



(12) Translation of
European patent specification

(11) NO/EP 3124481 B1

NORWAY

(19) NO
(51) Int Cl.
C07D 401/04 (2006.01)
A61K 31/4439 (2006.01)
A61K 31/5025 (2006.01)
A61P 5/26 (2006.01)
A61P 5/28 (2006.01)
A61P 35/00 (2006.01)
C07D 471/04 (2006.01)
C07D 487/04 (2006.01)

Norwegian Industrial Property Office

(21) Translation Published 2018.08.20

(80) Date of The European Patent Office Publication of the Granted Patent 2018.03.28

(86) European Application Nr. 16184263.8

(86) European Filing Date 2011.02.16

(87) The European Application's Publication Date 2017.02.01

(30) Priority 2010.02.16, US, 305082 P
2010.04.28, US, 329023 P
2010.09.30, US, 388457 P

(84) Designated Contracting States: AL ; AT ; BE ; BG ; CH ; CY ; CZ ; DE ; DK ; EE ; ES ; FI ; FR ; GB ; GR ; HR ; HU ; IE ; IS ; IT ; LI ; LT ; LU ; LV ; MC ; MK ; MT ; NL ; NO ; PL ; PT ; RO ; RS ; SE ; SI ; SK ; SM ; TR

Designated Extension States: BA ; ME

(73) Proprietor Aragon Pharmaceuticals, Inc., 12780 El Camino Real, Suite 301, San Diego, CA 92130, US-USA

(72) Inventor Smith, Nicholas, D, 1204 Beryl Street, San Diego, CA 92109, US-USA
Bonnefous, Celine, 4425 Via Sepulveda Unit 3, San Diego, CA 92122, US-USA
Julien, Jackaline, D., 517 1/2 Stratford Ct., Del Mar, CA 92014, US-USA

(74) Agent or Attorney OSLO PATENTKONTOR AS, Postboks 7007 M, 0306 OSLO, Norge

(54) Title **ANDROGEN RECEPTOR MODULATORS AND USES THEREOF**

(56) References Cited: WO-A1-2011/106570, WO-A2-2007/126765, CN-A- 101 032 483, WO-A2-2009/055053, WO-A2-2008/119015

Enclosed is a translation of the patent claims in Norwegian. Please note that as per the Norwegian Patents Acts, section 66i the patent will receive protection in Norway only as far as there is agreement between the translation and the language of the application/patent granted at the EPO. In matters concerning the validity of the patent, language of the application/patent granted at the EPO will be used as the basis for the decision. The patent documents published by the EPO are available through Espacenet (<http://worldwide.espacenet.com>) or via the search engine on our website here: <https://search.patentstyret.no/>

Patentkrav

- 1.** Farmasøytisk sammensetning for anvendelse ved behandling av en androgenreceptor-avhengig eller -mediert krefttype, omfattende 0,5 mg til 1000 mg av et 8-okso-6-tiokso-5,7-diazaspiro[3.4]oktanderivat eller et farmasøytisk akseptabelt salt eller N-oksid derav, sammen med minst én farmasøytisk akseptabel inaktiv ingrediens, hvor 8-okso-6-tiokso-5,7-diazaspiro[3.4]-oktanderivatet er:
- 5
- 5-(5-(3-Fluor-4-(2-(pyrrolidin-1-yl)etoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 10 5-(5-(4-((1-Metylpiperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 5-(5-(3-Fluor-4-(2-morfolinoetoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 15 5-(5-(3-Fluor-4-(2-(4-metylpiperazin-1-yl)etoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 5-(5-(3-Fluor-4-(3-morfolinopropoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 5-(5-(3-Fluor-4-(3-(4-metylpiperazin-1-yl)propoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 20 5-(5-(4-Fluor-3-(2-morfolinoetoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 5-(5-(4-Fluor-3-(3-morfolinopropoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 25 5-(5-(4-Fluor-3-(2-(4-metylpiperazin-1-yl)etoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 5-(5-(4-Fluor-3-(3-(4-metylpiperazin-1-yl)propoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;

