

1,5-NAPHTHYRIDINE DERIVATIVES AND
MELK INHIBITORS CONTAINING THE SAME

TECHNICAL FIELD

5 The present invention relates to a 1,5-naphthyridine derivative having an inhibitory activity against MELK, a method for the preparation thereof, and a pharmaceutical composition containing the compound as an active ingredient.

BACKGROUND ART

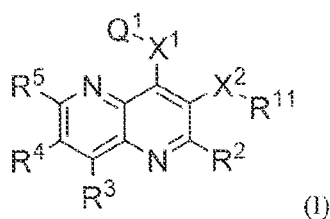
MELK, maternal embryonic leucine zipper kinase, was previously identified as a
10 new member of the snf1/AMPK serine-threonine kinase family that is involved in mammalian embryonic development (Heyer BS et al., Dev Dyn. 1999 Aug 215(4):344-51). The gene was shown to play an important role in stem cell renewal (Nakano I et al., J Cell Biol. 2005 Aug 1, 170(3):413-27), cell-cycle progression (Blot J et al., Dev Biol. 2002 Jan 15, 241(2):327-38; Seong HA et al., Biochem J. 2002 Feb 1, 361(Pt 3):597-604) and pre-
15 mRNA splicing (Vulsteke V et al., J Biol Chem. 2004 Mar 5, 279(10):8642-7. Epub 2003 Dec 29). In addition, through gene expression profile analysis using a genome-wide cDNA microarray containing 23,040 genes, MELK was recently shown to be up-regulated in breast cancer (Lin ML et al., Breast Cancer Res. 2007; 9 (1):R17, WO2006/016525, WO2008/023841). In fact, MELK is up-regulated in several cancer cells, for example
20 lung, bladder, lymphoma and cervical cancer cells (See WO2004/031413, WO2007/013665, and WO2006/085684, the disclosures of which are incorporated by reference herein). Northern blot analysis on multiple human tissues and cancer cell lines demonstrated that MELK was over-expressed at a significantly high level in a great majority of breast cancers and cell lines, but was not expressed in normal vital organs (heart, liver, lung and kidney)
25 (WO2006/016525). Furthermore, suppression of MELK expression by siRNA was shown to significantly inhibit growth of human breast cancer cells. Accordingly, MELK is considered to be a suitable target for cancer therapy in the treatment of a wide array of cancer types.

SUMMARY OF INVENTION

The present inventors have endeavored to develop an effective inhibitor of MELK and have found that a compound can selectively inhibit the activity of MELK.

The present invention relates to the following (1) to (24).

- 5 (1) A compound represented by formula (I) or a pharmaceutically acceptable salt thereof:



wherein,

- 10 X^1 is selected from the group consisting of a direct bond, $-NR^{12}$ -, $-O$ -, and $-S$ -;
 R^{12} is selected from the group consisting of a hydrogen atom, C_1 - C_6 alkyl and C_3 - C_{10} cycloalkyl;
 Q^1 is selected from the group consisting of C_3 - C_{10} cycloalkyl, C_6 - C_{10} aryl, 5- to 10-membered heteroaryl, 3- to 10-membered non-aromatic heterocyclyl, (C_3 - C_{10} cycloalkyl)- C_1 - C_6 alkyl, (C_6 - C_{10} aryl)- C_1 - C_6 alkyl, (5- to 10-membered heteroaryl)- C_1 - C_6 alkyl, and (3- to 10-membered non-aromatic heterocyclyl)- C_1 - C_6 alkyl; wherein Q^1 is optionally substituted with one or more substituents independently selected from A^1 ;
 X^2 is selected from the group consisting of $-CO$ -, $-S$ -, $-SO$ -, and $-SO_2$ -;
 R^{11} is selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, C_6 - C_{10} aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl;
 20 wherein R^{11} is optionally substituted with one or more substituents independently selected from A^2 ;
 R^5 is selected from the group consisting of a halogen atom, C_3 - C_{10} cycloalkyl, C_6 - C_{10} aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl;

wherein the cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A³;

R², R³, and R⁴ are independently selected from the group consisting of a hydrogen atom, a halogen atom, and C₁-C₆ alkyl;

5 A¹ and A³ are independently selected from the group consisting of a halogen atom, cyano, -COOR¹³, -CONR¹⁴R¹⁵, formyl, (C₁-C₆ alkyl)carbonyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, nitro, -NR¹⁶R¹⁷, -OR¹⁸, -S(O)_nR¹⁹, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein the alkyl/carbonyl, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are
10 optionally substituted with one or more substituents independently selected from A⁴;

A² is independently selected from the group consisting of a halogen atom, cyano, C₃-C₁₀ cycloalkyl, carboxy, formyloxy, (C₁-C₆ alkyl)carbonyloxy, hydroxy, C₁-C₆ alkoxy, amino, C₁-C₆ alkylamino, and di(C₁-C₆ alkyl)amino;

R¹³, R¹⁴, and R¹⁵ are independently selected from the group consisting of a
15 hydrogen atom, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A⁴; or R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form 3- to 10-membered
20 nitrogen-containing heterocyclyl, which is optionally substituted with one or more substituents independently selected from A⁴;

R¹⁶ and R¹⁸ are independently selected from the group consisting of a hydrogen atom, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, 3- to 10-membered non-aromatic heterocyclyl, and -COR²⁰; wherein
25 the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A⁴; R¹⁷ is selected from the group consisting of a hydrogen atom, and C₁-C₆ alkyl that is optionally substituted with one or more substituents independently selected from A⁴; or R¹⁶ and R¹⁷ together with

the nitrogen atom to which they are attached form 3- to 10-membered nitrogen-containing heterocyclyl, which is optionally substituted with one or more substituents independently selected from A⁴;

R¹⁹ is selected from the group consisting of C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, and 5- to 10-membered heteroaryl; wherein the alkyl, cycloalkyl, aryl, and heteroaryl are optionally substituted with one or more substituents independently selected from A⁴;

R²⁰ is selected from the group consisting of a hydrogen atom, -NR¹⁴R¹⁵, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A⁴;

n is an integer independently selected from 0 to 2;

A⁴ is independently selected from consisting of a halogen atom, cyano, -COOR²¹, -CONR²²R²³, formyl, (C₁-C₆ alkyl)carbonyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, nitro, -NR²⁴R²⁵, -OR²⁶, -S(O)_nR²⁷, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein the alkylcarbonyl, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A⁵;

R²¹, R²², and R²³ are independently selected from the group consisting of a hydrogen atom, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A⁵; or R²² and R²³ together with the nitrogen atom to which they are attached form 3- to 10-membered nitrogen-containing heterocyclyl, which is optionally substituted with one or more substituents independently selected from A⁵;

