acceptable salt thereof and one or more other therapeutically active pharmaceutical ingredients.

In specific embodiments, the cancer treated by the compounds of the present invention is leukemia, acute myeloid leukemia, colon cancer, gastric cancer, macular degeneration, acute monocytic leukemia, breast cancer, hepatocellular carcinoma, cone-rod dystrophy, alveolar soft part sarcoma, myeloma, skin melanoma, prostatitis, pancreatitis, pancreatic cancer, retinitis, adenocarcinoma, adenoiditis, adenoid cystic carcinoma, cataract, retinal degeneration, gastrointestinal stromal tumor, Wegener's granulomatosis, sarcoma, myopathy, prostate adenocarcinoma, Hodgkin's lymphoma, ovarian cancer, non-Hodgkin's lymphoma, multiple myeloma, chronic myeloid leukemia, acute lymphoblastic leukemia, renal cell carcinoma, transitional cell carcinoma, colorectal cancer, chronic lymphocytic leukemia, anaplastic large cell lymphoma, kidney cancer, breast cancer, cervical cancer.

In specific embodiments, the cancer prevented and/or treated in accordance with the present invention is basal cell carcinoma, goblet cell metaplasia, or a malignant glioma, cancer of the liver, breast, lung, prostate, cervix, uterus, colon, pancreas, kidney, stomach, bladder, ovary, or brain.

In specific embodiments, the cancer prevented and/or treated in accordance with the present invention include, but are not limited to, cancer of the head, neck, eye, mouth, throat, esophagus, esophagus, chest, bone, lung, kidney, colon, rectum or other gastrointestinal tract organs, stomach, spleen, skeletal muscle, subcutaneous tissue, prostate, breast, ovaries, testicles or other reproductive organs, skin, thyroid, blood, lymph nodes, kidney, liver, pancreas, and brain or central nervous system.

Specific examples of cancers that can be prevented and/or treated in accordance with present invention include, but are not limited to, the following: renal cancer, kidney cancer, glioblastoma multiforme, metastatic breast cancer; breast carcinoma; breast sarcoma; neurofibroma; neurofibromatosis; pediatric tumors; neuroblastoma; malignant melanoma; carcinomas of the epidermis; leukemias such as but not limited to, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemias such as myeloblastic, promyelocytic, myelomonocytic, monocytic, erythroleukemia leukemias and myclodysplastic syndrome, chronic leukemias such as but not limited to, chronic myelocytic (granulocytic) leukemia, chronic lymphocytic leukemia, hairy cell leukemia; polycythemia vera; lymphomas such as but not limited to Hodgkin's disease, non-Hodgkin's disease; multiple myelomas such as but not limited to smoldering multiple myeloma, nonsecretory myeloma, osteosclerotic myeloma, plasma cell leukemia, solitary plasmacytoma and extramedullary plasmacytoma; Waldenstrom's macroglobulinemia; monoclonal gammopathy of undetermined significance; benign monoclonal gammopathy; heavy chain disease; bone cancer and connective tissue sarcomas such as but not limited to bone sarcoma, myeloma bone disease, multiple myeloma, cholesteatoma-induced bone osteosarcoma, Paget's disease of bone, osteosarcoma, chondrosarcoma, Ewing's sarcoma, malignant giant cell tumor, fibrosarcoma ofbone, chordoma, periosteal sarcoma, soft-tissue sarcomas, angiosarcoma (hemangiosarcoma), fibrosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, neurilemmoma, rhabdomyosarcoma, and synovial sarcoma; brain tumors such as but not limited to, glioma, astrocytoma, brain stem glioma, ependymoma, oligodendroglioma, nonglial tumor, acoustic neurinoma, craniopharyngioma, medulloblastoma, meningioma, pineocytoma, pineoblastoma, and primary brain lymphoma; breast cancer including but not limited to adenocarcinoma, lobular (small cell) carcinoma, intraductal carcinoma, medullary breast cancer, mucinous breast cancer, tubular breast cancer, papillary breast cancer, Paget's disease (including juvenile Paget's disease) and inflammatory breast cancer; adrenal cancer such as but not limited to pheochromocytom and adrenocortical carcinoma; thyroid cancer such as but not limited to papillary or follicular thyroid cancer, medullary thyroid cancer and anaplastic thyroid cancer; pancreatic cancer such as but not limited to, insulinoma, gastrinoma, glucagonoma, vipoma, somatostatin-secreting tumor, and carcinoid or islet cell tumor; pituitary cancers such as but limited to Cushing's disease, prolactin-secreting tumor, acromegaly, and diabetes insipius; eye cancers such as but not limited to ocular melanoma such as iris melanoma, choroidal melanoma, and cilliary body melanoma, and retinoblastoma; vaginal cancers such as squamous cell carcinoma, adenocarcinoma, and melanoma; vulvar cancer such as squamous cell carcinoma, melanoma, adenocarcinoma, basal cell carcinoma, sarcoma, and Paget's disease; cervical cancers such as but not limited to, squamous cell carcinoma, and adenocarcinoma; uterine cancers such as but not limited to endometrial carcinoma and uterine sarcoma; ovarian cancers such as but not limited to, ovarian epithelial carcinoma, borderline tumor, germ cell tumor, and stromal tumor; cervical carcinoma; esophageal cancers such as but

not limited to, squamous cancer, adenocarcinoma, adenoid cyctic carcinoma, mucoepidermoid carcinoma, adenosquamous carcinoma, sarcoma, melanoma, plasmacytoma, verrucous carcinoma, and oat cell(small cell) carcinoma; stomach cancers such as but not limited to, adenocarcinoma, fungating (polypoid), ulcerating, superficial spreading, diffusely spreading, malignant lymphoma, liposarcoma, fibrosarcoma, and carcinosarcoma; colon cancers; KRAS mutated colorectal cancer; colon carcinoma; rectal cancers; liver cancers such as but not limited to hepatocellular carcinoma and hepatoblastoma, gallbladder cancers such as adenocarcinoma; cholangiocarcinomas such as but not limited to pappillary, nodular, and diffuse; lung cancers such as KRAS-mutated non-small cell lung cancer, non-small cell lung cancer, squamous cell carcinoma (epidermoid carcinoma), adenocarcinoma, large-cell carcinoma and small-cell lung cancer; lung carcinoma; testicular cancers such as but not limited to germinal tumor, seminoma, anaplastic, classic (typical), spermatocytic, nonseminoma, embryonal carcinoma, teratoma carcinoma, choriocarcinoma (yolk-sac tumor), prostate cancers such as but not limited to, androgen-independent prostate cancer, androgen-dependent prostate cancer, adenocarcinoma, leiomyosarcoma, and rhabdomyosarcoma; penal cancers; oral cancers such as but not limited to squamous cell carcinoma; basal cancers; salivary gland cancers such as but not limited to adenocarcinoma, mucoepidermoid carcinoma, and adenoidcystic carcinoma; pharynx cancers such as but not limited to squamous cell cancer, and verrucous; skin cancers such as but not limited to, basal cell carcinoma, squamous cell carcinoma and melanoma, superficial spreading melanoma, nodular melanoma, lentigo malignant melanoma, acrallentiginous melanoma; kidney cancers such as but not limited to renal cell cancer, adenocarcinoma, hypernephroma, fibrosarcoma, transitional cell cancer (renal pelvis and/or uterer); renal carcinoma; Wilms' tumor; bladder cancers such as but not limited to transitional cell carcinoma, squamous cell cancer, adenocarcinoma, carcinosarcoma. In addition, cancers include myxosarcoma, osteogenic sarcoma, endotheliosarcoma, lymphangioendotheliosarcoma, mesothelioma, synovioma, hemangioblastoma, epithelial carcinoma, cystadenocarcinoma, bronchogenic carcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma and papillary adenocarcinomas.

In certain embodiments cancers that can be prevented and/or treated in accordance with the present invention include, the following: pediatric solid tumor, Ewing's sarcoma, Wilms tumor, neuroblastoma, neurofibroma, carcinoma of the epidermis, malignant melanoma, cervical carcinoma, colon carcinoma, lung carcinoma, renal carcinoma, breast carcinoma, breast sarcoma, metastatic breast cancer, HIV-related Kaposi's sarcoma, prostate cancer, androgen-independent prostate cancer, androgen-dependent prostate cancer, neurofibromatosis, lung cancer, non-small cell lung cancer, KRAS-mutated non-small cell lung cancer, malignant melanoma, melanoma, colon cancer, KRAS-mutated colorectal cancer, glioblastoma multiforme, renal cancer, kidney cancer, bladder cancer, ovarian cancer, hepatocellular carcinoma, thyroid carcinoma,

rhabdomyosarcoma, acute myeloid leukemia, and multiple myeloma.

In certain embodiments, cancers and conditions associated therewith that are prevented and/or treated in accordance with the present invention are breast carcinomas, lung carcinomas, gastric carcinomas, esophageal carcinomas, colorectal carcinomas, liver carcinomas, ovarian carcinomas, thecomas, arrhenoblastomas, cervical carcinomas, endometrial carcinoma, endometrial hyperplasia, endometriosis, fibrosarcomas, choriocarcinoma, head and neck cancer, nasopharyngeal carcinoma, laryngeal carcinomas, hepatoblastoma, Kaposi's sarcoma, melanoma, skin carcinomas, hemangioma, cavernous hemangioma, hemangioblastoma, pancreas carcinomas, retinoblastoma, astrocytoma, glioblastoma, Schwannoma, oligodendroglioma, medulloblastoma, neuroblastomas, rhabdomyosarcoma, osteogenic sarcoma, leiomyosarcomas, urinary tract carcinomas, thyroid carcinomas, Wilm's tumor, renal cell carcinoma, prostate carcinoma, abnormal vascular proliferation associated with phakomatoses, edema (such as that associated with brain tumors), or Meigs' syndrome. In specific embodiment, the cancer an astrocytoma, an oligodendroglioma, a mixture of oligodendroglioma and an astrocytoma elements, an ependymoma, a meningioma, a pituitary adenoma, a primitive neuroectodermal tumor, a medullblastoma, a primary central nervous system (CNS) lymphoma, or a CNS germ cell tumor.

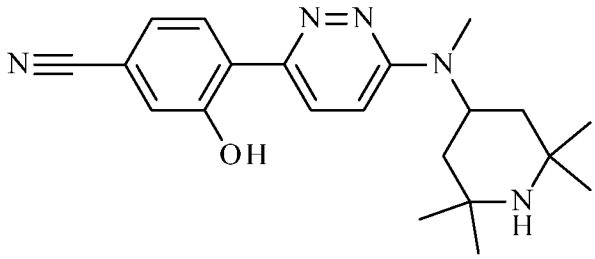
In specific embodiments, the cancer treated in accordance with the present invention is an acoustic neuroma, an anaplastic astrocytoma, a glioblastoma multiforme, or a meningioma.

In other specific embodiments, the cancer treated in accordance with the present invention is a brain stem glioma, a craniopharyngioma, an ependyoma, a juvenile pilocytic astrocytoma, a medulloblastoma, an optic nerve glioma, primitive neuroectodermal tumor, or a rhabdoid tumor.

EXAMPLES

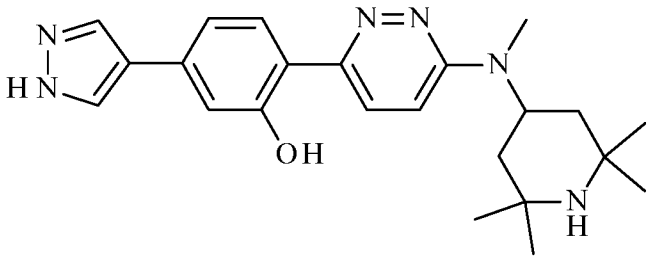
All compounds being the subject matter of the present application are disclosed and characterized in WO 2014/028459 (A1), WO 2014/116845 (A1) or WO 2015/017589 (A1). WO2014/028459 (A1), WO 2014/116845 (A1) and WO 2015/017589 (A1) disclose methods for the preparation of the compounds being the subject matter of the present application. WO2014/028459 (A1), WO 2014/116845 (A1) and WO 2015/017589 (A1) are hereby incorporated by reference.

Compound 1



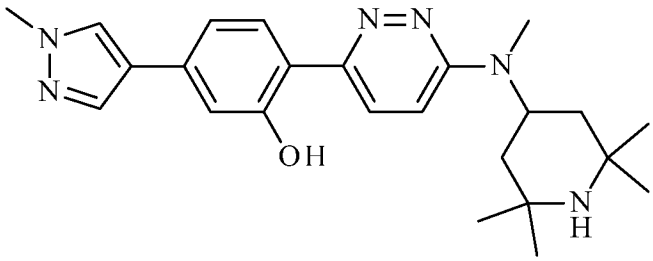
3-hydroxy-4-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)benzonitrile was prepared as described in WO2014/028459 (A1) on pages 59-60 for Example 5-1.

Compound 2



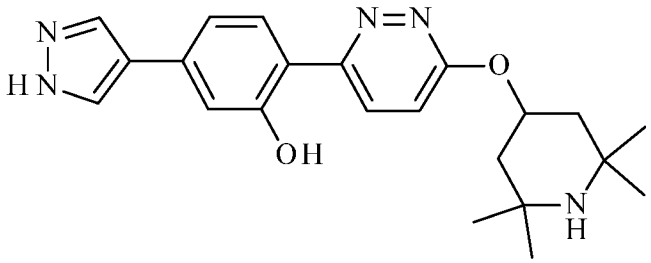
5-(1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol was prepared as described in WO2014/028459 (A1) on pages 69-71 for Example 14-1.

Compound 3



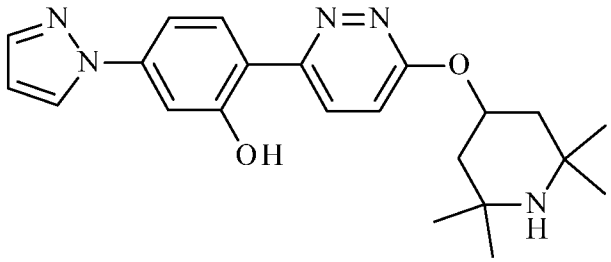
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenol was prepared as described in WO2014/028459 (A1) on page 74 for Example 16-2.