- 5-(5-(3-Fluor-4-(2-(4-methylpiperazin-1-yl)etoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-methylpikolinonitril;
- 5-(5-(3-Fluor-4-(2-(piperazin-1-yl)etoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 5 5-(5-(3-Fluor-4-(2-tiomorfolinoetoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 5-(5-(3-Fluor-4-(2-(piperidin-1-yl)etoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 10 5-(5-(4-(2-(4-Methylpiperazin-1-yl)etoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 5-(5-(3-Fluor-4-(2-(tetrahydro-2H-pyran-4-yl)etoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 5-(5-(2-Fluor-4-(2-(4-methylpiperazin-1-yl)etoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 15 5-(5-(2-Fluor-4-(3-(4-methylpiperazin-1-yl)propoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 5-(5-(3-Fluor-4-(3-(pyrrolidin-1-yl)propoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 20 5-(5-(4-(2-(1,1-Dioksidotiomorfolino)etoksy)-3-fluorfenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 5-(5-(2-Fluor-4-(2-(piperidin-1-yl)etoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 5-(5-(2-Fluor-4-((1-methylpiperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 25 3-Metyl-5-(5-(4-((1-methylpiperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)pikolinonitril;

- 5-(5-(3-Fluor-4-((1-metylpiperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-metylpikolinonitril;
- 5-(5-(3-Fluor-4-((1-metylpiperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 5 3-Metyl-5-(8-okso-5-(4-((tetrahydro-2H-pyran-4-yl)oksy)fenyl)-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)pikolinonitril;
- 3-Metyl-5-(8-okso-5-(4-((tetrahydro-2H-tiopyran-4-yl)oksy)fenyl)-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)pikolinonitril;
- 10 5-(8-Okso-5-(4-((tetrahydro-2H-pyran-4-yl)oksy)fenyl)-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 3-Metyl-5-(8-okso-6-tiokso-5-(4-(2-(4-(2,2,2-trifluoretyl)piperazin-1-yl)etoksy)fenyl)-5,7-diazaspiro[3.4]oktan-7-yl)pikolinonitril;
- 3-Metyl-5-(5-(4-(2-(4-metylpiperazin-1-yl)etoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)pikolinonitril;
- 15 5-(5-(4-((1,1-Dioksidotetrahydro-2H-tiopyran-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-metylpikolinonitril;
- 5-(5-(4-(2-(4-Acetylpiperazin-1-yl)etoksy)-3-fluorfenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 3-Metyl-5-(8-okso-5-(4-(piperidin-4-yloksy)fenyl)-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)pikolinonitril;
- 20 5-(8-Okso-5-(4-(piperidin-4-yloksy)fenyl)-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 5-(8-Okso-5-(4-((1-propionylpiperidin-4-yl)oksy)fenyl)-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;
- 25 5-(5-(4-((1-isobutyrylpiperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;

Etyl-4-(4-(7-(6-cyano-5-(trifluormetyl)pyridin-3-yl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-5-yl)fenoksy)piperidin-1-karboksylat;

5-(5-(4-((1-acetyl)piperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]-oktan-7-yl)-3-metylpikolinonitriil;

- 5 5-(5-(4-((1-Etyl)piperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]-oktan-7-yl)-3-metylpikolinonitriil;

5-(5-(4-((1-(2-hydroksyetyl)piperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-metylpikolinonitriil;

- 10 5-(5-(4-((1-(2-hydroksyetyl)piperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitriil;

5-(5-(4-((1-(metylsulfonyl)piperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitriil;

5-(5-(4-((1-Isopropyl)piperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitriil;

- 15 Etyl-2-(4-(4-(7-(6-cyano-5-(trifluormetyl)pyridin-3-yl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-5-yl)fenoksy)piperidin-1-yl)acetat;

4-(4-(7-(6-Cyano-5-(trifluormetyl)pyridin-3-yl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-5-yl)fenoksy)piperidin-1-karboksamid;

eller et farmasøytisk akseptabelt salt eller N-oksid derav.