R²⁴ and R²⁶ are independently selected from the group consisting of a hydrogen atom, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-

membered heteroaryl, 3- to 10-membered non-aromatic heterocyclyl, and $-\text{COR}^{28}$; wherein the alkyl, alkenyl, alkynyl cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A^5 ; R^{25} is selected from the group consisting of a hydrogen atom, and C_1 - C_6 alkyl that is optionally substituted
 5 with one or more substituents independently selected from A^5 ; or R^{24} and R^{25} together with the nitrogen atom to which they are attached form 3- to 10-membered nitrogen-containing heterocyclyl, which is optionally substituted with one or more substituents independently selected from A^5 ;

R^{27} is selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, C_6 - C_{10}
 10 aryl, and 5- to 10-membered heteroaryl; wherein the alkyl, cycloalkyl, aryl, and heteroaryl are optionally substituted with one or more substituents independently selected from A^5 ;

R^{28} is independently selected from the group consisting of a hydrogen atom, -
 $\text{NR}^{22}\text{R}^{23}$, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl C_3 - C_{10} cycloalkyl, C_6 - C_{10} aryl, 5- to 10-
 15 membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A^5 ;

A^5 is independently selected from consisting of a halogen atom, cyano, $-\text{COOR}^{31}$, -
 $\text{CONR}^{32}\text{R}^{33}$, formyl, $(C_1$ - C_6 alkyl)carbonyl, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, nitro,
 20 $-\text{NR}^{34}\text{R}^{35}$, $-\text{OR}^{36}$, $-\text{S}(\text{O})_n\text{R}^{37}$, C_3 - C_{10} cycloalkyl, C_6 - C_{10} aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein the alkylcarbonyl, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A^6 ;

R^{31} , R^{32} , and R^{33} are independently selected from the group consisting of a
 hydrogen atom, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_{10} cycloalkyl, C_6 - C_{10} aryl,
 25 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A^6 ; or R^{32} and R^{33} together with the nitrogen atom to which they are attached form 3- to 10-membered

nitrogen-containing heterocyclyl, which is optionally substituted with one or more substituents independently selected from A⁶;

R³⁴ and R³⁶ are independently selected from the group consisting of a hydrogen atom, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, 3- to 10-membered non-aromatic heterocyclyl, and -COR³⁸; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A⁶; R³⁵ is selected from the group consisting of a hydrogen atom, and C₁-C₆ alkyl that is optionally substituted with one or more substituents independently selected from A⁶; or R³⁴ and R³⁵ together with the nitrogen atom to which they are attached form 3- to 10-membered nitrogen-containing heterocyclyl, which is optionally substituted with one or more substituents independently selected from A⁶;

R³⁷ is selected from the group consisting of C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, and 5- to 10-membered heteroaryl; wherein the alkyl, cycloalkyl, aryl, and heteroaryl are optionally substituted with one or more substituents independently selected from A⁶;

R³⁸ is independently selected from the group consisting of a hydrogen atom, -NR³²R³³, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A⁶;

A⁶ is independently selected from consisting of a halogen atom, cyano, carboxy, -COOR⁴¹, -CONR⁴²R⁴³, formyl, (C₁-C₆ alkyl)carbonyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, nitro, -NR⁴⁴R⁴⁵, -OR⁴⁶, S(O)_nR⁴⁷, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein the alkylcarbonyl, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from the group consisting of a halogen atom, hydroxy, C₁-C₆ alkoxy, amino, C₁-C₆ alkylamino, and di(C₁-C₆ alkyl)amino;

R^{41} , R^{42} , and R^{43} are independently selected from the group consisting of a hydrogen atom, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_{10} cycloalkyl, C_6 - C_{10} aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from the group consisting of a halogen atom, hydroxy, C_1 - C_6 alkoxy, amino, C_1 - C_6 alkylamino, and di(C_1 - C_6 alkyl)amino;

R^{44} and R^{46} are independently selected from the group consisting of a hydrogen atom, C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, C_6 - C_{10} aryl, 5- to 10-membered heteroaryl, 3- to 10-membered non-aromatic heterocyclyl, and $-COR^{48}$;

R^{45} is selected from the group consisting of a hydrogen atom, and C_1 - C_6 alkyl;

R^{47} is selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, C_6 - C_{10} aryl, and 5- to 10-membered heteroaryl; and

R^{48} is independently selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, C_6 - C_{10} aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl.

(2) The compound or a pharmaceutically acceptable salt thereof according to above-mentioned (1), wherein Q^1 is selected from the group consisting of C_5 - C_7 cycloalkyl, phenyl, pyridyl, pyrazolyl, pyrimidinyl, and piperidyl; wherein Q^1 is optionally substituted with one or more substituents independently selected from A^1 .

(3) The compound or a pharmaceutically acceptable salt thereof according to above-mentioned (1) or (2), wherein X^2 is selected from the group consisting of $-CO-$ and $-SO_2-$; and R^{11} is selected from the group consisting of C_1 - C_6 alkyl and C_3 - C_7 cycloalkyl, which are optionally substituted with one or more substituents independently selected from the group consisting of hydroxy and a halogen atom.

(4) The compound or a pharmaceutically acceptable salt thereof according to any one of above-mentioned (1) to (3), wherein R^5 is phenyl substituted with one to three substituents independently selected from the group consisting of hydroxy, a halogen atom,

C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein the alkyl and alkoxy are optionally substituted with one or more halogen atoms.

(5) The compound or a pharmaceutically acceptable salt thereof according to any one of above-mentioned (1) to (4), wherein R² is a hydrogen atom.

5 (6) The compound or a pharmaceutically acceptable salt thereof according to any one of above-mentioned (1) to (5), wherein R³ is a hydrogen atom.

(7) The compound or a pharmaceutically acceptable salt thereof according to any one of above-mentioned (1) to (6), wherein R⁴ is a hydrogen atom.

(8) The compound or a pharmaceutically acceptable salt thereof according to any
10 one of above-mentioned (1) to (7), wherein X¹ is -NH-.

(9) The compound or a pharmaceutically acceptable salt thereof according to any one of above-mentioned (1) to (8), wherein the optional substituent of Q¹ is selected from the group consisting of hydroxy, amino, C₁-C₆ alkoxy, C₁-C₆ alkylamino, di(C₁-C₆ alkyl)amino, amino-C₁-C₆ alkyl, (C₁-C₆ alkylamino)-C₁-C₆ alkyl, di(C₁-C₆ alkyl)amino-C₁-
15 C₆ alkyl, amino-C₁-C₆ alkoxy, (C₁-C₆ alkylamino)-C₁-C₆ alkoxy, di(C₁-C₆ alkyl)amino-C₁-C₆ alkoxy, hydroxy-C₁-C₆ alkyl, (C₁-C₆ alkoxy)-C₁-C₆ alkyl, carboxy-C₁-C₆ alkyl, [(C₁-C₆ alkoxy)carbonyl]-C₁-C₆ alkyl, carbamoyl-C₁-C₆ alkyl, [N-(C₁-C₆ alkyl)carbamoyl]-C₁-C₆ alkyl, [N,N-di(C₁-C₆ alkyl)carbamoyl]-C₁-C₆ alkyl, (C₁-C₆ alkyl)carbonylamino, N-(C₁-C₆ alkyl)carbonyl-N-(C₁-C₆ alkyl)amino, pyrrolidinyl, piperidyl, and piperazinyl;

20 wherein the alkyl moiety of the group defined as the optional substituent of Q¹ is optionally substituted with a substituent selected from the group consisting of amino, C₁-C₆ alkylamino, di(C₁-C₆ alkyl)amino, hydroxy, C₁-C₆ alkoxy, pyrrolidinyl, piperidyl, and piperazinyl; and

wherein the pyrrolidinyl, piperidyl, and piperazinyl defined as the optional
25 substituent of Q¹ are optionally substituted with a substituent selected from the group consisting of C₁-C₆ alkyl, amino, C₁-C₆ alkylamino, di(C₁-C₆ alkyl)amino, hydroxy, C₁-C₆ alkoxy, pyrrolidinyl, piperidyl, and piperazinyl.