Compound 4



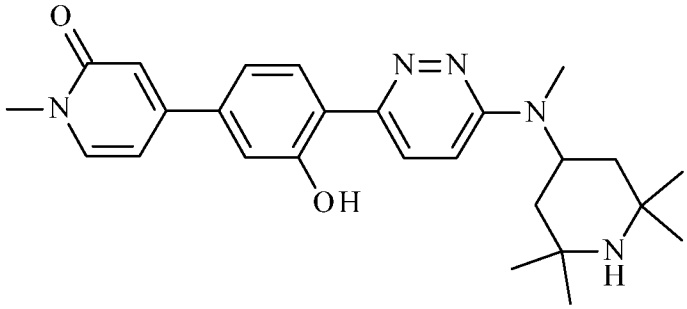
5-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)phenol was prepared as described in WO2014/028459 (A1) on pages 81-83 for Example 17-13.

Compound 5



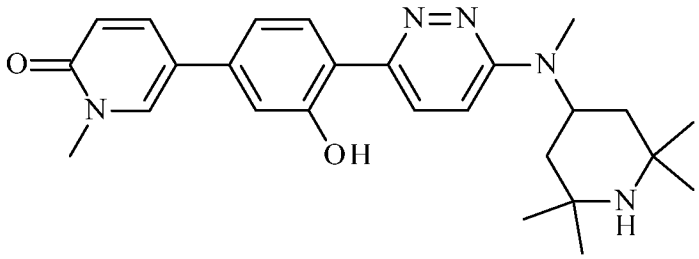
5-pyrazol-1-yl-2-[6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)-pyridazin-3-yl]-phenol was prepared as described in WO2014/028459 (A1) on page 81 for Example 17-12.

Compound 6



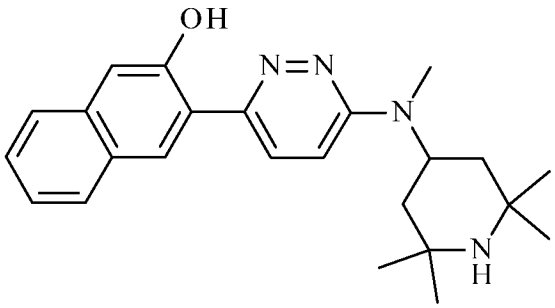
4-(3-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one was prepared as described in WO2014/028459 (A1) on pages 168-169 for Example 41-7.

Compound 7



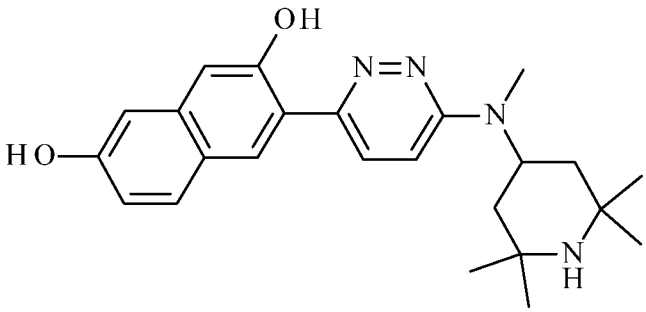
5-(3-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one was prepared as described in WO2014/028459 (A1) on page 168 for Example 14-6.

Compound 8



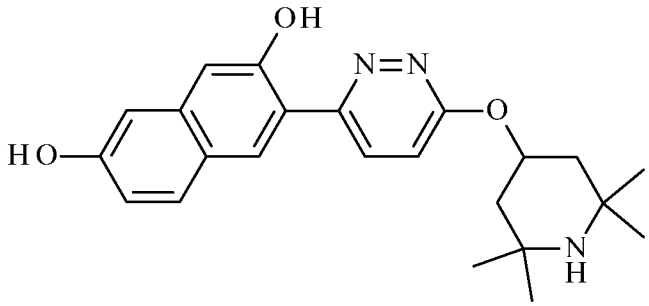
3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol was prepared as described in WO2014/028459 (A1) on page 55 for Example 3-1.

Compound 9



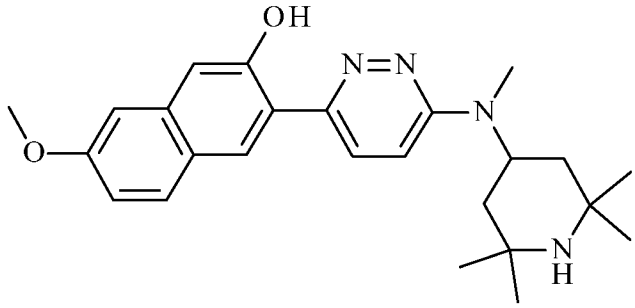
3-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalene-2,7-diol was prepared as described in WO2014/028459 (A1) on pages 92-93 for Example 20-2.

Compound 10



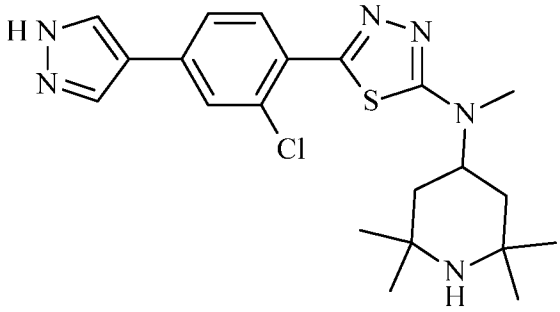
3-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)naphthalene-2,7-diol was prepared as described in WO2014/028459 (A1) on page 92 for Example 20-1.

Compound 11



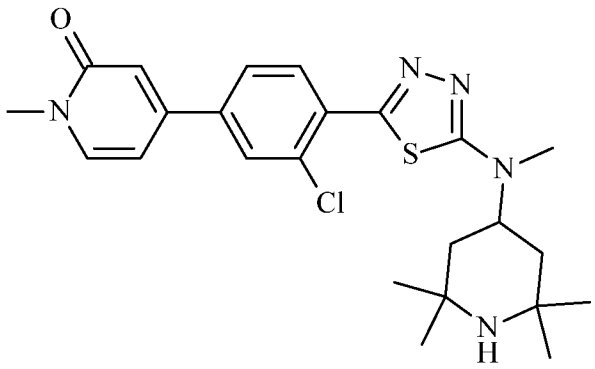
7-methoxy-3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol was prepared as described in WO2014/028459 (A1) on page 118 for Example 24-6.

Compound 12



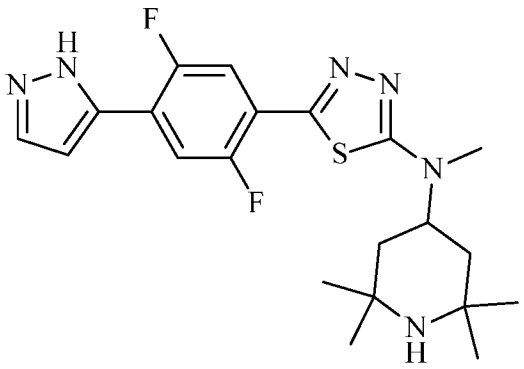
5-(2-Chloro-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine was prepared as described in WO2014/116845 (A1) on page 74 for Example 40.

Compound 13



4-(3-chloro-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)-1-methylpyridin-2(1H)-one was prepared as described in WO2014/116845 (A1) on page 74 for Example 39.

Compound 14



5-(2,5-difluoro-4-(1H-pyrazol-5-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine was prepared as described in WO2014/116845 (A1) on page 78 for Example 51.

Example 1

Monitoring expression levels of FoxM1 splice variants using real-time quantitative PCR

Human fibroblasts were plated at 10,000 cells/well in 200 µl DMEM with GlutaMAX and 10% FBS in 96-well plates in a cell culture incubator (37ºC, 5% CO2, 100% relative humidity). Cells were then treated with compounds at different concentrations (0.1-300 nM, each in 0.5% DMSO) in triplicate for 24 hours. RNA extraction was performed as per instructions mentioned in the Ambion® Cells-to-CT™ Kits from Applied Biosystems®. RNA samples were frozen at -20°C until further analysis. Relative expression levels of full-length FoxM1 (FoxM1_FL) or FoxM1 lacking exon VIIa (FoxM1_ΔVIIa) with GAPDH for internal control, was measured

using one-step multiplex reverse transcription-polymerase chain reaction (RT-PCR). TaqMan® FAM probes were used for relative quantitation of FoxM1_FL or FoxM1_ΔVIIa expression levels and TaqMan® VIC probes were used for relative quantitation of human GAPDH levels. The fidelity of the amplification methods was determined using the ΔΔCt relative quantification method for quantitative PCR.

Compounds induce alternative splicing of FoxM1 towards full-length FoxM1

To investigate an effect on splicing of FoxM1, human fibroblasts were treated for 24 hours with compounds of the present invention in dose response, and analysed by RT-qPCR for presence of mRNA including (FoxM1_FL) or excluding the exon VIIa (FoxM1_ΔVIIa). Figure 1 shows that all compounds increased expression of the FoxM1_FL mRNA. Correspondingly, the mRNAs for FoxM1_ΔVIIa declined. The data demonstrate that upregulation of FoxM1_FL with downregulation of FoxM1_ΔVIIa by treatment with compounds of present invention are directly correlated, indicating an effect of the compounds on alternative splicing of FoxM1. The resulting concentration dependence curves of the FoxM1_ΔVIIa splice variant were fitted to a Hill binding equation to yield IC50 values that are described in Table 1. The data demonstrate that all compounds affect FoxM1 splicing with various potencies, ranging from IC50 values from 0.7 to 345 nM. Taken together, the data underline a splicing modifying activity in the FoxM1 gene. This may result in arrest of cell cycle and induction of apoptosis, as the FoxM1_FL variant created by compound treatment is functionally inactive, and therefore will antagonize the pro-proliferating effect of functional FoxM1 (H. Ye, T.F. Kelly, U. Samadani, L. Lim, S. Rubio, D.G. Overdier, K.A. Roebuck, R.H. Costa, Mol. Cell Biol. 17 (1997) 1626–1641).

Compound	FoxM1_ΔVIIa IC50	SMN Protein EC50
1	41 nM	54 nM
2	0.9 nM	4 nM
3	9.8 nM	15 nM
4	17 nM	17 nM
5	278 nM	31 nM
6	1.5 nM	7 nM
7	167 nM	10 nM
8	3.7 nM	10 nM
9	0.7 nM	4 nM
10	-	18 nM
11	0.8 nM	6 nM

12	265 nM	34 nM
13	345 nM	50 nM
14	144 nM	85 nM

Table 1. Half-maximal effects for the FoxM1_ΔVIIa splice variant and for the SMN protein. FoxM1_ΔVIIa IC50 values were calculated from concentration dependence curves in Figure 1 using a Hill binding equation. SMN protein EC50 values were taken from Activity Tables on pages 189 to 192 of WO 2014/028459 (A1) on pages 124 to 141 of WO 2014/116845 (A1) and on pages 131 to 139 of WO 2015/017589 (A1).

Example 2

Monitoring expression levels of SMN splice variants using real-time quantitative PCR

Spinal muscular atrophy (SMA) is a neuromuscular disorder due to mutations in the Survival of Motor Neuron (SMN) gene. Loss of SMN is deleterious to motor neurons and results in neuromuscular insufficiency, a hallmark of the disease. From a genetic point of view, SMA is an autosomal recessive condition, caused by disruption of SMN1 gene, located in 5q13 (Lefebvre S. et al. (1995) Cell 80: 155-165). More than 98% of patients with spinal muscular atrophy have a homozygous disruption of SMN1 by deletion, rearrangement, or mutation. All these patients, however, retain at least one copy of the related SMN2 gene.

Compounds of present invention have been described in WO 2014/028459 (A1), WO 2014/116845 (A1) and in WO 2015/017589 (A1) as being effective splicing modifiers of the SMN2 gene and thus suitable for upregulation of SMN protein and thus for the treatment of SMA.

The potency of the compounds of present invention regarding SMN2 splicing modulation as assessed by the half-maximal effects (EC50) of SMN protein is evident from Activity Table on pages 189 to 192 of WO2014028459A1 and from Activity Table on pages 124 to 141 of WO2014116845A1.

The method of cellular SMN ELISA to measure the effects of compounds on SMN protein elevation is described on page 189 of WO2014028459A1 and on page 123 of WO2014116845A1.

Potency for splicing modulation of FoxM1 gene is linearly correlated to potency of splicing modulation of SMN2 gene

It has surprisingly been found that the potency of all compounds investigated to modulate splicing of SMN2 gene is linearly related to the potency to modulate splicing of FoxM1 gene.

Figure 2 shows a graph wherein the half-maximal effects for the FoxM1_ΔVIIa splice variant (IC50) have been plotted versus the half-maximal effects for the SMN protein (EC50).

A regression analysis of the values has resulted in a linear correlation according to the Equation 1:

$$Y = 0.102 * X + 15.2 \qquad \text{(Equation 1)}$$

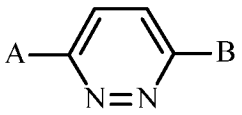
With Y = log(FoxM1_ΔVIIa IC50) and X = log(SMN protein EC50), this linear correlation allows the calculation of FoxM1_ΔVIIa IC50 values from SMN protein EC50 values according to Equation 2:

$$\text{FoxM1\_ΔVIIa IC50} = 10^{(0.102 * \log(\text{SMN protein EC50}) + 15.2)} \qquad \text{(Equation 2)}$$

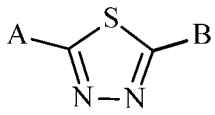
The slope of the linear correlation of Equation 1 is 0.102. Thereby the slope of the linear correlation suggests that on average, a 10-fold higher concentration (1/0.102 = 9.8) of each compound is needed to achieve 50% of splicing correction in the FoxM1 gene as compared to the SMN2 gene.