- 20 **2.** Farmasøytisk sammensetning for anvendelse ifølge krav 1, hvor 8-okso-6-tiokso-5,7-diazaspiro[3.4]oktanderivatet er:

5-(5-(4-((1-Metylpiperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]-oktan-7-yl)-3-(trifluormetyl)pikolinonitriil;

- 25 5-(5-(3-Fluor-4-(2-(piperidin-1-yl)etoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitriil;

- 5-(5-(2-Fluor-4-(2-(piperidin-1-yl)etoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro-
[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitрил;
- 5-(5-(2-Fluor-4-((1-metylpiperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro-
[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitрил;
- 5 3-Metyl-5-(5-(4-((1-metylpiperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-
diazaspiro[3.4]oktan-7-yl)pikolinonitрил;
- 5-(5-(3-Fluor-4-((1-metylpiperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro-
[3.4]oktan-7-yl)-3-metylpikolinonitрил;
- 10 5-(5-(3-Fluor-4-((1-metylpiperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro-
[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitрил;
- 3-Metyl-5-(8-okso-5-(4-(piperidin-4-yloksy)fenyl)-6-tiokso-5,7-diazaspiro[3.4]-
oktan-7-yl)pikolinonitрил;
- 5-(8-Okso-5-(4-(piperidin-4-yloksy)fenyl)-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-
3-(trifluormetyl)pikolinonitрил;
- 15 5-(8-Okso-5-(4-((1-propionylpiperidin-4-yl)oksy)fenyl)-6-tiokso-5,7-diazaspiro-
[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitрил;
- 5-(5-(4-((1-isobutyrylpiperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro-
[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitрил;
- 20 Etyl-4-(4-(7-(6-cyano-5-(trifluormetyl)pyridin-3-yl)-8-okso-6-tiokso-5,7-diazaspiro-
[3.4]oktan-5-yl)fenoksy)piperidin-1-karboksylat;
- 5-(5-(4-((1-acetylpiperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]-
oktan-7-yl)-3-metylpikolinonitрил;
- 5-(5-(4-((1-Etylpiperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]-
oktan-7-yl)-3-metylpikolinonitрил;
- 25 5-(5-(4-((1-(2-Hidroksyetyl)piperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-
diazaspiro[3.4]oktan-7-yl)-3-metylpikolinonitрил;

5-(5-(4-((1-(2-hydroksyetyl)piperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;

5-(5-(4-((1-(metylsulfonyl)piperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;

5 5-(5-(4-((1-Isopropylpiperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;

Etyl-2-(4-(4-(7-(6-cyano-5-(trifluormetyl)pyridin-3-yl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-5-yl)fenoksy)piperidin-1-yl)acetat;

10 4-(4-(7-(6-Cyano-5-(trifluormetyl)pyridin-3-yl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-5-yl)fenoksy)piperidin-1-karboksamid;

eller et farmasøytisk akseptabelt salt eller N-oksid deriv.

3. Farmasøytisk sammensetning for anvendelse ifølge krav 1, hvor 8-okso-6-tiokso-5,7-diazaspiro[3.4]oktanderivatet er:

15 5-(5-(3-Fluor-4-(2-(4-metyl piperazin-1-yl)etoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;

5-(5-(3-Fluor-4-(3-(4-metyl piperazin-1-yl)propoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;

5-(5-(4-Fluor-3-(2-(4-metyl piperazin-1-yl)etoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;

20 5-(5-(4-Fluor-3-(3-(4-metyl piperazin-1-yl)propoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;

5-(5-(3-Fluor-4-(2-(4-metyl piperazin-1-yl)etoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-metyl pikolinonitril;

25 5-(5-(3-Fluor-4-(2-(piperazin-1-yl)etoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;

5-(5-(4-(2-(4-Metyl piperazin-1-yl)etoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;

5-(5-(2-Fluor-4-(2-(4-metyl piperazin-1-yl)etoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;

5 5-(5-(2-Fluor-4-(3-(4-metyl piperazin-1-yl)propoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;

3-Metyl-5-(8-okso-6-tiokso-5-(4-(2-(4-(2,2,2-trifluoretyl)piperazin-1-yl)etoksy)fenyl)-5,7-diazaspiro[3.4]oktan-7-yl)pikolinonitril;

10 3-Metyl-5-(5-(4-(2-(4-metyl piperazin-1-yl)etoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)pikolinonitril;

5-(5-(4-(2-(4-Acetyl piperazin-1-yl)etoksy)-3-fluorfenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;

eller et farmasøytisk akseptabelt salt eller N-oksid derav.