(10) The compound or a pharmaceutically acceptable salt thereof according to

above-mentioned (9), wherein the optional substituent of Q¹ is selected from the group consisting of hydroxy, amino, di(C₁-C₆ alkyl)amino, C₁-C₆ alkyl, di(C₁-C₆ alkyl)amino-C₁-C₆ alkyl, di(C₁-C₆ alkyl)amino-C₁-C₆ alkoxy, di(C₁-C₆ alkyl)amino, [(amino-C₁-C₆ alkyl)carbonyl]amino, N-(C₁-C₆ alkyl)piperidyl, di(C₁-C₆ alkyl)amino-pyrrolidin-1-yl, amino-pyrrolidin-1-yl, (pyrrolidin-1-yl)-C₁-C₆ alkyl, (C₁-C₆ alkyl)amino-piperidin-1-yl, amino-piperidin-1-yl, hydroxy-C₁-C₆ alkyl, [di(C₁-C₆ alkyl)amino-C₁-C₆ alkyl]amino, [4-(C₁-C₆ alkyl)-piperazin-1-yl]-C₁-C₆ alkyl, (piperazin-1-yl)-C₁-C₆ alkyl, pyrrolidinylcarbonyl-amino, (hydroxy-pyrrolidin-1-yl)-C₁-C₆ alkyl, morpholinyl-C₁-C₆ alkyl, [N-(hydroxy-C₁-C₆ alkyl)-N-(C₁-C₆ alkyl)amino]-C₁-C₆ alkyl, and (CD₃)₂N-C₁-C₆ alkyl.

(11) The compound or a pharmaceutically acceptable salt thereof according to above-mentioned (1), which is selected from the group consisting of the following compounds:

1-(6-chloro-4-(4-((dimethylamino)methyl) cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;

1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((4-(dimethylamino)cyclohexyl)amino)-1,5-naphthyridin-3-yl)ethanone;

1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-((4-(dimethylamino)cyclohexyl)amino)-1,5-naphthyridin-3-yl)ethanone;

cyclopropyl(6-(3,5-dichloro-4-hydroxyphenyl)-4-(4-((dimethylamino)methyl)-cyclohexylamino)-1,5-naphthyridin-3-yl)methanone;

(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(4-((dimethylamino)methyl)-cyclohexylamino)-1,5-naphthyridin-3-yl)(cyclopropyl)methanone;

1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((4-(dimethylamino)methyl)cyclohexyl)-amino)-1,5-naphthyridin-3-yl)ethanone;

1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-((4-((dimethylamino)methyl)cyclohexyl)-amino)-1,5-naphthyridin-3-yl)ethanone;

1-(6-(3-chloro-4-hydroxy-5-methoxyphenyl)-4-((4-((dimethylamino)methyl)-

- cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;
- 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((4-(2-(dimethylamino)ethyl)cyclohexyl)-amino)-1,5-naphthyridin-3-yl)ethanone;
- 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(4-(2-(dimethylamino)ethyl)-cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;
- 5 1-(4-(4-((dimethylamino)methyl)cyclohexylamino)-6-(4-hydroxy-3-(trifluoromethoxy)-phenyl)-1,5-naphthyridin-3-yl)ethanone;
- 2,6-dichloro-4-(8-((4-((dimethylamino)methyl)cyclohexylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)phenol;
- 10 2-chloro-4-(8-((4-((dimethylamino)methyl)cyclohexylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-fluorophenol;
- 2-chloro-4-(8-((4-((dimethylamino)methyl)cyclohexylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-methoxyphenol;
- 2,6-dichloro-4-(8-((4-(dimethylamino)cyclohexylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)phenol;
- 15 2,6-dichloro-4-(8-((4-((dimethylamino)methyl)phenylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)phenol;
- 2-chloro-4-(8-((4-((dimethylamino)methyl)phenylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-fluorophenol;
- 20 2-chloro-4-(8-((4-((dimethylamino)methyl)phenylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-methoxyphenol;
- 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((3-(2-(pyrrolidin-1-yl)ethyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone;
- 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(3-(2-(pyrrolidin-1-yl)ethyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone;
- 25 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((6-(2-(dimethylamino)ethoxy)pyridin-3-yl)-amino)-1,5-naphthyridin-3-yl)ethanone;
- 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-((6-(2-

- (dimethylamino)ethoxy)pyridin-3-yl)amino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3-chloro-4-hydroxy-5-methoxyphenyl)-4-((6-(2-(dimethylamino)ethoxy)pyridin-3-yl)amino)-1,5-naphthyridin-3-yl)ethanone;
 2,6-dichloro-4-(8-((6-(2-(dimethylamino)ethoxy)pyridin-3-yl)amino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)phenol;
 2-chloro-4-(8-((6-(2-(dimethylamino)ethoxy)pyridin-3-yl)amino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-fluorophenol;
 2-chloro-4-(8-((6-(2-(dimethylamino)ethoxy)pyridin-3-yl)amino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-methoxyphenol;
 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((1-methylpiperidin-4-yl)methylamino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((4-((dimethylamino)d6methyl)cyclohexyl)-amino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((4-(2-(dimethylamino)ethyl)phenyl)amino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-((4-(2-(dimethylamino)ethyl)phenyl)amino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3-chloro-4-hydroxy-5-methoxyphenyl)-4-((4-(2-(dimethylamino)ethyl)phenyl)-amino)-1,5-naphthyridin-3-yl)ethanone;
 2-chloro-4-(8-((4-(dimethylamino)cyclohexyl)amino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-fluorophenol;
 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)-amino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(4-((4-methylpiperazin-1-yl)methyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(4-((4-methylpiperazin-1-yl)methyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(4-(2-(pyrrolidin-1-yl)ethyl)piperidin-1-yl)-