Claims

1. A FoxM1 gene splicing modifier selected from a compound of formula (I) or a compound of formula (VI)



(I)



(VI), wherein

A is 2-hydroxy-phenyl which is substituted with:

0, 1, 2, or 3 substituents independently selected from C_{1-4} alkyl, oxo, oxime, hydroxy, halo-C_{1-4} alkyl, dihalo-C_{1-4} alkyl, trihalo-C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxy-C_{3-7} cycloalkyl, halo-C_{1-4} alkoxy, dihalo-C_{1-4} alkoxy, trihalo-C_{1-4} alkoxy, hydroxy, cyano, halogen, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, heteroaryl, C_{1-4} alkyl substituted with hydroxy, C_{1-4} alkoxy substituted with aryl, amino, -C(O)NH-C_{1-4}alkyl-heteroaryl, -NHC(O)-C_{1-4} alkylheteroaryl, C_{1-4} alkyl-C(O)NH-heteroaryl, C_{1-4}alkyl-NHC(O)-heteroaryl, C_{3-7} cycloalkyl, 5-7 membered cycloalkenyl, or 5, 6 or 9 membered heterocycle containing 1 or 2 heteroatoms independently, selected from S, O and N,

wherein two C_{1-4} alkyl groups can combine with the atoms to which they are bound to form a 5-6 membered ring;

wherein heteroaryl has 5, 6 or 9 ring atoms, 1, 2 or 3 ring heteroatoms selected from N, O and S, and is substituted with 0, 1, or 2 substituents independently selected from oxo, hydroxy, nitro, halogen, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkoxy, C_{3-7} cycloalkyl, C_{1-4} alkyl-OH, trihalo-C_{1-4} alkyl, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, -C(O)NH_2, -NH_2, NO_2, hydroxy-C_{1-4}alkylamino, hydroxy-C_{1-4} alkyl, 4-7 membered heterocycle-C_{1-4} alkyl, amino-C_{1-4} alkyl, mono-C_{1-4}alkylamino-C_{1-4} alkyl, and di-C_{1-4}alkylamino-C_{1-4} alkyl; or

A is 2-naphthyl optionally substituted at the 3 position with hydroxy and additionally substituted with 0, 1, or 2 substituents selected from hydroxy, cyano, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-5} alkoxy, wherein the alkoxy is unsubstituted or substituted with hydroxy, C_{1-4} alkoxy, amino, -NHC(O)-C_{1-4} alkyl, -NHC(O)O-C_{1-4} alkyl, C_{1-4} alkylene-4-7 membered heterocycle, 4-7 membered heterocycle, mono-C_{1-4} alkylamino, and di- C_{1-4} alkylamino; or

A is 6 membered heteroaryl having 1-3 ring nitrogen atoms and which is substituted by phenyl or a heteroaryl having 5 or 6 ring atoms, 1 or 2 ring heteroatoms independently selected from N, O and S and is substituted with 0, 1, or 2 substituents independently selected from cyano, C_{1-4} alkyl, mono-C_{1-4} alkylamino,

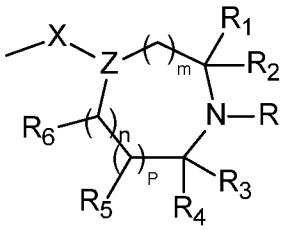
di-C_{1-4}alkylamino, hydroxy-C_{1-4} alkylamino, hydroxy-C_{1-4} alkyl, amino-C_{1-4} alkyl and mono-C_{1-4} alkylamino-C_{1-4} alkyl, and di-C_{1-4}alkylamino-C_{1-4} alkyl; or

A is bicyclic heteroaryl having 9 to 10 ring atoms, 1, 2, or 3 ring heteroatoms independently selected from N, O or S, and which is substituted with 0, 1, or 2 substituents independently selected from cyano, oxime, halogen, hydroxy, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkoxy substituted with hydroxy, amino, mono-C_{1-4} alkylamino, and di-C_{1-4} alkylamino; or

A is tricyclic heteroaryl having 12 or 13 ring atoms, 1, 2, or 3 ring heteroatoms independently selected from N, O or S, and which is substituted with 0, 1, or 2 substituents independently selected from cyano, halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkoxy substituted with hydroxy, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, and heteroaryl having 5, 6 or 9 ring atoms, 1, 2 or 3 ring heteroatoms selected from N, O and S, and which is substituted with 0, 1, or 2 substituents independently selected from oxo, hydroxy, nitro, halogen, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkoxy, C_{3-7} cycloalkyl, C_{1-4} alkyl-OH, trihalo-C_{1-4} alkyl, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, -C(O)NH_2, -NH_2, -NO_2, hydroxy-C_{1-4} alkylamino, hydroxy-C_{1-4} alkyl, 4-7 membered heterocycle-C_{1-4} alkyl, amino-C_{1-4} alkyl, mono-C_{1-4} alkylamino-C_{1-4} alkyl and di-C_{1-4} alkylamino-C_{1-4} alkyl; or

A is phenyl which is substituted with 0, 1, 2, or 3 substituents independently selected from C_{1-4} alkyl, oxo, oxime, hydroxy, halo-C_{1-4} alkyl, dihalo-C_{1-4} alkyl, trihalo-C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxy-C_{3-7} cycloalkyl, halo-C_{1-4} alkoxy, dihalo-C_{1-4} alkoxy, trihalo-C_{1-4} alkoxy, cyano, halogen, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, heteroaryl, C_{1-4} alkyl substituted with hydroxy, C_{1-4} alkoxy substituted with aryl, -C(O)NH-C_{1-4} alkyl- heteroaryl, -NHC(O)-C_{1-4} alkylheteroaryl, C_{1-4} alkyl-C(O)NH-heteroaryl, C_{1-4} alkyl-NHC(O)-heteroaryl, C_{3-7} cycloalkyl, 5-7 membered cycloalkenyl or 5, 6 or 9 membered heterocycle containing 1 or 2 heteroatoms, independently, selected from S, 0 and N;
wherein two C_{1-4} alkyl groups can combine with the atoms to which they are bound to form a 5-6 membered ring;
wherein heteroaryl has 5, 6 or 9 ring atoms, 1, 2 or 3 ring heteroatoms selected from N, 0 and S and is substituted with 0, 1, or 2 substituents independently selected from oxo, hydroxy, nitro, halogen, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkoxy, C_{3-7} cycloalkyl, C_{1-4} alkyl-OH, trihalo-C_{1-4} alkyl, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, -C(O)NH_2, -NH_2,-NO_2, hydroxy-C_{1-4} alkylamino, hydroxy-C_{1-4} alkyl, 4-7 memberered heterocycle-C_{1-4} alkyl, amino-C_{1-4} alkyl, mono-C_{1-4} alkylamino-

C_{1-4} alkyl, and di-C_{1-4} alkylamino-C_{1-4} alkyl;

B is a group of the formula  , wherein

m, n and p are independently selected from 0 or 1;

R, R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen and C_{1-4} alkyl, wherein alkyl is optionally substituted with hydroxy, amino, mono-C_{1-4} akylamino or di-C_{1-4} akylamino;

R_5 and R_6 are independently selected from hydrogen and fluorine; or

R and R_3, taken in combination form a fused 5 or 6 membered heterocyclic ring having 0 or 1 additional ring heteroatoms selected from N, O or S; or

R_1 and R_3, taken in combination form a C_{1-3} alkylene group; or

R_1 and R_5, taken in combination form a C_{1-3} alkylene group; or

R_3 and R_4, taken in combination with the carbon atom to which they attach, form a spirocyclic C_{3-6} cycloAlkyl;

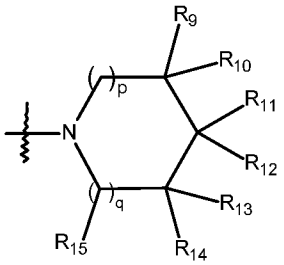
X is CR_AR_B, O, NR_7 or a bond;

R_7 is hydrogen, or C_{1-4} alkyl;

R_A and R_B are independently selected from hydrogen and C_{1-4} alkyl, or R_A and R_B, taken in combination, form a divalent C_{2-5} alkylene group;

Z is CR_8 or N; with the proviso that when Z is N, X is a bond;

R_8 is hydrogen or taken in combination with R_6 form a double bond; or

B is a group of the formula  , wherein

p and q are independently selected from the group consisting of 0, 1, and 2;

R_9 and R_{13} are independently selected from hydrogen and C_{1-4} alkyl;

R_{10} and R_{14} are independently selected from hydrogen, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, and C_{1-4} alkyl optionally substituted with hydroxy, amino, mono-C_{1-4} alkylamino or di-C_{1-4} alkylamino;

R_{11} is hydrogen, C_{1-4} alkyl, amino, mono-C_{1-4} alkylamino, or di-C_{1-4} alkylamino;

R_{12} is hydrogen or C_{1-4} alkyl; or

R_9 and R_{11} taken in combination form a saturated azacycle having 4 to 7 ring atoms which is optionally substituted with one to three C_{1-4} alkyl groups; or

R_{11} and R_{12}, taken in combination form a saturated azacycle having 4 to 7 ring atoms which is optionally substituted with one to three C_{1-4} alkyl groups.

or a pharmaceutically acceptable salt thereof;

for use in the treatment, prevention and/or delay of progression of cancer.

2. The FoxM1 gene splicing modifier according to claim 1, wherein

A is 2-hydroxy-phenyl which is substituted with:

0, 1, 2, or 3 substituents independently selected from C_{1-4} alkyl, oxo, oxime, hydroxy, halo-C_{1-4} alkyl, dihalo-C_{1-4} alkyl, trihalo-C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxy-C_{3-7} cycloalkyl, halo-C_{1-4} alkoxy, dihalo-C_{1-4} alkoxy, trihalo-C_{1-4} alkoxy, hydroxy, cyano, halogen, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, heteroaryl, C_{1-4} alkyl substituted with hydroxy, C_{1-4} alkoxy substituted with aryl, amino, -C(O)NH-C_{1-4}alkyl-heteroaryl, -NHC(O)-C_{1-4} alkylheteroaryl, C_{1-4} alkyl-C(O)NH-heteroaryl, C_{1-4}alkyl-NHC(O)-

heteroaryl, C_{3-7} cycloalkyl, 5-7 membered cycloalkenyl, or 5, 6 or 9 membered heterocycle containing 1 or 2 heteroatoms independently, selected from S, O and N,

wherein two C_{1-4} alkyl groups can combine with the atoms to which they are bound to form a 5-6 membered ring;

wherein heteroaryl has 5, 6 or 9 ring atoms, 1, 2 or 3 ring heteroatoms selected from N, O and S, and is substituted with 0, 1, or 2 substituents independently selected from oxo, hydroxy, nitro, halogen, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkoxy, C_{3-7} cycloalkyl, C_{1-4} alkyl-OH, trihalo-C_{1-4} alkyl, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, -C(O)NH_2, -NH_2, NO_2, hydroxy-C_{1-4}alkylamino, hydroxy-C_{1-4} alkyl, 4-7 membered heterocycle-C_{1-4} alkyl, amino-C_{1-4} alkyl, mono-C_{1-4}alkylamino-C_{1-4} alkyl, and di-C_{1-4}alkylamino-C_{1-4} alkyl; or

A is 2-naphthyl optionally substituted at the 3 position with hydroxy and additionally substituted with 0, 1, or 2 substituents selected from hydroxy, cyano, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-5} alkoxy, wherein the alkoxy is unsubstituted or substituted with hydroxy, C_{1-4} alkoxy, amino, -NHC(O)-C_{1-4} alkyl, -NHC(O)O-C_{1-4} alkyl, C_{1-4} alkylene-4-7 membered heterocycle, 4-7 membered heterocycle, mono-C_{1-4} alkylamino, and di- C_{1-4} alkylamino; or

A is phenyl which is substituted with 0, 1, 2, or 3 substituents independently selected from C_{1-4} alkyl, oxo, oxime, hydroxy, halo-C_{1-4} alkyl, dihalo-C_{1-4} alkyl, trihalo-C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxy-C_{3-7} cycloalkyl, halo-C_{1-4} alkoxy, dihalo-C_{1-4} alkoxy, trihalo-C_{1-4} alkoxy, cyano, halogen, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, heteroaryl, C_{1-4} alkyl substituted with hydroxy, C_{1-4} alkoxy substituted with aryl, -C(O)NH-C_{1-4} alkyl- heteroaryl, -NHC(O)-C_{1-4} alkylheteroaryl, C_{1-4} alkyl-C(O)NH-heteroaryl, C_{1-4} alkyl-NHC(O)-heteroaryl, C_{3-7} cycloalkyl, 5-7 membered cycloalkenyl or 5, 6 or 9 membered heterocycle containing 1 or 2 heteroatoms, independently, selected from S, 0 and N;

wherein two C_{1-4} alkyl groups can combine with the atoms to which they are bound to form a 5-6 membered ring;

wherein heteroaryl has 5, 6 or 9 ring atoms, 1, 2 or 3 ring heteroatoms selected from N, 0 and S and is substituted with 0, 1, or 2 substituents independently selected from oxo, hydroxy, nitro, halogen, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkoxy, C_{3-7} cycloalkyl, C_{1-4} alkyl-OH, trihalo-C_{1-4} alkyl, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, -C(O)NH_2, -NH_2,-NO_2, hydroxy-C_{1-4} alkylamino, hydroxy-C_{1-4} alkyl, 4-7 memberered heterocycle-C_{1-4} alkyl, amino-C_{1-4} alkyl, mono-C_{1-4} alkylamino-C_{1-4} alkyl, and di-C_{1-4} alkylamino-C_{1-4} alkyl;

or a pharmaceutically acceptable salt thereof;

for use in the treatment, prevention and/or delay of progression of cancer.

3. The FoxM1 gene splicing modifier according to any of claims 1 or 2, wherein

A is 2-hydroxy-phenyl substituted with one additional substituent selected from cyano and heteroaryl; or

A is 2-naphthyl optionally substituted at the 3 position with hydroxy and additionally substituted with 0 or 1 substituents selected from hydroxy and C_{1-4} alkoxy; or

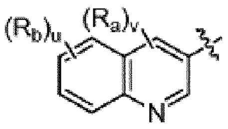
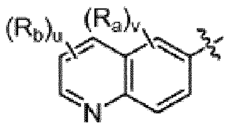
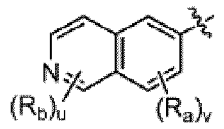
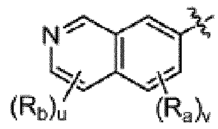
A is phenyl which is substituted with two or three substituents independently selected from halogen and heteroaryl;

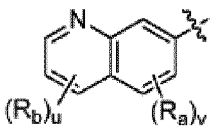
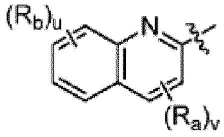
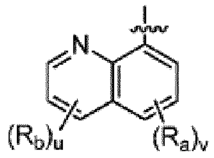
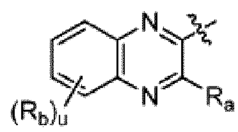
wherein heteroaryl has 5 or 6 ring atoms of which 1 or 2 are nitrogen and is substituted with 0, 1, or 2 substituents independently selected from C_{1-4} alkyl and hydroxy;

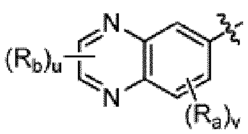
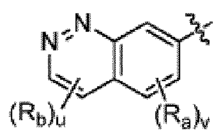
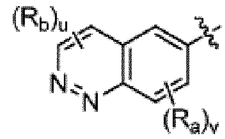
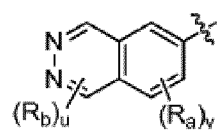
or a pharmaceutically acceptable salt thereof;

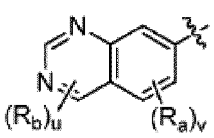
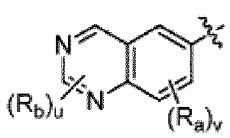
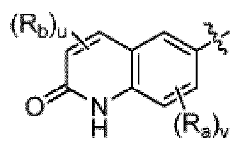
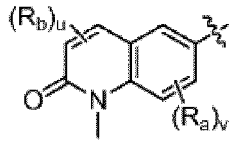
for use in the treatment, prevention and/or delay of progression of cancer.