15 **4.** Farmasøytisk sammensetning for anvendelse ifølge krav 1, hvor 8-okso-6-tiokso-5,7-diazaspiro[3.4]oktanderivatet er:

5-(5-(3-Fluor-4-(2-morfolinoetoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;

5-(5-(3-Fluor-4-(3-morfolinopropoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;

20 5-(5-(4-Fluor-3-(2-morfolinoetoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;

5-(5-(4-Fluor-3-(3-morfolinopropoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;

eller et farmasøytisk akseptabelt salt eller N-oksid derav.

5. Farmasøytisk sammensetning for anvendelse ifølge krav 1, hvor 8-okso-6-tiokso-5,7-diazaspiro[3.4]oktanderivatet er:

5-(5-(3-Fluor-4-(2-(pyrrolidin-1-yl)etoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;

5 5-(5-(3-Fluor-4-(2-tiomorfolinoetoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;

5-(5-(3-Fluor-4-(2-(tetrahydro-2H-pyran-4-yl)etoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;

10 5-(5-(3-Fluor-4-(3-(pyrrolidin-1-yl)propoksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;

3-Metyl-5-(8-okso-5-(4-((tetrahydro-2H-pyran-4-yl)oksy)fenyl)-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)pikolinonitril;

3-Metyl-5-(8-okso-5-(4-((tetrahydro-2H-tiopyran-4-yl)oksy)fenyl)-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)pikolinonitril;

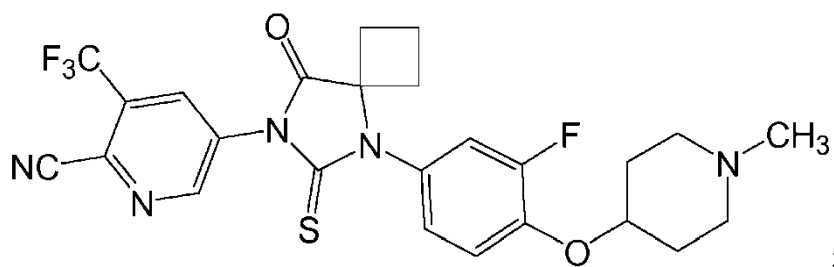
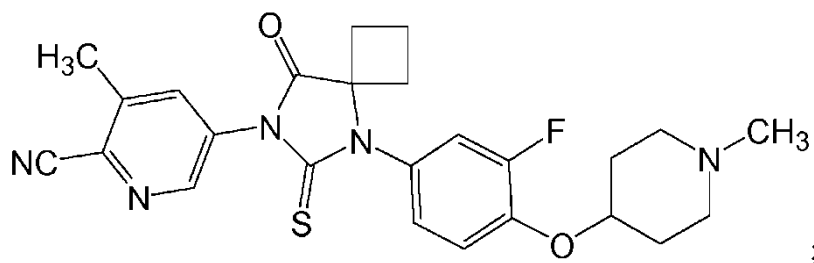
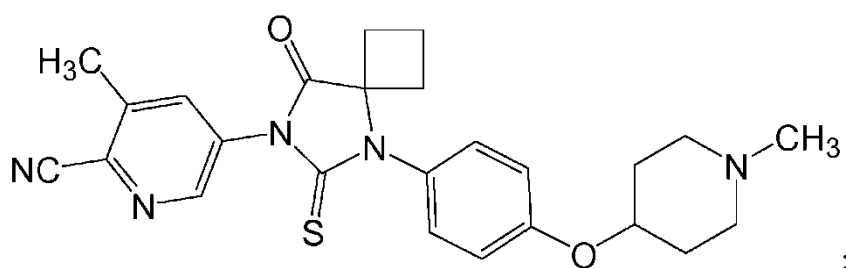
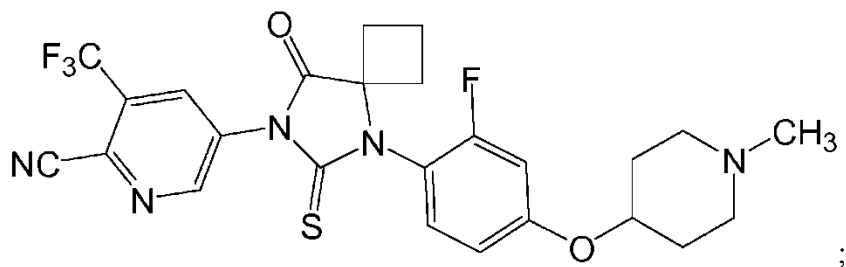
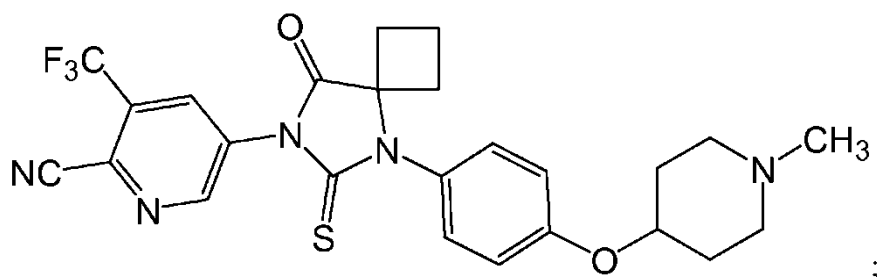
15 5-(8-Okso-5-(4-((tetrahydro-2H-pyran-4-yl)oksy)fenyl)-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;