- 1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(4-(2-(pyrrolidin-1-yl)ethyl)piperidin-1-yl)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(6-(2-(dimethylamino)ethylamino)pyridin-3-ylamino)-1,5-naphthyridin-3-yl)ethanone;
 5 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(6-(2-(dimethylamino)ethylamino)-pyridin-3-ylamino)-1,5-naphthyridin-3-yl)ethanone;
 (S)-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)(cyclopropyl)methanone;
 10 1-(4-((2-(3-aminopyrrolidin-1-yl)pyrimidin-5-yl)amino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone;
 1-(4-(4-((dimethylamino)methyl)cyclohexylamino)-6-(1H-pyrazol-4-yl)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(4-(hydroxymethyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;
 15 1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-{4-[(dimethylamino)methyl]-cyclohexylamino}-1,5-naphthyridin-3-yl]-2-hydroxyethanone;
 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(1-methylpiperidin-4-ylamino)-1,5-naphthyridin-3-yl)ethanone;
 20 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(1-methylpiperidin-4-ylamino)-1,5-naphthyridin-3-yl)ethanone;
 1-[6-[3,5-dichloro-4-hydroxyphenyl]-4-[4-(morpholinomethyl)cyclohexylamino]-1,5-naphthyridin-3-yl]ethanone;
 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(4-(((2-hydroxyethyl)(methyl)amino)methyl)-cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;
 25 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(4-(((2-hydroxyethyl)(methyl)amino)methyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3,5-difluoro-4-hydroxyphenyl)-4-(4-

- ((dimethylamino)methyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((6-(3-(dimethylamino)pyrrolidin-1-yl)pyridin-3-yl)amino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-((6-(3-(dimethylamino)pyrrolidin-1-yl)-pyridin-3-yl)amino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(6-(3-(methylamino)pyrrolidin-1-yl)pyridin-3-yl)amino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(6-(3-(methylamino)pyrrolidin-1-yl)-pyridin-3-yl)amino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(1H-benzo[d]imidazol-5-yl)-4-(4-((dimethylamino)methyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;
 1-(4-((4-((dimethylamino)methyl)cyclohexylamino)-6-(pyridin-4-yl)-1,5-naphthyridin-3-yl)ethanone;
 5-(7-acetyl-8-(4-((dimethylamino)methyl)cyclohexylamino)-1,5-naphthyridin-2-yl)-pyrimidine-2-carbonitrile;
 1-(6-(3,5-dimethyl-1H-pyrazol-4-yl)-4-(4-((dimethylamino)methyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;
 1-(4-(4-((dimethylamino)methyl)cyclohexylamino)-6-(4-hydroxy-3,5-dimethylphenyl)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(4-(pyrrolidin-1-ylmethyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(4-(pyrrolidin-1-ylmethyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(4-(pyrrolidin-1-ylmethyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(4-((4-methylpiperazin-1-yl)methyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;
 1-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-yl)amino)-6-(3,5-dichloro-4-

hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone;

1-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3-chloro-5-fluoro-4-hydroxy-phenyl)-1,5-naphthyridin-3-yl)ethanone;

1-(4-(4-aminocyclohexylamino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone;

1-[4-(4-aminocyclohexylamino)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl]ethanone;

1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(4-((4-methylpiperazin-1-yl)methyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;

N-(4-(3-acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino)-cyclohexyl)-2-amino-3-methylbutanamide;

1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(4-(piperazin-1-ylmethyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;

(S)-1-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone;

(S)-1-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3-chloro-5-fluoro-4-hydroxy-phenyl)-1,5-naphthyridin-3-yl)ethanone;

N-(4-((3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl)amino)cyclohexyl)-2-aminopropanamide;

N-(4-(3-acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino)-cyclohexyl)-2-aminopropanamide;

(S)-N-((1R,4S)-4-(3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl-amino)cyclohexyl)pyrrolidine-2-carboxamide;

(S)-N-((1R,4S)-4-(3-acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino)cyclohexyl)pyrrolidine-2-carboxamide;

1-(6-(3-hydroxypyrrolidin-1-yl)-4-(4-((3-hydroxypyrrolidin-1-yl)methyl)cyclohexyl-amino)-1,5-naphthyridin-3-yl)ethanone;

1-(6-(pyrrolidin-1-yl)-4-(4-(pyrrolidin-1-ylmethyl)cyclohexylamino)-1,5-

naphthyridin-3-yl)ethanone;

N-(4-(3-acetyl-6-(3,5-dichloro-4-hydroxy phenyl)-1,5-naphthyridin-4-ylamino)-cyclohexyl)-2-amino-3-methylbutanamide;

[6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-[4-(dimethylamino)cyclohexylamino]-1,5-naphthyridin-3-yl](cyclopropyl)methanone;

cyclopropyl[6-(3,5-dichloro-4-hydroxyphenyl)-4-[4-(dimethylamino)cyclohexylamino]-1,5-naphthyridin-3-yl]methanone;

1-(4-{4-[(dimethylamino)methyl]cyclohexylamino}-6-(1H-pyrrolo[2,3-b]pyridin-5-yl)-1,5-naphthyridin-3-yl)ethanone;

(S)-{4-[6-(3-aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}(cyclopropyl)methanone;

1-(4-{4-[(dimethylamino)methyl]cyclohexyl amino}-6-(4-methoxyphenyl)-1,5-naphthyridin-3-yl)ethanone;

1-[6-(3,5-dichloro-4-methoxyphenyl)-4-{4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl]ethanone;

1-(4-{4-[(dimethylamino)methyl]cyclohexylamino}-6-(6-hydroxypyridin-3-yl)-1,5-naphthyridin-3-yl)ethanone;

5-(7-acetyl-8-{4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-2-yl)picolinonitrile;

1-(4-{4-[(dimethylamino)methyl]cyclohexylamino}-6-(4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone;

1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-{[4-(dimethylamino)cyclohexyl]methylamino}-1,5-naphthyridin-3-yl)ethanone;

1-[6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-{[4-(dimethylamino)cyclohexyl]methylamino}-1,5-naphthyridin-3-yl]ethanone;

1-[6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(4-hydroxycyclohexylamino)-1,5-naphthyridin-3-yl]ethanone;

1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-(4-hydroxycyclohexylamino)-1,5-

- naphthyridin-3-yl]ethanone;
- 1-[6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-{*cis*-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl]ethanone;
- 1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-{*cis*-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl]ethanone;
- 5 [(R)-1-{4-[6-(3-aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}ethanone;
- (R)-1-{4-[6-(3-aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}ethanone;
- (R)-1-{4-[6-(3-aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}ethanone;
- 10 (R)-(4-{[6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino}-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl) (cyclopropyl)methanone;
- (R)-(4-{[6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino}-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl) (cyclopropyl)methanone;
- 1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-{[*trans*-4-(dimethylamino)cyclohexylamino]-1,5-naphthyridin-3-yl}-2-hydroxyethanone dihydrochloride;
- 15 1-[6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-({*trans*-4-[(dimethylamino)methyl]cyclohexylamino)-1,5-naphthyridin-3-yl}]-2-hydroxyethanone dihydrochloride;
- 1-[6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-({*trans*-4-[(dimethylamino)methyl]cyclohexylamino)-1,5-naphthyridin-3-yl}]propan-1-one dihydrochloride;
- 20 1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-({*trans*-4-[(dimethylamino)methyl]cyclohexylamino)-1,5-naphthyridin-3-yl}]propan-1-one dihydrochloride;
- (S)-1-(4-{[6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino}-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)propan-1-one trihydrochloride;
- 25 (S)-1-(4-{[6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino}-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)propan-1-one trihydrochloride;
- 1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-({4-[(R)-3-fluoropyrrolidin-1-yl]methyl]cyclohexylamino)-1,5-naphthyridin-3-yl]ethanone dihydrochloride;