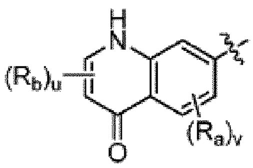
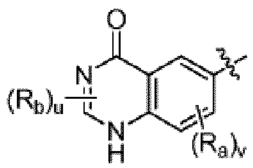
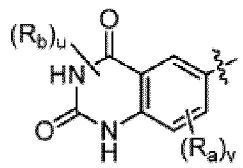
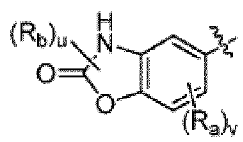
4. The FoxM1 gene splicing modifier according to claim 1, wherein A is selected from

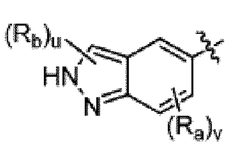
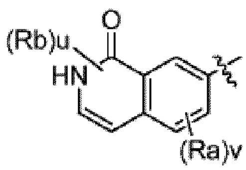
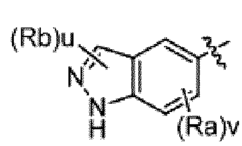
 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

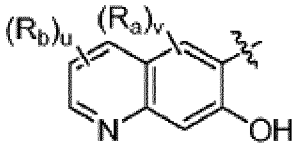
 ,  ,  ,  ,

 ,  and  ;

wherein u and v are each, independently, 0, 1, 2 or 3; and each R_a and R_b are, independently, selected from cyano, halogen, hydroxy, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{3-7} cycloalkyl, heterocyclyl, heteroaryl, heterocyclyl-C_{1-4} alkyl, C_{1-4} alkyl-aryl, C_{1-4} alkyl-heterocyclyl, C_{1-4} alkyl-heteroaryl, C_{1-4} alkoxy-aryl, C_{1-4} alkoxy-heterocyclyl, C_{1-4} alkoxy-heteroaryl, and C_{1-4} alkoxy substituted with hydroxy, C_{1-4} alkoxy, amino, mono-C_{1-4} alkylamino and di-C_{1-4} alkylamino; or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

5. The FoxM1 gene splicing modifier according to claim 1, wherein A is substituted adjacent to the point of attachment of the pyridazinyl-moiety of formula (I) or the thiadiazolyl-moiety of formula (VI) with halo, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, or hydroxy, and further in another position by 0, 1, or 2 additional substituents as defined in claim 1.

6. The FoxM1 gene splicing modifier according to claim 1, wherein A is selected from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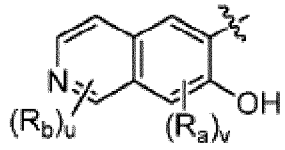
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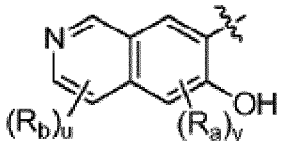
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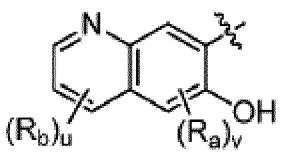
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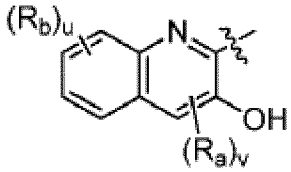
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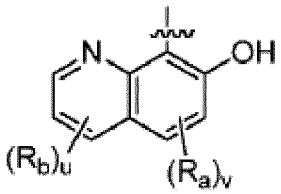
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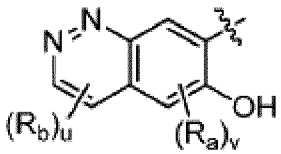
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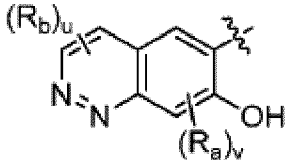
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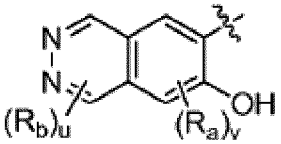
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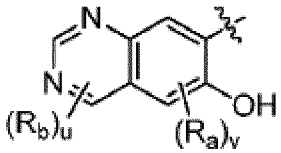
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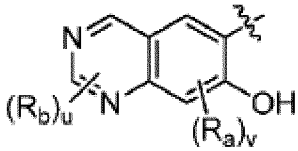
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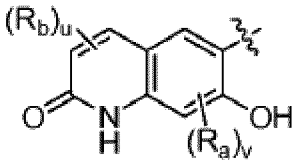
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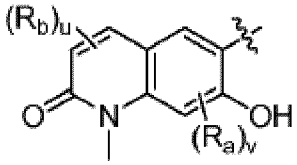
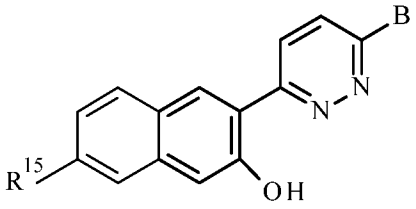


wherein u and v are each, independently, 0, 1, 2 or 3; and each R_a and R_b are, independently, selected from cyano, halogen, hydroxy, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{3-7} cycloalkyl, heterocyclyl, heteroaryl, heterocyclyl-C_{1-4} alkyl, C_{1-4} alkyl-aryl, C_{1-4} alkyl-heterocyclyl, C_{1-4} alkyl-heteroaryl, C_{1-4} alkoxy-aryl, C_{1-4} alkoxy-heterocyclyl, C_{1-4} alkoxy-heteroaryl, C_{1-4} alkoxy substituted with hydroxy, C_{1-4} alkoxy, amino, mono-C_{1-4} alkylamino and di-C_{1-4} alkylamino; or a pharmaceutically acceptable salt

thereof; for use in the treatment, prevention and/or delay of progression of cancer.

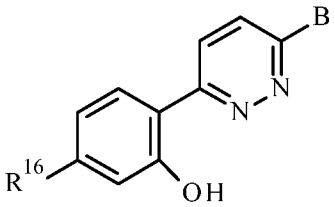
7. The FoxM1 gene splicing modifier according to any of claims 1 to 6, wherein A is substituted by one or more substituents as describedin any of claims 1 to 6, wherein one of the substituents of A is hydroxy in ortho-positon to the pyridazine of formula (I) or to the thiadiazole of formula (VI); or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

8. The FoxM1 gene splicing modifier according to claim 1 selected from a compound of formula (II):



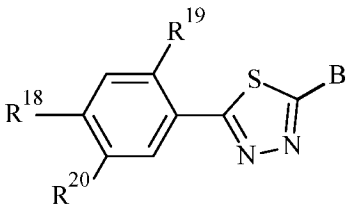
(II), wherein B is as defined in claim 1 and R^{15} is hydrogen, hydroxy, or C_{1-4} alkoxy, wherein alkoxy is optionally substituted with hydroxy, methoxy, amino, mono-methylamino, di-methylamino or morpholine; or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

9. The FoxM1 gene splicing modifier according to claim 1 selected from a compound of formula (III):



(III), wherein B is as defined in claim 1 and R^{16} is cyano, 5-membered heteroaryl having two ring nitrogen atoms, or 6-membered heteroaryl having one ring nitrogen atom; wherein the 5-membered heteroaryl is optionally substituted with C_{1-4} alkyl; wherein the 6-membered heteroaryl is optionally substituted with one or two substituents selected from C_{1-4} alkyl and hydroxy; or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

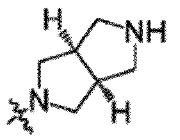
10. The FoxM1 gene splicing modifier according to claim 1 selected from a compound of formula (VII):



(VII), wherein B is as defined in claim 1 and R^{18} is 5-

membered heteroaryl having two ring nitrogen atoms or 6-membered heteroaryl having one ring nitrogen atom; wherein the 5-membered heteroaryl is optionally substituted with C_{1-4} alkyl; wherein the 6-membered heteroaryl is optionally substituted with one or two substituents selected from C_{1-4} alkyl and hydroxy; R^{19} is hydrogen or halogen; and R^{20} is hydrogen or halogen; or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

11. The FoxM1 gene splicing modifier according to any of claims 1 to 10, wherein B is selected from the group consisting of



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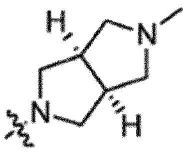

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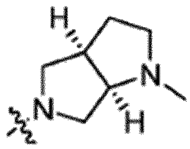

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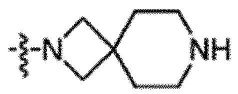

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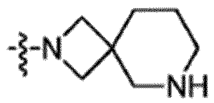

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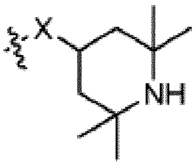

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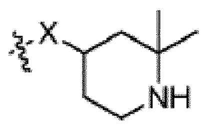

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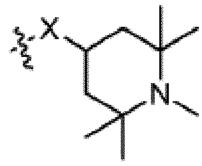

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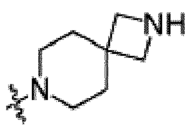

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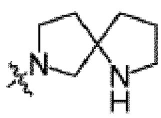

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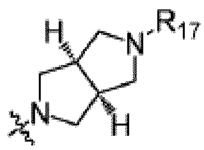
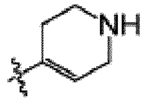
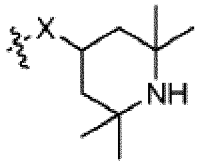


, and


wherein X is O or -$N(CH_3)$-; and R_{17} is hydrogen or methyl;
or a pharmaceutically acceptable salt thereof;
for use in the treatment, prevention and/or delay of progression of cancer.

12. The FoxM1 gene splicing modifier according to any of claims 1 to 11, wherein B is

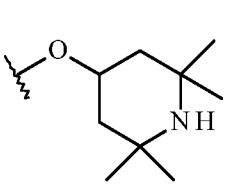


and X is O or -N(CH_3)-; or a pharmaceutically acceptable salt thereof;
for use in the treatment, prevention and/or delay of progression of cancer.

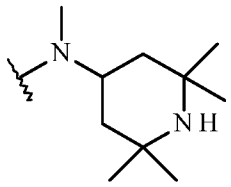
13. The FoxM1 gene splicing modifier according to any of claims 1 to 12, wherein X is O; or a pharmaceutically acceptable salt thereof;
for use in the treatment, prevention and/or delay of progression of cancer.

14. The FoxM1 gene splicing modifier according to any of claims 1 to 12, wherein X is -N(CH_3)-; or a pharmaceutically acceptable salt thereof;
for use in the treatment, prevention and/or delay of progression of cancer

15. The FoxM1 gene splicing modifier according to any of claims 1 to 12, wherein B is

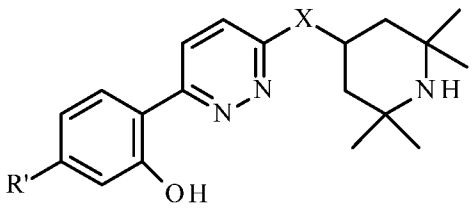


or

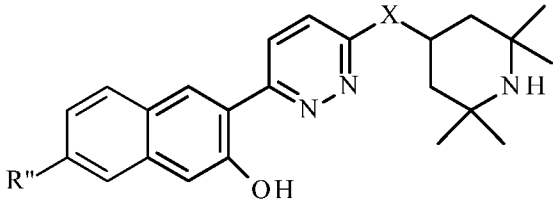


; or a pharmaceutically acceptable salt thereof;
for use in the treatment, prevention and/or delay of progression of cancer.

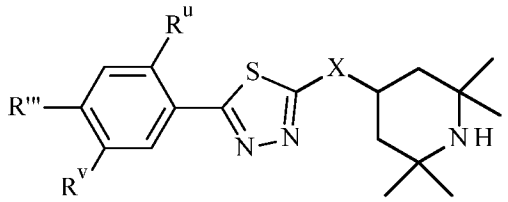
16. A FoxM1 gene splicing modifier selected from a compound of formula (IV) or of formula (V) or of formula (VIII):



(IV)



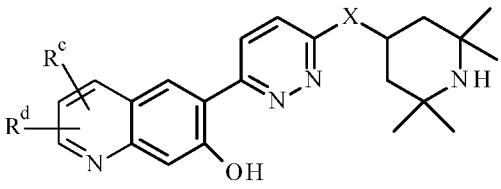
(V)



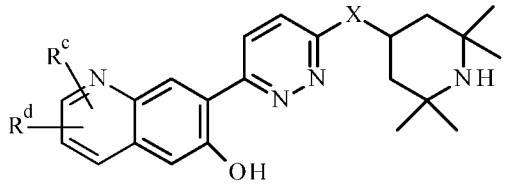
(VIII), wherein

X is -O- or -N(CH_3)-; R' is cyano, pyrazolyl optionally substituted with methyl, or pyridinyl substituted with methyl and hydroxy; R" is hydrogen, methyl or methoxy; R'" is pyrazolyl optionally substituted with methyl, or pyridinyl substituted with methyl and hydroxy; R^u is hydrogen, chloro or fluoro; R^v is hydrogen, chloro or fluoro; or a pharmaceutically acceptable salt thereof; for use in the treatment, prevention and/or delay of progression of cancer.