5-(5-(4-((1,1-Dioksidotetrahydro-2H-tiopyran-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-metylpikolinonitril;

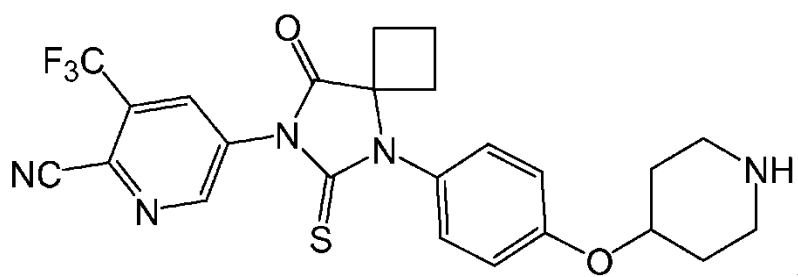
20 5-(5-(4-(2-(1,1-Dioksidotiomorfolino)etoksy)-3-fluorfenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril;

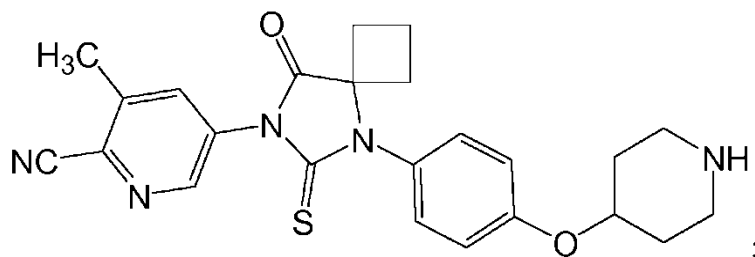
eller et farmasøytisk akseptabelt salt eller N-oksid derav.

6. Farmasøytisk sammensetning for anvendelse ifølge krav 1, hvor 8-okso-6-tiokso-5,7-diazaspiro[3.4]oktanderivatet er:



5





eller et farmasøytisk akseptabelt salt eller N-oksid deriv.

7. Farmasøytisk sammensetning for anvendelse ifølge krav 1, hvor 8-okso-6-tiokso-5,7-diazaspiro[3.4]oktanderivatet er:

- 5 (i) 5-(5-(4-((1-metylpiiperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril eller et farmasøytisk akseptabelt salt eller N-oksid deriv; eller
- (ii) 5-(5-(2-fluor-4-((1-metylpiiperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril eller et farmasøytisk
10 akseptabelt salt eller N-oksid deriv; eller
- (iii) 3-metyl-5-(5-(4-((1-metylpiiperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)pikolinonitril eller et farmasøytisk akseptabelt salt eller N-
oksid deriv; eller
- (iv) 5-(5-(3-fluor-4-((1-metylpiiperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-
15 diazaspiro[3.4]oktan-7-yl)-3-metylpiikolinonitril eller et farmasøytisk akseptabelt salt eller N-oksid deriv; eller
- (v) 5-(5-(3-fluor-4-((1-metylpiiperidin-4-yl)oksy)fenyl)-8-okso-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)-3-(trifluormetyl)pikolinonitril eller et farmasøytisk akseptabelt salt eller N-oksid deriv; eller
- 20 (vi) 3-metyl-5-(8-okso-5-(4-(piiperidin-4-yloksy)fenyl)-6-tiokso-5,7-diazaspiro[3.4]oktan-7-yl)pikolinonitril eller et farmasøytisk akseptabelt salt eller N-oksid deriv; eller
- (vii) 5-(8-okso-5-(4-(piiperidin-4-yloksy)fenyl)-6-tiokso-5,7-diazaspiro[3.4]oktan-
7-yl)-3-(trifluormetyl)pikolinonitril eller et farmasøytisk akseptabelt salt eller N-
25 oksid deriv.