(S)-(4-((6-(3-aminopiperidin-1-yl)pyridin-3-yl)amino)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)(cyclobutyl)methanone dihydrochloride;

(6-(3,5-dichloro-4-hydroxyphenyl)-4-((4-((dimethylamino)methyl)cyclohexyl)amino)-1,5-naphthyridin-3-yl)(cyclobutyl)methanone dihydrochloride;

5 (6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-((4-((dimethylamino)methyl)cyclohexyl)amino)-1,5-naphthyridin-3-yl)(cyclobutyl)methanone dihydrochloride;

(S)-(4-{{6-(3-aminopiperidin-1-yl)pyridin-3-yl}amino}-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)(cyclobutyl)methanone;

10 (R)-1-(4-((6-(3-aminopiperidin-1-yl)pyridin-3-yl)amino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)propan-1-one trihydrochloride;

(R)-1-(4-{{6-(3-aminopiperidin-1-yl)pyridin-3-yl}amino}-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)-2-methylpropan-1-one trihydrochloride;

15 1-[6-(3,5-dichloro-5-4-hydroxyphenyl)-4-({trans-4-[(dimethylamino)methyl]cyclohexyl}amino)-1,5-naphthyridin-3-yl]-2-methylpropan-1-one dihydrochloride;

1-[6-chloro-4-({trans-4-[(dimethylamino)methyl]cyclohexyl}amino)-1,5-naphthyridin-3-yl]-2-methylpropan-1-one dihydrochloride;

and pharmaceutically acceptable salts thereof.

20 (12) The compound or a pharmaceutically acceptable salt thereof according to above-mentioned (1), which is selected from the group consisting of the following compounds:

1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(trans-4-(dimethylamino)cyclohexyl)amino)-1,5-naphthyridin-3-yl)ethanone;

25 cyclopropyl (6-(3,5-dichloro-4-hydroxyphenyl)-4-(trans-4-((dimethylamino)methyl)-cyclohexylamino)-1,5-naphthyridin-3-yl) methanone;

(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(trans-4-((dimethylamino)methyl)-cyclohexylamino)-1,5-naphthyridin-3-yl)(cyclopropyl) methanone;

- 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((*trans*-4-
 ((dimethylamino)methyl)cyclohexyl)- amino)-1,5-naphthyridin-3-yl) ethanone;
- 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-((*trans*-4-((dimethylamino)methyl)-
 cyclohexyl)amino)-1,5-naphthyridin-3-yl) ethanone;
- 5 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((*trans*-4-(2-
 (dimethylamino)ethyl)cyclohexyl)- amino)-1,5-naphthyridin-3-yl) ethanone;
- (S)-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3,5-dichloro-4-
 hydroxyphenyl)-1,5-naphthyridin-3-yl)(cyclopropyl)methanone;
- 1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-{*trans*-4-[(dimethylamino)methyl]cyclo-
 10 hexylamino}-1,5-naphthyridin-3-yl]-2-hydroxyethanone;
- 1-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3,5-dichloro-4-
 hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone;
- 1-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3-chloro-5-fluoro-4-
 hydroxy- phenyl)-1,5-naphthyridin-3-yl)ethanone;
- 15 (S)-1-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3,5-dichloro-4-hydroxy-
 phenyl)-1,5-naphthyridin-3-yl)ethanone;
- (S)-1-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3-chloro-5-fluoro-4-
 hydroxy-phenyl)-1,5-naphthyridin-3-yl)ethanone;
- (S)-{4-[6-(3-aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3-chloro-5-fluoro-4-
 20 hydroxy- phenyl)-1,5-naphthyridin-3-yl} (cyclopropyl) methanone;
- (R)-1-{4-[6-(3-aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3,5-dichloro-4-hydroxy-
 phenyl)-1,5-naphthyridin-3-yl} ethanone;
- (R)-1-{4-[6-(3-aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3-chloro-5-fluoro-4-
 hydroxyphenyl)-1,5-naphthyridin-3-yl} ethanone;
- 25 and pharmaceutically acceptable salts thereof.

(13) A pharmaceutical composition comprising as an active ingredient a compound
 or a pharmaceutically acceptable salt thereof according to any one of above-mentioned (1)
 to (12).

(14) An MELK inhibitor comprising as an active ingredient a compound or a pharmaceutically acceptable salt thereof according to any one of above-mentioned (1) to (12).

(15) An MELK-expression modulating agent comprising as an active ingredient a compound or a pharmaceutically acceptable salt thereof according to any one of above-mentioned (1) to (12).

(16) An antitumor agent comprising as an active ingredient a compound or a pharmaceutically acceptable salt thereof according to any one of above-mentioned (1) to (12).

(17) A therapeutic and/or preventive agent for a disease that involves overexpression of MELK, comprising as an active ingredient a compound or a pharmaceutically acceptable salt thereof according to any one of above-mentioned (1) to (12).

(18) The therapeutic and/or preventive agent according to above-mentioned (17), wherein the disease is cancer.

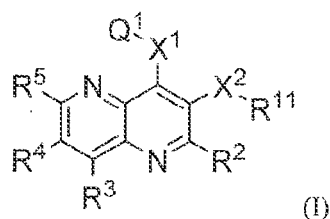
(19) The therapeutic and/or preventive agent according to above-mentioned (18), wherein the cancer is selected from the group consisting of breast cancer, lung cancer, bladder cancer, lymphoma, and uterine cancer.

(20) A method for treating and/or preventing a disease that involves overexpression of MELK, which comprises administering an effective amount of a compound or a pharmaceutically acceptable salt thereof according to any one of above-mentioned (1) to (12) to a subject in need thereof.

(21) A compound or a pharmaceutically acceptable salt thereof according to any one of above-mentioned (1) to (12) for use in a treatment and/or prevention of a disease that involves overexpression of MELK.

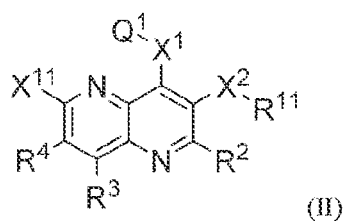
(22) Use of a compound or a pharmaceutically acceptable salt thereof according to any one of above-mentioned (1) to (12) in the manufacture of a therapeutic and/or preventive agent for a disease that involves overexpression of MELK.