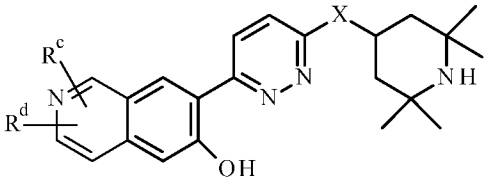
17. A FoxM1 gene splicing modifier selected from a compound of formula (IX) or of formula (X) or of formula (XI) or of formula (XII) or of formula (XIII) or of formula (XIV) or of formula (XV):



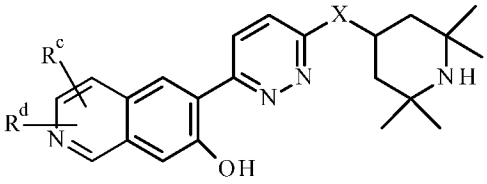
(IX),



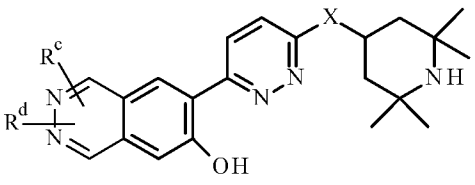
(X),



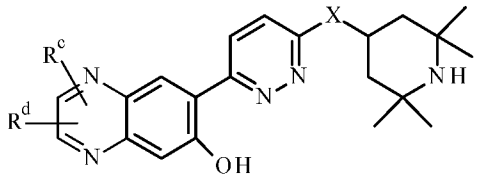
(XI),



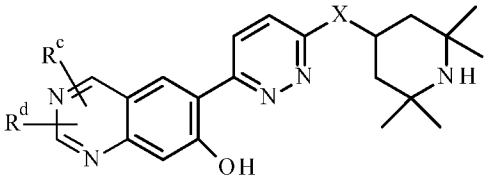
(XII),



(XIII),



(XIV),



(XV),

wherein X is -O- or -N(CH_3)-; and each R^C and R^d are, independently, selected from hydrogen, cyano, halogen, hydroxy, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{3-7} cycloalkyl, heterocyclyl, heteroaryl, heterocyclyl-C_{1-4} alkyl, C_{1-4} alkyl-aryl, C_{1-4} alkyl-heterocyclyl, C_{1-4} alkyl-heteroaryl, C_{1-4} alkoxy-aryl, C_{1-4} alkoxy-heterocyclyl, C_{1-4} alkoxy-heteroaryl, C_{1-4} alkoxy substituted with hydroxy, C_{1-4} alkoxy, amino, mono-C_{1-4} alkylamino and di-C_{1-4} alkylamino; or a pharmaceutically acceptable salt thereof; for use in

the treatment, prevention and/or delay of progression of cancer.

18. A FoxM1 gene splicing modifier according to any of claims 1 to 17 selected from the group consisting of:
6-(naphthalen-2-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
6-(benzo[b]thio-phen-2-yl)-N-methyl-N-(2,2,6,6-tetra-methylpiperidin-4-yl)pyridazin-3-amine;
2-(6-(2,2,6,6-tetra methylpiperidin-4-ylamino)-pyridazin-3-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetra-methylpiperidin-4-yl)amino)pyridazin-3-yl)benzo[b]-thiophene-5-carbonitrile;
6-(quinolin-3-yl)-N-(2,2,6,6-tetramethyl-piperidin-4-yl)pyridazin-3-amine;
3-(benzo[b]-thiophen-2-yl)-6-(2,2,6,6-tetra-methylpiperidin-4-yloxy)pyridazine;
2-(6-(methyl-(2,2,6,6-tetra-methylpiperidin-4-yl)amino)-pyridazin-3-yl)phenol;
6-(6-(methyl-(2,2,6,6-tetra-methylpiperidin-4-yl)amino)-pyridazin-3-yl)naphthalen-2-ol;
6-(benzo[b]-thiophen-2-yl)-N-(2,2,6,6-tetra-methylpiperidin-4-yl)pyridazin-3-amine;
7-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoquinoline;
6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoquinoline;
N-methyl-6-(quinolin-7-yl)-N-(2,2,6,6-tetramethyl-piperidin-4-yl)pyridazin-3-amine;
N-methyl-6-(quinolin-6-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
6-(isoquinolin-7-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
6-(isoquinolin-6-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
6-(imidazo[1,2-a]pyridin-6-yl-pyridazin-3-yl)-methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amine
methyl-[6-(6-phenyl-pyridin-3-yl)-pyridazin-3-yl]-(2,2,6,6-tetramethyl-piperidin-4-yl)-amine;
methyl-[6-(6-pyrrol-1-yl-pyridin-3-yl)-pyridazin-3-yl]-(2,2,6,6-tetra methyl-piperidin-4-yl)-amine;
methyl-(6-quinoxalin-2-yl-pyridazin-3-yl)-(2,2,6,6-tetramethyl-piperidin-4-yl)-amine;
methyl-(6-quinolin-3-yl-pyridazin-3-yl)-(2,2,6,6-tetramethyl-piperidin-4-yl)-amine;
N-methyl-6-(phthalazin-6-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
6-(benzo[c][1,2,5]oxa-diazol-5-yl)-N-(2,2,6,6-tetramethyl-piperidin-4-yl)pyridazin-3-amine;
6-(benzo[d]thiazol-5-yl)-N-(2,2,6,6-tetramethyl-piperidin-4-yl)pyridazin-3-amine;
6-(2-methylbenzo-[d]oxazol-6-yl)-N-(2,2,6,6-tetramethyl-piperidin-4-yl)pyridazin-3-amine;
3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
5-chloro-2-(6-(methyl(1 ,2,2,6,6-pentamethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
3-(6-(2,2,6,6-tetramethylpiperidin-4-ylamino)pyridazin-3-yl)naphthalen-2-ol;
5-chloro-2-(6-(1 ,2,2,6,6-pentamethylpiperidin-4-ylamino)pyridazin-3-yl)phenol;

4-hydroxy-3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)benzonitrile;
3-[6-(2,2,6,6-tetramethyl-piperidin-4-yloxy)-pyridazin-3-yl]-naphthalen-2-ol;
2-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-4-trifluoromethylphenol;
2-fluoro-6-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-phenol;
3,5-dimethoxy-2-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-phenol;
4,5-dimethoxy-2-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-phenol;
5-methoxy-2-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-phenol;
4,5-difluoro-2-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-phenol;
5-fluoro-2-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-phenol;
3-hydroxy-4-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)benzonitrile;
1-allyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
6-(benzo[b]thiophen-2-yl)-N-(1 ,2,2,6,6-pentamethylpiperidin-4-yl)pyridazin-3-amine;
N-allyl-3-hydroxy-4-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)benzamide;
2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
5-(5-methyl-oxazol-2-yl)-2-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-phenol;
5-(4-hydroxymethyl)-1H-pyrazole-1-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4 yl)amino)pyridazin-3-yl)phenol;
5-(1 H-imidazole-1-yl)-2-(6-(methyl(2,2,6,6-tetramethyl-piperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(4-amino-1H-pyrazole-1-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(4-amino-1H-pyrazol-1-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(3-amino-pyrazol-1-yl)-2 -{6-[methyl-(2,2,6,6-tetra methyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)phenol;

2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenol;
5-(5-amino-1H-pyrazol-1-yl)-2-(6-(methyl-(2,2,6,6-tetramethyl-piperidin-4-yl) amino)pyridazin-3-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(1H-pyrazol-1-yl)phenol;
2-{6-[(2-hydroxy-ethyl)-(2,2,6,6-tetra methyl-piperidn-4-yl)-amino]-pyridazin-3-yl}-5-pyrazol-1-yl-phenol;
2-(6-(piperidin-4-yloxy)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
2-(6-(((2S,4R, 6 R)-2,6-dimethylpiperidin-4-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
5 2-(6-((2, 6-di-methylpiperidin-4-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
2-(6-((2, 6-di-methylpiperidin-4-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
5-(1H-pyrazol-1-yl)-2-(6-(pyrrolidin-3-yloxy)pyridazin-3-yl)phenol;
2-(6-((-2-methylpiperidin-4-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
(S)-5-(1H-pyrazol-1-yl)-2-(6-(pyrrolidin-3-ylmethoxy)pyridazin-3-yl)phenol;
(R)-5-(1H-pyrazol-1-yl)-2-(6-(pyrrolidin-3-yl methoxy)pyridazin-3-yl)phenol;
2-(6-((3-fluoropiperidin-4-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)-phenol;
2-[6-(1,2,2,6,6-pentamethyl-piperidin-4-yloxy)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
5-pyrazol-1-yl-2-[6-((2,2,6,6-tetramethylpiperidin-4-yloxy)-pyridazin-3-yl]-phenol;
5-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)phenol;
2-(6-piperazin-1-yl-pyridazin-3-yl)-5-pyrazol-1-yl-phenol;
3-[6-(azetidin-3-yl-amino)-pyridazin-3-yl]-naphthalen-2-ol;
2-[6-(azetidin-3-ylamino)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(3, 5-di methyl-piperazin-1-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(7-methyl-2,7-diaza-spiro[4.4]non-2-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-(6-[1,4]diazepan-1-yl-pyridazin-3-yl)-5-pyrazol-1-yl-phenol;
2-{6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-pyridazin-3-yl}-5-pyrazol-1-yl-phenol;
2-[6-(3, 6-diaza-bicyclo[3.2.1]oct-3-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(2, 7-diaza-spiro[3.5]non-7-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(3-hydroxy-methyl-piperazin-1-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(1, 7-diaza-spiro[4.4]non-7-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(4-am in o-4-methyl-piperidin-1-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(3-dimethyl-amino-piperidin-1-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(1 ,2,2,6,6-pentamethyl-piperidin-4-ylamino)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-[6-(3, 3-di methyl-piperazin-1-yl)-pyridazin-3-yl]-5-pyrazol-1-yl-phenol;
2-(6-(7-(2-hydroxyethyl)-2,7-diazaspiro[4.4]-nonan-2-yl)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;

2-(6-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
3-(6-(piperazin-1-yl)pyridazin-3-yl)naphthalene-2,7-diol;
5-pyrazol-1-yl-2-[6-(1,2,3,6-tetrahydro-pyridin-4-yl)-pyridazin-3-yl]-phenol;
2-(6-piperidin-4-yl-pyridazin-3-yl)-5-pyrazol-1-yl-phenol;
3-(6-(1 ,2,3,6-tetra-hydropyridin-4-yl)pyridazin-3-yl)naphthalen-2-ol;
3-(6-(1 ,2, 3, 6-tetrahydropyridin-4-yl)pyridazin-3-yl)naphthalene-2,7-diol;
3-(6-(2,2,6,6-tetramethyl-1 ,2,3, 6-tetrahydropyridin-4-yl)pyridazin-3-yl)naphthalene-2,7-diol;
3-(6-(1-methyl-1 ,2,3,6-tetrahydropyridin-4-yl)pyridazin-3-yl)naphthalene-2,7-diol;
3-(6-(piperidin-4-yl)pyridazin-3-yl)naphthalene-2,7-diol;
3-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)naphthalene-2,7-diol;
3-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalene-2,7-diol;
3-(6-((2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalene-2,7-diol;
[3-(7-hydroxy-6-{6-[methyl-(2,2,6,6-tetra methyl-piperidin-4-yl)-amino]-pyridazin-3-yl}-naphthalen-2-yloxy)-propyl]-carbamic acid tert-butyl ester;
7-(3-amino-propoxy)-3-{6-[methyl-(2,2,6,6-tetramethyl-piperidin-4-yl)-amino]-pyridazin-3-yl}naphthalen-2-ol;
N-[3-(7-hydroxy-6-{6-[methyl-(2,2,6,6-tetra methyl-piperidin-4-yl)-amino]-pyridazin-3-yl}naphthalen-2-yloxy)-propyl]-acetamide;
7-(3-hydroxypropoxy)-3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
7-(3-methoxypropoxy)-3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
7-(2-morpholinoethoxy)-3-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)naphthalen-2-ol;
3-(6-(piperidin-4-ylmethyl)pyridazin-3-yl)naphthalen-2-ol;
5-(1H-pyrazol-1-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)methyl)pyridazin-3-yl)phenol;
3-methoxy-2-(6-(methyl(2,2,6-trimethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(5-methyloxazol-2-yl)phenol;
2-(6-((6S)-6-((S)-1-hydroxyethyl)-2,2-d imethylpiperidin-4-yloxy)pyridazin-3-yl)-5-(1H pyrazol-1-yl)phenol;
7-hydroxy-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2-naphthonitrile;
3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-7-(piperidin-1-ylmethyl)naphthalen-2-ol;
3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-7-(pyrrolidin-1-ylmethyl)naphthalen-2-ol;

1-bromo-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalene-2,7-diol;
1-chloro-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalene- 2,7-diol;
7-methoxy-3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
7-methoxy-3-(6-(methyl(1,2,2,6,6-pentamethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
7-(3,6-dihydro-2H-pyran-4-yl)-3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
3-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-7-(tetrahydro-2H-pyran-4-yl)naphthalen-2-ol;
7-(difluoromethyl)-3-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
7-((4-hydroxy-2 -methyl butan-2-yl)oxy)-3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
7-(3-hydroxy-3-methylbutoxy)-3-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)benzene-1,3-diol;
3-methoxy-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1 H pyrazol-4-yl)phenol;
5-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-(trifluoromethoxy)phenol;
2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)-3-(trifluoromethoxy)phenol;
2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)-3-(trifluoromethoxy)phenol;
4-(3-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(trifluoromethoxy)phenyl)-1-methylpyridin-2(1H)-one;
3-methoxy-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenol;
3-methoxy-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(5,6,7,8-tetrahydroimidazo[1 ,2-a]pyridin-3-yl)phenol;
3-methoxy-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino) pyridazn-3-yl)-5-(pyridin-3-yl)phenol;
5-(1-cyclopentyl-1 H -pyrazol-4-yl)-3-meth oxy-2 -(6-(methyl(2,2,6,6-tetra methylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;