- 8.** Farmasøytisk sammensetning for anvendelse ifølge et hvilket som helst av kravene 1 til 7, hvor dosen er for administrasjon én gang daglig eller i oppdelte doser i intervaller i løpet av dagen.
- 9.** Farmasøytisk sammensetning for anvendelse ifølge et hvilket som helst av kravene 1 til 8, for anvendelse ved behandling av prostatakreft eller brystkreft i en menneskelig pasient.
- 10.** Farmasøytisk sammensetning for anvendelse ifølge krav 9, hvor krefttypen er en hormonavhengig krefttype.
- 11.** Sammensetning for anvendelse ifølge et hvilket som helst av kravene 1 til 10, i enkeltdoseringsform eller i form av oppdelte doser.
- 12.** Farmasøytisk sammensetning for anvendelse ifølge et hvilket som helst av kravene 1 til 11, ytterligere omfattende et ytterligere farmasøytisk aktivt middel, for eksempel et anti-kreftmiddel, for eksempel hvor anti-kreftmidlet omfatter
- (i) gossypol, genasense, polyfenol E, Chlorofusin, all trans-retinsyre (ATRA), bryostatin, tumornekrosefaktor-relatert apoptose-induserende ligand (TRAIL), 5-aza-2'-deoksycytidin, all trans-retinsyre, doksorubicin, vinkristin, etoposid, gemcitabin, imatinib, geldanamycin, 17-N-Allylamino-17-Demetoksygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412 eller PD184352, paklitaksel eller en analog av paklitaksel, eller
- (ii) abirateron, adriamycin, daktinomycin, bleomycin, vinblastin, cisplatin, acivicin; aklarubicin; acodazolhydroklorid; akronin; adozelesin; aldesleukin; altretamin; ambomycin; amentantronacetat; aminoglutetimid; amsakrin; anastrozol; antramycin; asparaginase; asperlin; azacitidin; azetepa; azotomycin; batimastat; benzodepa; bicalutamid; bisantrenhydroklorid; bisnafiddimesylat; bizelesin; bleomycinsulfat; brekvinarnatrium; bropirimin; busulfan; kaktinomycin; kalusteron; karacemid; karbetimer; karboplatin; karmustin; karubicinhydroklorid; karzelesin; cedefingol; klorambucil; cirolemycin; kladribin; krisnatolmesylat; cyklofosfamid; cytarabin; dakarbazin; daunorubicinhydroklorid; decitabin; deksormaplatin; dezaguanin; dezaguaninmesylat; diazikvon; doksorubicin; doksorubicinhydroklorid; droloksifen; droloksifencitrat; dromostanolonpropionat; duazomycin; edatreksat; eflornitinhydroklorid; elsamitrucin; enloplatin; enpromat; epiropidin; epirubicinhydroklorid; erbulozol; esorubicinhydroklorid; estramustin;