(23) A process for preparing a compound of formula (I):

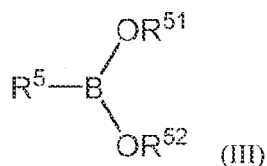


or a pharmaceutically acceptable salt thereof according to any one of above-mentioned (1) to (12), wherein R⁵ is phenyl optionally substituted with one or more substituents independently selected from selected from A³; and Q¹, X¹, X², R¹¹, R², R³, R⁴, and A³ are the groups as defined in any one of above-mentioned (1) to (10); which comprises:

reacting a compound represented by formula (II):

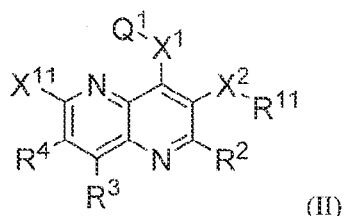


wherein Q¹, X¹, X², R¹¹, R², R³, and R⁴ are the groups as defined above, with the proviso that the groups may have one or more protecting groups, and X¹¹ is a halogen atom such as a chlorine atom; with a compound represented by formula (III):



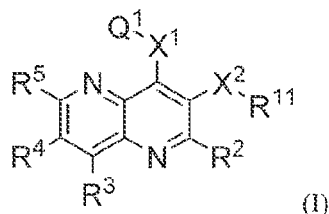
wherein R⁵ is as defined above with the proviso that the group of R⁵ may have one or more protecting groups, and R⁵¹ and R⁵² are independently selected from the group consisting of C₁-C₆ alkyl, or R⁵¹ and R⁵² together with the boron atom to which they are attached form 5- to 7-membered cyclic boronic acid ester optionally substituted with one or more substituents independently selected from the group consisting of C₁-C₆ alkyl.

(24) A compound represented by formula (II) or a pharmaceutically acceptable salt thereof:



wherein Q^1 , X^1 , X^2 , R^{11} , R^2 , R^3 , and R^4 are the groups as defined in one of above-mentioned (1) to (10) with the proviso that the groups may have one or more protecting groups, and X^{11} is a halogen atom.

According to one aspect of the invention, there is provided a compound represented by formula (I) or a pharmaceutically acceptable salt thereof:



wherein,

X^1 is -NH-;

Q^1 is selected from the group consisting of C_5 - C_7 cycloalkyl, phenyl, pyridyl, pyrazolyl, pyrimidinyl, and piperidyl; wherein Q^1 is optionally substituted with one or more substituents independently selected from A^1 ;

X^2 is selected from the group consisting of -CO- and -SO₂-;

R^{11} is selected from the group consisting of C_1 - C_6 alkyl and C_3 - C_7 cycloalkyl, which are optionally substituted with one or more substituents independently selected from the group consisting of hydroxy and a halogen atom;

R^5 is phenyl substituted with one to three substituents independently selected from the group consisting of hydroxy, a halogen atom, C_1 - C_6 alkyl, and C_1 - C_6 alkoxy wherein the

alkyl and alkoxy are optionally substituted with one or more halogen atoms;

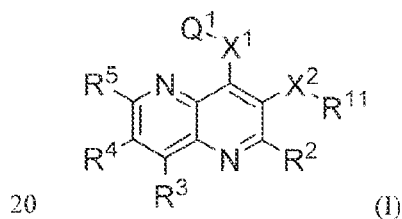
R^2 , R^3 , and R^4 are hydrogen atoms;

A^1 is independently selected from the group consisting of hydroxy, amino, C₁-C₆ alkoxy, C₁-C₆ alkylamino, di(C₁-C₆ alkyl)amino, amino-C₁-C₆ alkyl, (C₁-C₆ alkylamino)-C₁-C₆ alkyl, di(C₁-C₆ alkyl)amino-C₁-C₆ alkyl, amino-C₁-C₆ alkoxy, (C₁-C₆ alkylamino)-C₁-C₆ alkoxy, di(C₁-C₆ alkyl)amino-C₁-C₆ alkoxy, hydroxy-C₁-C₆ alkyl, (C₁-C₆ alkoxy)-C₁-C₆ alkyl, carboxy-C₁-C₆ alkyl, [(C₁-C₆ alkoxy)carbonyl]-C₁-C₆ alkyl, carbamoyl-C₁-C₆ alkyl, [N-(C₁-C₆ alkyl)carbamoyl]-C₁-C₆ alkyl, [N,N-di(C₁-C₆ alkyl)carbamoyl]-C₁-C₆ alkyl, (C₁-C₆ alkyl)carbonylamino, N-(C₁-C₆ alkyl)carbonyl-N-(C₁-C₆ alkyl)amino, pyrrolidinyl, piperidyl, and piperazinyl;

wherein the pyrrolidinyl, piperidyl, and piperazinyl defined as A^1 are optionally substituted with a substituent selected from the group consisting of C₁-C₆ alkyl, amino, C₁-C₆ alkylamino, di(C₁-C₆ alkyl)amino, hydroxy, C₁-C₆ alkoxy, pyrrolidinyl, piperidyl, and piperazinyl; and

wherein the alkyl moiety of the group defined as A^1 is optionally substituted with a substituent selected from the group consisting of amino, C₁-C₆ alkylamino, di(C₁-C₆ alkyl)amino, hydroxy, C₁-C₆ alkoxy, pyrrolidinyl, piperidyl, and piperazinyl.

According to another aspect of the invention, there is provided a compound represented by formula (I):



or a pharmaceutically acceptable salt thereof, wherein,

X^1 is -NH-; and Q^1 is selected from the group consisting of C₅-C₇ cycloalkyl such as cyclohexyl and pyridyl; wherein Q^1 is optionally substituted with one or more substituents independently selected from A^1 ;

A¹ is independently selected from the group consisting of hydroxy, amino, C₁-C₆ alkoxy, C₁-C₆ alkylamino, di(C₁-C₆ alkyl)amino, amino-C₁-C₆ alkyl, (C₁-C₆ alkylamino)-C₁-C₆ alkyl, di(C₁-C₆ alkyl)amino-C₁-C₆ alkyl, amino-C₁-C₆ alkoxy, (C₁-C₆ alkylamino)-C₁-C₆ alkoxy, di(C₁-C₆ alkyl)amino-C₁-C₆ alkoxy, hydroxy-C₁-C₆ alkyl, (C₁-C₆ alkoxy)-C₁-C₆ alkyl, carboxy-C₁-C₆ alkyl, [(C₁-C₆ alkoxy)carbonyl]-C₁-C₆ alkyl, carbamoyl-C₁-C₆ alkyl, [N-(C₁-C₆ alkyl)carbamoyl]-C₁-C₆ alkyl, [N,N-di(C₁-C₆ alkyl)carbamoyl]-C₁-C₆ alkyl, (C₁-C₆ alkyl)carbonylamino, N-(C₁-C₆ alkyl)carbonyl-N-(C₁-C₆ alkyl)amino, pyrrolidinyl, piperidyl, and piperazinyl;

wherein the pyrrolidinyl, piperidyl, and piperazinyl defined as A¹ are optionally substituted with a substituent selected from the group consisting of C₁-C₆ alkyl, amino, C₁-C₆ alkylamino, di(C₁-C₆ alkyl)amino, hydroxy, C₁-C₆ alkoxy, pyrrolidinyl, piperidyl, and piperazinyl; and wherein the alkyl moiety of the group defined as A¹ is optionally substituted with a substituent selected from the group consisting of amino, C₁-C₆ alkylamino, di(C₁-C₆ alkyl)amino, hydroxy, C₁-C₆ alkoxy, pyrrolidinyl, piperidyl, and piperazinyl;