3' 5-dimethoxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-[1,1'-biphenyl]-3-ol;
3-(benzyloxy)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(5-methyloxazol-2-yl)phenol;
3-ethoxy-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(5-methyloxazol-2-yl)phenol;
5 3-(cyclopropylmethoxy)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)-pyridazin-3-yl)-5-(5-methyloxazol-2-yl)phenol;
2-methyl-5-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-1 H benzo[d]imidazol-6-ol;
5-chloro-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(1H-pyrazol-1-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
3-hydroxy-4-(6-((2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)benzonitrile;
2-(6-((2,2-dimethylpiperidin-4-yl)oxy)pyridazin-3-yl)-5-(1H-pyrazol-1-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(1H-pyrazol-4-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(4,5,6, 7-tetrahydropyrazolo[1,5-a]pyridin-3-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(4,5,6,7-tetrahydropyrazolo[1,5-a] pyrazin-3-yl)phenol;
4-(1 H-indol-2-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
4-(cyclopent-1-en-1-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(1H-pyrazol-3-yl)phenol;
4-(4-hydroxy-3-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3 yl)phenyl)pyridin-2-ol;
4-(4-hyd roxy-3-(6-((2,2,6,6-tetra methylpiperidin-4-yl)oxy)pyridazin-3-yl)phenyl)-1-methylpyridin-2-(1H)-one;
4-(4-hydroxy-3-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)phenyl)pyridin-2-ol;
5-(1 H-indazol-7-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
4-chloro-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;
4-fluoro-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;

5-fluoro-4-(1 H-imidazol-4-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-fluoro-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(1H-pyrazol-4-yl)phenol;
5-fluoro-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(1H-pyrazol-5-yl)phenol;
5,6-hydroxy-5-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2,3-dihydro-1H-inden-1-one;
6-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-1 ,4-dihydroindeno[1 ,2-c]pyrazol-7-ol;
6-hydroxy-5-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2,3-dihydro-1H-inden-1-one oxime hydrochloride salt;
5-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2,3-dihydro-1H-indene-1,6-diol;
2-amino-6-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-8H-indeno[1 ,2-d]thiazol-5-ol hydrochloride salt;
15 9-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5,6-dihydroimidazo[5, 1-a]isoquinolin-8-ol hydrochloride salt;
4-hydroxy-3-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-N-((1-methyl-1H-pyrazol-4-yl)methyl)benzamide;
4-(4-(hydroxymethyl)-1H-pyrazol-1-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)methyl)pyridazin-3-yl)phenol;
6-(3-(benzyloxy)isoquinolin-6-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
6-(1-(benzyloxy)isoquinolin-7-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
3-fluoro-5-(2-methoxypyridin-4-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol hydrochloride salt;
4-(3-fluoro-5-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)pyridin-2(1H)-one hydrochloride salt;
4-(3-fluoro-5-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one hydrochloride salt;
5-(3-fluoro-5-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one hydrochloride salt;
3-fluoro-5-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)phenol hydrochloride salt;
5-chloro-3-fluoro-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-

yl)phenol hydrochloride salt;
3-fluoro-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol hydrochloride salt;
3-fluoro-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-methyl-1 H pyrazol-4-yl)phenol hydrochloride salt;
5-(5-methoxypyridin-3-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(3-hydroxy-4-(6-methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl) phenyl)pyridin-2-ol;
4-(3-hydroxy-4-(6-methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)pyridin-2-ol;
5-(6-methoxypyridin-3-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
15 5-(3-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)-3-(trifluoromethyl)pyridin-2-ol;
5-(3-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one;
4-(3-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one;
5-(2-methoxypyridin-4-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
4-(3-hydroxy-4-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)phenyl)pyridin-2-ol;
5-(6-(dimethylamino)pyridin-3-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
4-(3-hyd roxy-4-(6-((2,2,6,6-tetra methylpiperidin-4-yl)oxy)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(pyrimidin-5-yl)phenol;
5-(3-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl) phenyl)pyridin-3-ol;
1-cyclopropyl-4-(3-hyd roxy-4-(6-(methyl(2,2,6,6-tetra methylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)pyridin-2(1H)-one;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1,2,3,6-tetrahydropyridin-4-yl)phenol;
5-(cyclopent-1-en-1-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(3,6-dihydro-2H-pyran-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-

yl)amino)pyridazin-3-yl)phenol;
5-(imidazo[1 ,5-a]pyridin-7-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(imidazo[1 ,2-a]pyridin-7-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(2-methylpyridin-4-yl)phenol;
5-(1 H-imidazol-2-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
5-(1 H-imidazol-4-yl)-2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3 -yl)phenol;
5-(imidazo[1 ,2-a]pyrazin-3-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(5,6,7,8-tetrahydroimidazo[1 ,2-a]pyrazin-3-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(4-methyl-1H-imidazol-2-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-methyl-1H-imidazol-4-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-methyl-1H imidazol-5-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(4-nitro-1H-imidazol-2-yl)phenol;
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(2-methyl-1H imidazol-4-yl)phenol;
5-(1,2-dimethyl-1H-imidazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol;
1-(3-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)-1H-pyrazole-4-carboxamide;
2-(6-((3aR,6aS)-5-(2-hydroxyethyl)hexahydropyrrolo[3,4-c]pyrrol-2 (1H)-yl)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol ;
2-(6-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol;
2-(6-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)-5-(1 Hpyrazol-4-yl)phenol;
4-(3-hydroxy-4-(6-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one;
4-(3-hydroxy-4-(6-((3aR, 6aR)-1-methylhexahydropyrrolo[3,4-b]pyrrol-5(1H)-

yl)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one;
2-(6-(2, 7-diazaspiro[4.5]decan-2-yl)pyridazin-3-yl)-5-(1H-pyrazol-4-yl)phenol; and
4-(4-(6-(2,7-diazaspiro[4.5]decan-2-yl)pyridazin-3-yl)-3-hydroxyphenyl)-1-methylpyridin-2(1H)-one;
5-(2-Methoxy-4-(1H-pyrazol-1-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
6-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)naphthalen-2-ol;
5-(2-Methoxyquinolin-3-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(3-Methoxynaphthalen-2-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-Methoxy-4-(1H-pyrazol-1-yl)phenyl)-N-(1,2,2,6,6-pentamethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-Methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-Methoxy-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
4-(3-Methoxy-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)-1-methylpyridin-2(1H)-one;
5-(3-Methoxy-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)pyridin-2-ol;
5-(3-Methoxy-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)-1-methylpyridin-2(1H)-one;
N-Methyl-5-(2-methyl-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
1-Methyl-4-(4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-3-(trifluoromethoxy)phenyl)pyridin-2(1H)-one;
5-(4-(3,5-Dimethyl-1H-pyrazol-4-yl)-2-methoxyphenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-Methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
2-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenol;
2-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-5-(1H-pyrazol-1-yl)phenol;
5-(3-Hydroxy-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)-1-methylpyridin-2(1H)-one;

4-(3-Hydroxy-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)-1-methylpyridin-2(1H)-one;
5-(3-Hydroxy-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)pyridin-2-ol;
3-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)naphthalene-2,7-diol;
3-(5-((3aR,6aS)-Hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,4-thiadiazol-2-yl)naphthalene-2,7-diol;
3-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)naphthalen-2-ol hydrobromide salt;
3-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)quinolin-2-ol;
2-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-4-(1H-pyrazol-1-yl)phenol;
5-(2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
3-Chloro-2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenol;
5-(2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
3-Methoxy-2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-5-(5-methyloxazol-2-yl)phenol;
2-(2-Methoxy-4-(1H-pyrazol-1-yl)phenyl)-5-(1 ,2,3,6-tetrahydropyridin-4-yl)-1,3,4-thiadiazole;
2-(5-(piperazin-1-yl)-1,3,4-thiadiazol-2-yl)-5-(1H-pyrazol-1-yl)phenol;
5-(7-Methoxyquinolin-6-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
6-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)quinolin-7-ol;
3-methoxy-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)benzonitrile;
3-fluoro-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)benzonitrile;
methyl 3-fluoro-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)benzoate;
5-(2-methoxy-4-(3-(methylamino)-1H-pyrazol-1-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
7-methoxy-6-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)quinoline-2-carbonitrile;
4-(3-methoxy-4-(5-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)-1,3,4-thiadiazol-2-yl)phenyl)-

1-methylpyridin-2(1H)-one;
4-(3-chloro-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)-1-methylpyridin-2(1H)-one;
5-(2-Chloro-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-Chloro-4-(4,5, 6, 7-tetrahydropyrazolo[1, 5-a]pyridin-3-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
N-methyl-5-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine Hydrochloride salt;
2-(2-chloro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-5-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)-1,3,4-thiadiazole;
5-(2-chloro-4-(6-methoxypyridin-3-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(4-(6-aminopyridin-3-yl)-2-fluorophenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-fluoro-4-(3-methyl-1H-pyrazol-5-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-fluoro-4-(1H-pyrazol-5-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2,3-difluoro-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2,3-difluoro-4-(1H-pyrazol-5-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2,5-difluoro-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2,5-difluoro-4-(1H-pyrazol-5-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2,6-difluoro-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
2-(2,5-difluoro-4-(1H-pyrazol-4-yl)phenyl)-5-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,4-thiadiazole;
5-(2-chloro-5-fluoro-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(3-fluoro-5-(1H-pyrazol-4-yl)pyridin-2-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(4-(2-aminopyrimidin-4-yl)-2-chlorophenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(5-(2-aminopyrimidin-4-yl)-2-chlorophenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-

4-yl)-1,3,4-thiadiazol-2-amine;
5-(4-(2,4-dimethylthiazol-5-yl)-2,5-difluorophenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(4-(2,4-dimethylthiazol-5-yl)-2,3-difluorophenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
4-(3-hydroxy-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)am ino)-1,3,4-thiadiazol-2-yl)-5-(trifluoromethoxy)phenyl)-1-methylpyridin-2(1H)-one;
5-(2-fluoro-6-methoxy-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
2-(2-fluoro-6-methoxy-4-(1H-pyrazol-4-yl)phenyl)-5-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,4-thiadiazole;
5-(2,3-difluoro-6-methoxy-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
6-methoxy-2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-3,4-dihydroisoquinolin-1(2H)-one;
5-(2-Chloro-4-(1H-pyrazol-1-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-Chloro-4-(1H-1,2,3-triazol-1-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-chloro-4-(2H-1,2,3-triazol-2-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-chloro-4-(1 H-1 ,2,4-triazol-1-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(4-(3-amino-1H-pyrazol-1-yl)-2-chlorophenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
2-(2-chloro-4-(1 H-imidazol-1-yl)phenyl)-5-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,4-thiadiazole;
5-(2-Chloro-4-(1H-imidazol-1-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-fluoro-4-(1 H-imidazol-1-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-methoxy-4-(1H-pyrazol-5-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(4-(2,4-dimethylthiazol-5-yl)-2-methoxyphenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-methoxy-4-(pyridin-3-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-fluoro-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-

1,3,4-thiadiazol-2-amine;
5-(2-methoxy-4-(2-methoxypyridin-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2-methoxy-4-(6-methoxypyridin-3-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
2-(2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-5-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,4-thiadiazole;
2-(2-chloro-4-(1H-pyrazol-4-yl)phenyl)-5-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,4-thiadiazole;
2-(2-Chloro-4-(1H-pyrazol-4-yl)phenyl)-5-((3aR, 6a R)-1-methylhexahyd ropyrrolo[3,4-b]pyrrol-5(1H)-yl)-1,3,4-thiadiazole;
1-(4-(5-(2-chloro-4-(1H-pyrazol-4-yl)phenyl)-1,3,4-thiadiazol-2-yl)morpholin-2-yl)-N,N-dimethylmethanamine;
2-(2-chloro-4-(1H-pyrazol-4-yl)phenyl)-5-(2-methyl-2,7-diazaspiro[4.5]decan-7-yl)-1,3,4-thiadiazole;
2-(2-fluoro-4-(1H-pyrazol-4-yl)phenyl)-5-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,4-thiadiazole;
2-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-5-(2,6-diazaspiro[3.5]nonan-2-yl)-1,3,4-thiadiazole;
2-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-5-(2, 7-diazaspiro[3.5]nonan-2-yl)-1,3,4-thiadiazole;
2-(5-(Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-5-(1H-pyrazol-1-yl)phenol;
5-(3-chloro-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)pyridin-2(1H)-one;
2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-5-(3-(methylamino)-1H-pyrazol-1-yl)phenol;
3-fluoro-2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)am ino)-1,3,4-thiadiazol-2-yl)-5-(1H-pyrazol-4-yl)phenol;
3,4-d ifluoro-2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-5-(1H-pyrazol-4-yl)phenol;
6-hydroxy-5-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-2,3-dihydro-1H-inden-1-one;
2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)-5-(1H-pyrazol-4-yl)phenol;
2-(5-(2,6-diazaspiro[3.5]nonan-2-yl)-1,3,4-thiadiazol-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenol;
2-(5-(2,7-diazaspiro[3.5]nonan-2-yl)-1,3,4-thiadiazol-2-yl)-5-(1-methyl-1H-pyrazol-4-

yl)phenol;
3-fluoro-2-(5-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,4-thiadiazol-2-yl)-5-(1H-pyrazol-4-yl)phenol Di-hydrochloride salt;
3-Chloro-2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)am ino)-1,3,4-thiadiazol-2-yl)-5-(1H-pyrazol-4-yl)phenol;
2-(2-methoxy-4-(1H-pyrazol-1-yl)phenyl)-5-((2,2,6,6-tetramethylpiperidin-4-yl)methyl)-1,3,4-thiadiazole;
2-(2,3-difluoro-4-(1H-pyrazol-4-yl)phenyl)-5-(2, 7-diazaspiro[3.5]nonan-2-yl)-1,3,4-thiadiazole;
2-(5-(2,7-diazaspiro[3.5]nonan-2-yl)-1,3,4-thiadiazol-2-yl)-3-fluoro-5-(1H-pyrazol-4-yl)phenol;
4-methoxy-1-methyl-3-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)quinolin-2(1H)-one;
4-hydroxy-1-methyl-3-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)quinolin-2(1H)-one;
3-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)quinolin-2(1H)-one;
1-methyl-3-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)quinolin-2(1H)-one;
2-(2-Chloro-4-(1H-pyrazol-4-yl)phenyl)-5-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)yl)-1,3,4-thiadiazole Hydrochloride Salt;
2-(2-Chloro-4-(1H-pyrazol-4-yl)phenyl)-5-(2, 7-diazaspiro[4 .5]decan-2-yl)-1,3,4-thiadiazole Hydrochloride Salt;
(R)-(4-(5-(2-chloro-4-(1H-pyrazol-4-yl)phenyl)-1,3,4-thiadiazol-2-yl)piperazi n-2-yl)methanol Hydrochloride Salt;
2-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)benzo[b]thiophene-5-carbonitrile; and
5-(3-chlorobenzo[b]thiophen-2-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
7-hydroxy-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-2(1H)-one;
6-(6-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)quinolin-7-ol;
7-hydroxy-1-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-2(1H)-one;
6-(6-(methyl(1,2,2,6,6-pentamethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-morpholinoquinolin-7-ol;