estramustinfosfatnatrium; etanidazol; etoposid; etoposidfosfat; etoprin; fadrozol-
 hydroklorid; fazarabin; fenretinid; floksuridin; fludarabinfosfat; fluoruracil;
 fluorcitabin; foskvidon; fostriecinnatrium; gemcitabin; gemcitabinhydroklorid;
 hydroksyurea; idarubicinhydroklorid; ifosfamid; iimofosin; interleukin II (medregnet
 5 rekombinant interleukin II, eller rIL2), interferon alfa-2a; interferon alfa-2b;
 interferon alfa-n1; interferon alfa-n3; interferon beta-1a; interferon gamma-1b;
 iproplatin; irinotekanhydroklorid; lanreotidacetat; letrozol; leuprolidacetat; liarozol-
 hydroklorid; lometreksolnatrium; lomustin; losoksantronhydroklorid; masoprokol;
 maytansin; mekloreteaminhydroklorid; megestrolacetat; melengestrolacetat;
 10 melfalan; menogaril; merkaptopurin; metotreksat; metotreksatnatrium; metoprin;
 meturedapa; mitindomid; mitokarsin; mitokromin; mitogillin; mitomalcin;
 mitomycin; mitosper; mitotan; mitoksantronhydroklorid; mykofenolsyre;
 nokodazoi; nogalamycin; ormaplatin; oksisuran; pegaspargase; peliomycin;
 pentamustin; peplomycinsulfat; perfosfamid; pipobroman; piposulfan;
 15 piroksantronhydroklorid; plikamycin; plomestan; porfimernatrium; porfiromycin;
 prednimustin; prokarbazinhydroklorid; puromycin; puromycinhydroklorid;
 pyrazofurin; riboprin; rogletimid; safingol; safingolhydroklorid; semustin;
 simtrazen; sparfosatnatrium; sparsomycin; spirogermaniumhydroklorid;
 spiromustin; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin;
 20 tekogalannatrium; tegafur; teloksantronhydroklorid; temoporfin; teniposid;
 teroksiron; testolakton; tiamiprin; tioguanin; tiotepa; tiazofurin; tirapazamin;
 toremifencitrat; trestolonacetat; triciribinfosfat; trimetreksat;
 trimetreksatglukuronat; triptorelin; tubulozolhydroklorid; uracilsennep; uredepa;
 vaporetid; verteporfin; vinblastinsulfat; vinkristinsulfat; vindesin; vindesinsulfat;
 25 vinepidinsulfat; vinglycinatsulfat; vinleurosinsulfat; vinorelbintartrat; vinrosidin-
 sulfat; vinzolidinsulfat; vorozol; zeniplatin; zinostatin; eller zorubicinhydroklorid,
 eller

(iii) Dolastatin 10, Mivobulinisetionat, Vinkristin, NSC-639829, Diskodermolid,
 ABT-751, Altorhyrtiner (så som Altorhyrtin A og Altorhyrtin C), Spongistatiner (så
 30 som Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5,
 Spongistatin 6, Spongistatin 7, Spongistatin 8 og Spongistatin 9), Cemadotin-
 hydroklorid, Epotiloner (så som Epotilon A, Epotilon B, Epotilon C, Epotilon D,
 Epotilon E, Epotilon F, Epotilon B-N-oxid, Epotilon A-N-oxid, 16-aza-Epotilon B,
 21-aminoepotilon B, 21-hydroksyepotilon D, 26-fluorepotilon, Auristatin PE,
 35 Soblidotin, Vinkristinsulfat, Cryptofycin 52, Vitilevuamid, Tubulysin A, Canadensol,
 Centaureidin, Onkocidin A1 Fijianolid B, Laulimalid, Narkosin, Naskapin,
 Hemiasterlin, Vanadocenacetylacetonat, Indanocin-Eleuterobiner (så som

Desmetylleuterobin, Desaetylleuterobin, Isoeleuterobin A og Z-Eleuterobin), Caribaeoside, Caribaeolin, Halikondrin B, Diazonamid A, Taccalonolid A, Diozostatin, (-)-Fenylahistin, Myoseverin B eller Resverastatinfosfatnatrium.

13. Farmasøytisk sammensetning for anvendelse ifølge krav 12, hvor det
5 ytterligere farmasøytisk aktive middel er et antibiotikum, et antiøstrogen, et
antiandrogen, en gonadotropin-frigivende hormonanalog, et trombolytisk middel, et
anti-emetisk middel, et middel som er nyttig ved behandling av anemi, et middel
som er nyttig ved behandling av neutropeni, en kortikosteroid, et analgesikum, en
kinasehemmer, en HSP90-hemmer, en histondeacetylase (HDAC)-hemmer eller et
10 ikke-steroidalt anti-inflammatorisk legemiddel.

14. Farmasøytisk sammensetning for anvendelse ifølge et hvilket som helst av
kravene 1 til 13, formulert i oral doseringsform.

15. Farmasøytisk sammensetning for anvendelse ifølge et hvilket som helst av
kravene 1 til 14, formulert i oral doseringsform og inneholdende 8-okso-6-tiokso-
15 5,7-diazaspiro[3.4]oktanderivatet i en mengde fra 1 mg til 500 mg.