X² is selected from the group consisting of -CO-; and R¹¹ is selected from the group consisting of C₁-C₆ alkyl and C₃-C₇ cycloalkyl, which are optionally substituted with one substituent selected from the group consisting of hydroxy and a halogen atom;

R², R³, and R⁴ are hydrogen atoms; and

R⁵ is phenyl substituted with one hydroxy and two halogen atoms.

In one aspect of the definitions of formula (I) indicated hereinbefore, the optional substituent of Q¹ is selected from the group consisting of hydroxy, amino, di(C₁-C₆ alkyl)amino, C₁-C₆ alkyl, di(C₁-C₆ alkyl)amino-C₁-C₆ alkyl, di(C₁-C₆ alkyl)amino-C₁-C₆ alkoxy, di(C₁-C₆ alkyl)amino, [(amino-C₁-C₆ alkyl)carbonyl]amino, N-(C₁-C₆ alkyl)piperidyl, di(C₁-C₆ alkyl)amino-pyrrolidin-1-yl, amino-pyrrolidin-1-yl, (pyrrolidin-1-yl)-C₁-C₆ alkyl, (C₁-C₆ alkyl)amino-piperidin-1-yl, amino-piperidin-1-yl, hydroxy-C₁-C₆ alkyl, [di(C₁-C₆ alkyl)amino-C₁-C₆ alkyl]amino, [4-(C₁-C₆ alkyl)-piperazin-1-yl]-C₁-C₆ alkyl, (piperazin-1-yl)-C₁-C₆ alkyl, pyrrolidinylcarbonyl-amino, (hydroxy-pyrrolidin-1-yl)-

C₁-C₆ alkyl, morpholinyl-C₁-C₆ alkyl, [N-(hydroxy-C₁-C₆ alkyl)-N-(C₁-C₆ alkyl)amino]-C₁-C₆ alkyl, and (CD₃)₂N-C₁-C₆ alkyl.

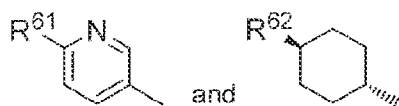
In another aspect, X¹ is -NH-; and Q¹ is selected from the group consisting of C₅-C₇ cycloalkyl such as cyclohexyl and pyridyl; wherein Q¹ is optionally substituted with one or more substituents independently selected from A¹;

A¹ is independently selected from the group consisting of hydroxy, amino, C₁-C₆ alkoxy, C₁-C₆ alkylamino, di(C₁-C₆ alkyl)amino, amino-C₁-C₆ alkyl, (C₁-C₆ alkylamino)-C₁-C₆ alkyl, di(C₁-C₆ alkyl)amino-C₁-C₆ alkyl, amino-C₁-C₆ alkoxy, (C₁-C₆ alkylamino)-C₁-C₆ alkoxy, di(C₁-C₆ alkyl)amino-C₁-C₆ alkoxy, hydroxy-C₁-C₆ alkyl, (C₁-C₆ alkoxy)-C₁-C₆ alkyl, carboxy-C₁-C₆ alkyl, [(C₁-C₆ alkoxy)carbonyl]-C₁-C₆ alkyl, carbamoyl-C₁-C₆ alkyl, [N-(C₁-C₆ alkyl)carbamoyl]-C₁-C₆ alkyl, [N,N-di(C₁-C₆ alkyl)carbamoyl]-C₁-C₆ alkyl, (C₁-C₆ alkyl)carbonylamino, N-(C₁-C₆ alkyl)carbonyl-N-(C₁-C₆ alkyl)amino, pyrrolidinyl, piperidyl, and piperazinyl;

wherein the pyrrolidinyl, piperidyl, and piperazinyl defined as A¹ are optionally substituted with a substituent selected from the group consisting of C₁-C₆ alkyl, amino, C₁-C₆ alkylamino, di(C₁-C₆ alkyl)amino, hydroxy, C₁-C₆ alkoxy, pyrrolidinyl, piperidyl, and piperazinyl; and

wherein the alkyl moiety of the group defined as A¹ is optionally substituted with a substituent selected from the group consisting of amino, C₁-C₆ alkylamino, di(C₁-C₆ alkyl)amino, hydroxy, C₁-C₆ alkoxy, pyrrolidinyl, piperidyl, and piperazinyl.

In another aspect, X¹ is -NH-; Q¹ is selected from the group consisting of cyclohexyl and pyridyl represented by the following formulae:



wherein R⁶¹ is amino-piperidin-1-yl, (C₁-C₆ alkyl)amino-piperidin-1-yl and di(C₁-C₆ alkyl)amino-C₁-C₆ alkyl; and R⁶² is selected from the group consisting of di(C₁-C₆ alkyl)amino, and di(C₁-C₆ alkyl)amino-C₁-C₆ alkyl. In one embodiment, R⁶¹ is 3-amino-

piperidin-1-yl and R⁶² is dimethylamino, or dimethylamino-methyl.

In one aspect, X¹ is a direct bond; and Q¹ is selected from the group consisting of 5-membered nitrogen-containing aromatic heterocyclyl such as pyrrolyl, pyrazolyl, and imidazolyl, and 3- to 10-membered nitrogen-containing non-aromatic heterocyclyl such as pyrrolidinyl, piperidyl, piperazinyl, and morpholinyl in which the nitrogen atom of the heteroaryl or heterocyclyl attaches to the naphthylidene ring; wherein Q¹ is optionally substituted with one or more substituents independently selected from A¹.