4-chloro-2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
3-bromo-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
3-ethyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
3-(1H-imidazol-1-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-(1-methyl-1H-imidazol-4-yl)quinolin-7-ol;
3-isopropyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoline-3,7-diol;
7-hydroxy-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoline-3-carbonitrile;
6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
4-(dimethylamino)-2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
3-chloro-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
4-methoxy-2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
6-(3-(benzyloxy)isoquinolin-6-yi)-N-methyi-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
8-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinoline-1,6-diol;
7-(6-(methyl(1,2,2,6,6-pentamethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
1-cyclopropyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
6-(1-(benzyloxy)isoquinolin-7-yi)-N-methyi-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine;
7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-6-ol;
2-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-6-ol;
2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(1-methyl-1Hpyrazol-4-yl)quinoIin-7-ol;
2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;

4-ethoxy-2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
4-chloro-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-6-ol;
6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-(tetrahydro-2H-pyran-4-yl)quinolin-7-ol;
3-chloro-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-6-ol;
3-bromo-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-6-ol;
3-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-6-ol;
5-bromo-3-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-6-ol;
6-hydroxy-1-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-4(1H)-one;
2,3-dimethyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoxalin-6-ol;
2-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoxaIin-6-ol;
3-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoxaIin-6-ol;
4-methoxy-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
4-(azetidin-1-yl)-2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
7-hydroxy-2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoline-4-carbonitrile;
4-cyclopropyl-2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
4-(3,6-dihydro-2H-pyran-4-yl)-2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;
2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(tetrahydro-2Hpyran-4-yl)quinolin-7-ol;
2-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-4-(oxetan-3-yl)quinolin-7-ol;
4-(dimethylamino)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinolin-7-ol;

7-hydroxy-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinazolin-4(1H)-one;
6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinazolin-7-ol;
7-hydroxy-1-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3,4-dihydroquinolin-2(1H)-one;
7-hydroxy-1-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3,4-dihydroquinolin-2(1H)-one;
7-hydroxy-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinoline-1-carbonitrile;
7-hydroxy-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoline-2-carbonitrile;
6-hydroxy-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoline-2-carbonitrile;
6-hydroxy-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinoline-1-carboxamide;
7-hydroxy-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoline-2-carboxamide;
6-hydroxy-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoline-2-carboxamide;
methyl6-hydroxy-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinoline-2-carboxylate;
6-hydroxy-7-(6-(piperazin-1-yl)pyridazin-3-yl)quinoline-2-carbonitrile;
7-hydroxy-6-(6-(piperazin-1-yl)pyridazin-3-yl)quinoline-2-carbonitrile;
7-(6-(piperazin-1-yl)pyridazin-3-yl)isoquinolin-6-ol;
7-(6-(1,2,3,6-tetrahydropyridin-4-yl)pyridazin-3-yl)quinolin-6-ol;
1-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-7-ol;
1-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
1,3-dimethyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
7-hydroxy-3-methyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinoline-1-carbonitrile;
1-amino-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
7-hydroxy-1,3-dimethyl-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)quinazoline-2,4(1H,3H)-dione;
6-hydroxy-5-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-

yl)benzo[d]oxazoi-2(3H)-one;
2-methyl-5-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2H-indazol-6-ol;
1-methyl-5-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-1H-indazol-6-ol;
6-hydroxy-2-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-1(2H)-one;
2-ethyl-6-hydroxy-7-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoquinolin-1(2H)-one;
1-ethoxy-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
7-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoquinoline-1,6-diol;
7-(6-(methyl(2,2,6,6-tetramethyl-piperidin-4-yl)amino)-pyridazin-3-yl)-3-phenylisoquinolin-6-ol;
3-methyl-7-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
3-cyclopropyl-7-(6-(methyl(2,2,6,6-tetramethyl-piperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
3-isopropyl-7-(6-(methyl(2,2,6,6-tetramethyl-piperidin-4-yl)amino)pyridazin-3-yl)isoquinolin-6-ol;
3-propyl-7-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)-pyridazin-3-yl)isoquinolin-6-ol;
3-isopropyl-7-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)-pyridazin-3-yl)isoquinolin-6-ol; and
3-methyl-7-(6-(piperazin-1-yl)pyridazin-3-yl)isoquinolin-6-ol;
or a pharmaceutically acceptable salt thereof;
for use in the treatment, prevention and/or delay of progression of cancer.

19. A FoxM1 gene splicing modifier selected from the group consisting of:
3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
3-hydroxy-4-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)benzonitrile;
5-(1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenol
2-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenol;
5-pyrazol-1-yl-2-[6-((2,2,6,6-tetramethylpiperidin-4-yloxy)-pyridazin-3-yl]-phenol;
5-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)phenol;
3-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)naphthalene-2,7-diol;

3-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalene-2,7-diol;
7-methoxy-3-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)naphthalen-2-ol;
5-(3-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one;
4-(3-hydroxy-4-(6-(methyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)phenyl)-1-methylpyridin-2(1H)-one;
4-(3-chloro-4-(5-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,3,4-thiadiazol-2-yl)phenyl)-1-methylpyridin-2(1H)-one;
5-(2-Chloro-4-(1H-pyrazol-4-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
5-(2,5-difluoro-4-(1H-pyrazol-5-yl)phenyl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine;
or a pharmaceutically acceptable salt thereof;
for use in the treatment, prevention and/or delay of progression of cancer.

20. The FoxM1 gene splicing modifier according to any of claims 1 to 19 or a pharmaceutically acceptable salt thereof for use in the treatment, prevention and/or delay of progression of cancer, wherein the FoxM1 gene splicing modifier induces a transcriptionally inactive FoxM1 variant.

21. The FoxM1 gene splicing modifier according to any of claims 1 to 20 or a pharmaceutically acceptable salt thereof for use in the treatment, prevention and/or delay of progression of cancer, wherein the FoxM1 gene splicing modifier induces the transcriptionally inactive FoxM1 variant FoxM1A.

22. The FoxM1 gene splicing modifier according to any of claims 1 to 21 or a pharmaceutically acceptable salt thereof for use in the treatment, prevention and/or delay of progression of cancer, wherein the FoxM1 gene is the human FoxM1 gene.

23. The FoxM1 gene splicing modifier according to any of claims 1 to 22 or a pharmaceutically acceptable salt thereof for use in the treatment, prevention and/or delay of progression of cancer, wherein the cancer is selected from the group consisting of cancer of the liver, prostate, brain, breast, lung, colon, pancreas, skin, cervix, ovary, mouth, blood and nervous system.

24. The FoxM1 gene splicing modifier according to any of claims 1 to 22 or a pharmaceutically acceptable salt thereof for use in the treatment, prevention and/or delay of progression of cancer, wherein the cancer is selected from the group consisting of leukemia, acute myeloid leukemia, colon cancer, gastric cancer, macular degeneration,

acute monocytic leukemia, breast cancer, hepatocellular carcinoma, cone-rod dystrophy, alveolar soft part sarcoma, myeloma, skin melanoma, prostatitis, pancreatitis, pancreatic cancer, retinitis, adenocarcinoma, adenoiditis, adenoid cystic carcinoma, cataract, retinal degeneration, gastrointestinal stromal tumor, Wegener's granulomatosis, sarcoma, myopathy, prostate adenocarcinoma, Hodgkin's lymphoma, ovarian cancer, non-Hodgkin's lymphoma, multiple myeloma, chronic myeloid leukemia, acute lymphoblastic leukemia, renal cell carcinoma, transitional cell carcinoma, colorectal cancer, chronic lymphocytic leukemia, anaplastic large cell lymphoma, kidney cancer, breast cancer, and cervical cancer.

25. Use of a FoxM1 gene splicing modifier according to any of claims 1 to 22 for the preparation of a medicament for the treatment, prevention and/or delay of progression of cancer.

26. Use of a FoxM1 gene splicing modifier according to any of claims 1 to 22 for the treatment, prevention and/or delay of progression of cancer.

27. A method for the treatment, prevention and/or delay of progression of cancer comprising administering an effective amount of a FoxM1 gene splicing modifier according to any of claims 1 to 22 to a subject.

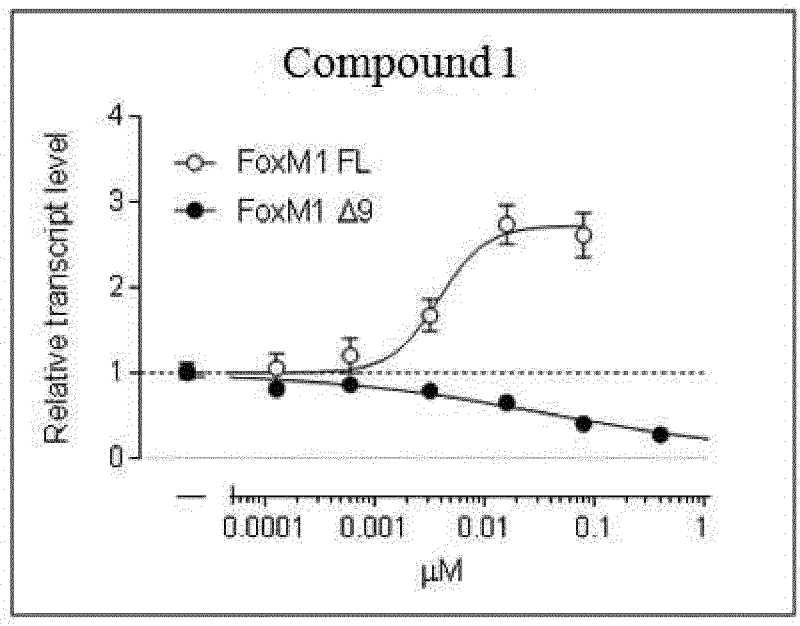
28. A pharmaceutical composition comprising a FoxM1 gene splicing modifier according to any of claims 1 to 22 for use in the treatment, prevention and/or delay of progression of cancer.

29. A combination comprising a therapeutically effective amount of a FoxM1 gene splicing modifier according to any of claims 1 to 22 or a pharmaceutically acceptable salt thereof and one or more therapeutically active co-agents.

30. The invention as described herein before.

***

Fig. 1A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FoxM1 Δ9
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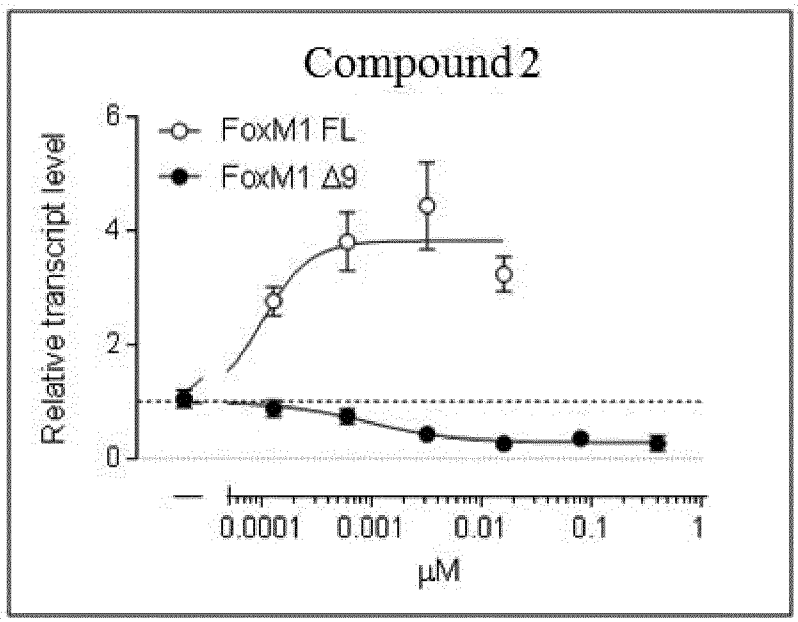
0.1
1
µM

Fig. 1B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Relative transcript level
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FoxM1 Δ9
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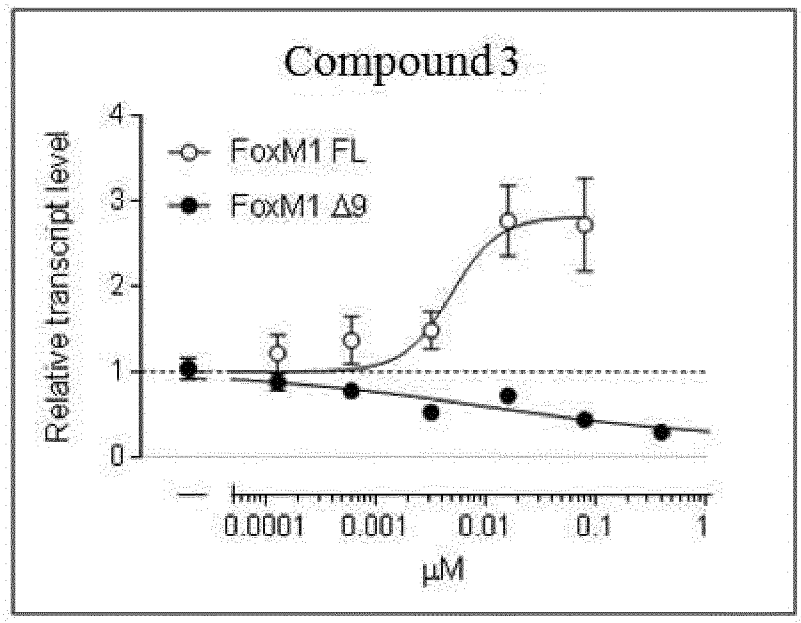
µM

Fig. 1C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Relative transcript level
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FoxM1 Δ9
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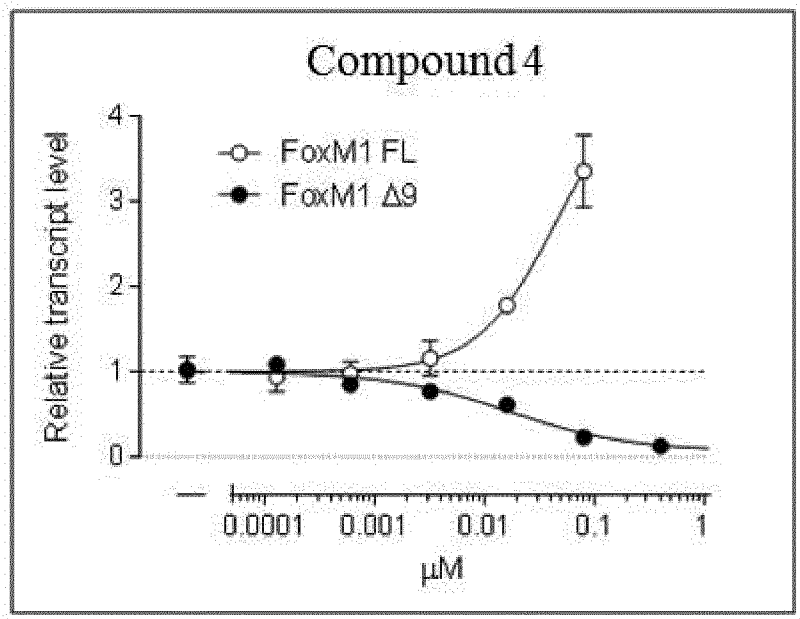
µM

Fig. 1D


Compound 4
Relative transcript level
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FoxM1 Δ9
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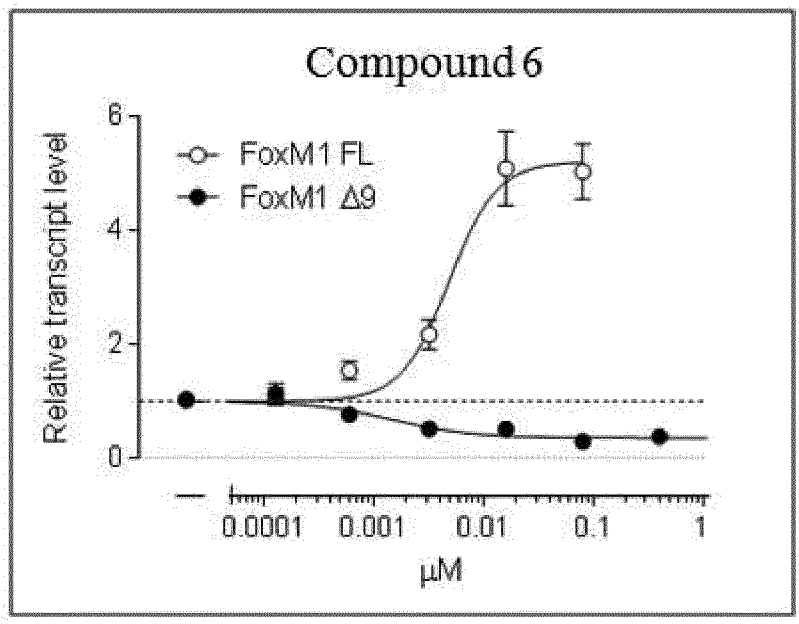
1
µM

Fig. 1E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Relative transcript level
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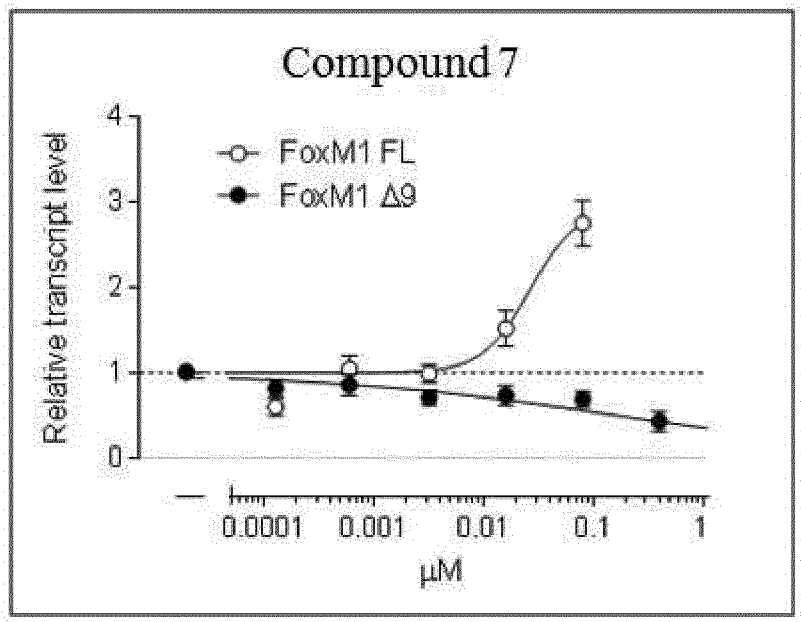
µM

Fig. 1F


Compound 7
Relative transcript level
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FoxM1 Δ9
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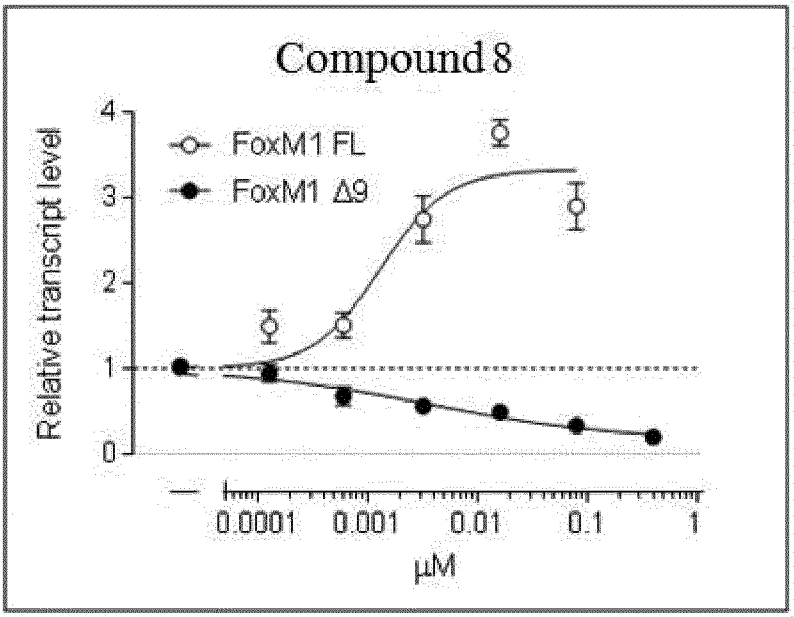
µM

Fig. 1G


Compound 8
Relative transcript level
FoxM1 FL
FoxM1 Δ9
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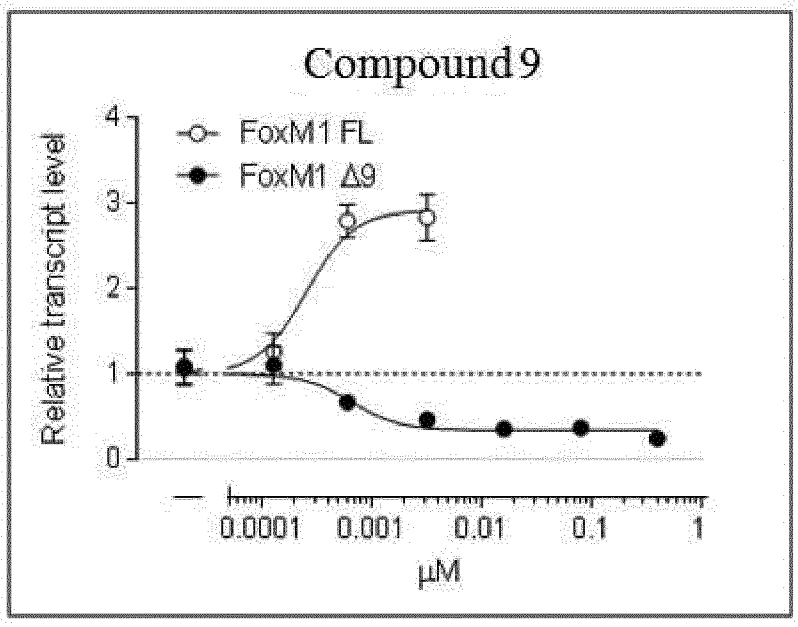
0.01
0.1
1
µM

Fig. 1H


Compound 9
Relative transcript level
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FoxM1 Δ9
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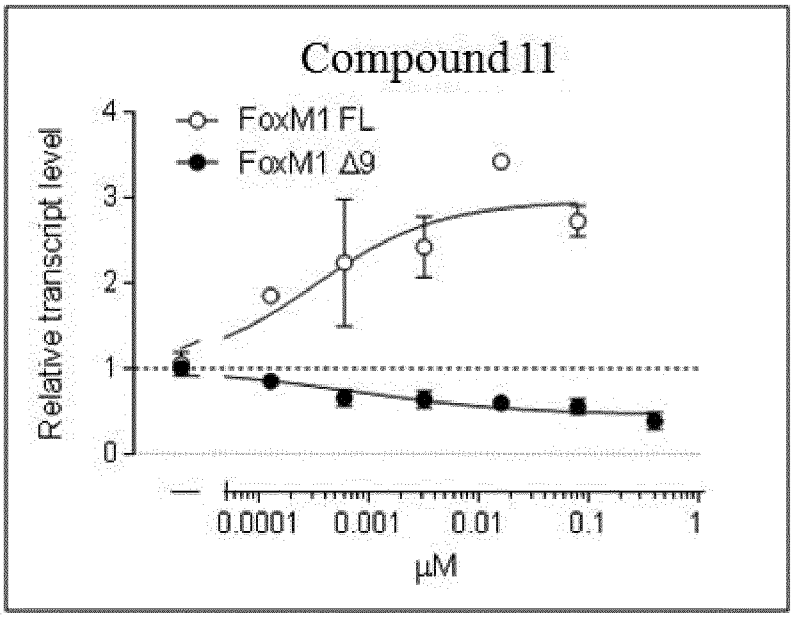
µM

Fig. 1I


Compound 11
FoxM1 FL
FoxM1 Δ9
Relative transcript level
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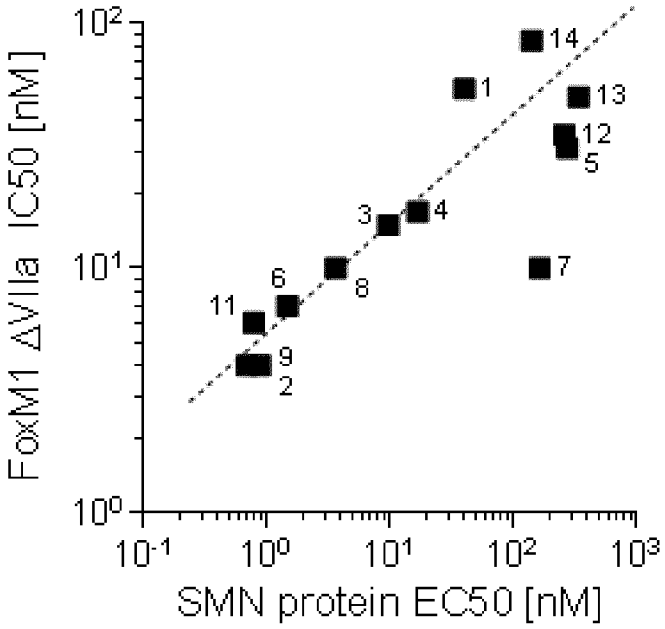
1
2
3
4
0.0001
0.001
0.01
0.1
1
µM

Fig. 2


FoxM1 ΔVIIa IC50 [nM]
SMN protein EC50 [nM]
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10^1
10^2
10^-1
10^0
10^1
10^2
10^3
14
1
13
12
5
3
4
7
6
8
11
9
2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2016/052597

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed:

      [X] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

      [ ] in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      [ ] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/052597

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/433 A61K31/435 A61K31/4353 A61K31/437 A61K31/438
A61K31/4436 A61K31/454 A61K31/4545 A61K31/4709 A61K31/506
A61K31/5377 A61P35/00 A61K45/06 A61K31/501 A61K31/502

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)
A61K A61P

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, BIOSIS, CHEM ABS Data, EMBASE, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/003604 A2 (NOVO NORDISK AS [DK]; HOHLWEG ROLF [DK]; ANDERSEN KNUD ERIK [DK]; SOER) 11 January 2007 (2007-01-11) abstract page 42, lines 25-30 page 73; example 14 page 95; example 55 page 111; example 79 -----	1,2, 20-30
X	WO 2011/082732 A1 (MERCK PATENT GMBH [DE]; STIEBER FRANK [DE]; WIENKE DIRK [DE]) 14 July 2011 (2011-07-14) abstract page 25, line 5 page 34, line 20 page 36, line 5 page 263, line 30 claims 7,8 -----	1,2, 20-30

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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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	Date of mailing of the international search report
6 April 2016	06/05/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Garabatos-Perera, J

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/133561 A2 (NEUROGEN CORP [US]; XU YUELIAN [US]; CALDWELL TIMOTHY M [US]; XIE LING) 22 November 2007 (2007-11-22) abstract page 96; example 350 page 41, lines 9-10	1,20-30
X	EP 2 014 656 A2 (TRANSTECH PHARMA [US]) 14 January 2009 (2009-01-14) page 33; examples 19,20 paragraph [0083]	1,20-30
X	WO 03/074500 A2 (SANOFI SYNTHELABO [FR]; ARANYI PETER [HU]; BALAZS LASZLO [HU]; BATA IM) 12 September 2003 (2003-09-12) page 41; compound 9.28 page 1, line 31	1,20-30
X	WO 2008/145681 A2 (BOEHRINGER INGELHEIM INT [DE]; EBEL HEINER [DE]; PETERS STEFAN [DE]; H) 4 December 2008 (2008-12-04) page 41; compound 53 malignant diseases; page 50 combinations; page 56	1-3, 20-30
A	WO 2014/116845 A1 (NOVARTIS AG [CH]; AXFORD JAKE [US]; DALES NATALIE [US]; SUNG MOO JE [U) 31 July 2014 (2014-07-31) cited in the application the whole document	1-30
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A	CN 103 965 169 A (PENG ZHENGZHONG) 6 August 2014 (2014-08-06) abstract claims	1-30

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C(Continuation). 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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A	EP 2 298 896 A1 (TRUSTEES OF THE UNIVERSITY OF ILLIONIS BOARD OF [US]) 23 March 2011 (2011-03-23) cited in the application abstract claims	1-30

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