In still another aspect, X¹ is a direct bond; and Q¹ is selected from the group consisting of 5-membered nitrogen-containing aromatic heterocyclyl such as pyrrolyl, pyrazolyl, imidazolyl, and 3- to 10-membered nitrogen-containing non-aromatic heterocyclyl such as pyrrolidinyl, piperidyl, piperazinyl, and morpholinyl in which the nitrogen atom of the heteroaryl or heterocyclyl attaches to the naphthylidene ring; wherein Q¹ is optionally substituted with one or more substituents independently selected from A¹;

A¹ is independently selected from the group consisting of hydroxy, amino, C₁-C₆ alkoxy, C₁-C₆ alkylamino, di(C₁-C₆ alkyl)amino, amino-C₁-C₆ alkyl, (C₁-C₆ alkylamino)-C₁-C₆ alkyl, di(C₁-C₆ alkyl)amino-C₁-C₆ alkyl, amino-C₁-C₆ alkoxy, (C₁-C₆ alkylamino)-C₁-C₆ alkoxy, di(C₁-C₆ alkyl)amino-C₁-C₆ alkoxy, hydroxy-C₁-C₆ alkyl, (C₁-C₆ alkoxy)-C₁-C₆ alkyl, carboxy-C₁-C₆ alkyl, [(C₁-C₆ alkoxy)carbonyl]-C₁-C₆ alkyl, carbamoyl-C₁-C₆ alkyl, [N-(C₁-C₆ alkyl)carbamoyl]-C₁-C₆ alkyl, [N,N-di(C₁-C₆ alkyl)carbamoyl]-C₁-C₆ alkyl, (C₁-C₆ alkyl)carbonylamino, N-(C₁-C₆ alkyl)carbonyl-N-(C₁-C₆ alkyl)amino, pyrrolidinyl, piperidyl, and piperazinyl;

wherein the pyrrolidinyl, piperidyl, and piperazinyl defined as A¹ are optionally substituted with a substituent selected from the group consisting of C₁-C₆ alkyl, amino, C₁-C₆ alkylamino, di(C₁-C₆ alkyl)amino, hydroxy, C₁-C₆ alkoxy, pyrrolidinyl, piperidyl, and piperazinyl; and wherein the alkyl moiety of the group defined as A¹ is optionally substituted with a substituent selected from the group consisting of amino, C₁-C₆ alkylamino, di(C₁-C₆ alkyl)amino, hydroxy, C₁-C₆ alkoxy, pyrrolidinyl, piperidyl, and piperazinyl.

In one aspect, X^2 is selected from the group consisting of -CO-; and R^{11} is selected from the group consisting of C_1 - C_6 alkyl and C_3 - C_7 cycloalkyl, which are optionally substituted with one substituent selected from the group consisting of hydroxy and a halogen atom.

5 In another aspect, X^2 is -CO-; and R^{11} is selected from the group consisting of methyl, hydroxymethyl and cyclopropyl.

In one aspect, R^5 is phenyl substituted with one hydroxy and two halogen atoms. In another aspect, R^5 is selected from the group consisting of 3,5-dichloro-4-hydroxyphenyl, 3,5-difluoro-4-hydroxyphenyl, and 3-chloro-5-fluoro-4-hydroxyphenyl.

10 According to one aspect of the invention, there is provided a the compound or a pharmaceutically acceptable salt thereof, which is selected from the group consisting of the following compounds:

1-(6-chloro-4-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone;

15 1-{6-(3,5-dichloro-4-hydroxyphenyl)-4-[(*trans*-4-(dimethylamino)cyclohexylamino)-1,5-naphthyridin-3-yl]}ethanone;

1-{6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-[(*trans*-4-(dimethylamino)cyclohexylamino)-1,5-naphthyridin-3-yl]}ethanone;

20 cyclopropyl(6-(3,5-dichloro-4-hydroxyphenyl)-4-[(*trans*-4-[(dimethylamino)methyl]-cyclohexylamino)-1,5-naphthyridin-3-yl])methanone;

(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-[(*trans*-4-[(dimethylamino)methyl]cyclohexylamino)-1,5-naphthyridin-3-yl])(cyclopropyl)methanone;

25 1-{6-(3,5-dichloro-4-hydroxyphenyl)-4-[(*trans*-4-[(dimethylamino)methyl]cyclohexylamino)-1,5-naphthyridin-3-yl]}ethanone;

1-{6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-[(*trans*-4-[(dimethylamino)methyl]cyclohexylamino)-1,5-naphthyridin-3-yl]}ethanone;

1-(6-(3-chloro-4-hydroxy-5-methoxyphenyl)-4-[(*trans*-4-[(dimethylamino)methyl]-

- cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone;
 1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-({*trans*-4-[2-(dimethylamino)ethyl]cyclohexyl)-amino)-1,5-naphthyridin-3-yl]ethanone;
 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-{*trans*-4-[2-(dimethylamino)ethyl]-
 5 cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone;
 1-(4-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-6-[4-hydroxy-3-(trifluoro-methoxy)phenyl]-1,5-naphthyridin-3-yl)ethanone;
 2,6-dichloro-4-(8-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)phenol;
 10 6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-({*trans*-4-[(dimethylamino)methyl]cyclohexylamino)-3-methylsulfonyl-1,5-naphthyridine;
 6-(3-chloro-4-hydroxy-5-methoxyphenyl)-4-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-3-methylsulfonyl-1,5-naphthyridine;
 2,6-dichloro-4-{8-[*trans*-4-(dimethylamino)cyclohexylamino]-7-(methylsulfonyl)-
 15 1,5-naphthyridin-2-yl}phenol;
 2,6-dichloro-4-(8-(4-((dimethylamino)methyl)phenylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)phenol;
 2-chloro-4-(8-(4-((dimethylamino)methyl)phenylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-fluorophenol;
 20 2-chloro-4-(8-(4-((dimethylamino)methyl)phenylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-methoxyphenol;
 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(3-(2-(pyrrolidin-1-yl)ethyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(3-(2-(pyrrolidin-1-yl)ethyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone;
 25 amino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(6-(2-(dimethylamino)ethoxy)pyridin-3-yl)-amino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(6-(2-(dimethylamino)ethoxy)pyridin-

- 3-ylamino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3-chloro-4-hydroxy-5-methoxyphenyl)-4-(6-(2-(dimethylamino)ethoxy)pyridin-3-ylamino)-1,5-naphthyridin-3-yl)ethanone;
 2,6-dichloro-4-(8-(6-(2-(dimethylamino)ethoxy)pyridin-3-ylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)phenol;
 5 2-chloro-4-(8-(6-(2-(dimethylamino)ethoxy)pyridin-3-ylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-fluorophenol;
 2-chloro-4-(8-(6-(2-(dimethylamino)ethoxy)pyridin-3-ylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-methoxyphenol;
 10 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((1-methylpiperidin-4-yl)methylamino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(*trans*-4-((dimethylamino- d_6)-methyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(4-(2-(dimethylamino)-ethyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone;
 15 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(4-(2-(dimethylamino)ethyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3-chloro-4-hydroxy-5-methoxyphenyl)-4-(4-(2-(dimethylamino)ethyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone;
 20 2-chloro-4-(8-(*trans*-4-(dimethylamino)cyclohexylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-fluorophenol;
 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-ylamino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(4-((4-methylpiperazin-1-yl)methyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone;
 25 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(4-((4-methylpiperazin-1-yl)methyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone;
 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(4-(2-(pyrrolidin-1-yl)ethyl)piperidin-1-yl)-

- 1,5-naphthyridin-3-yl)ethanone;
- 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(4-(2-(pyrrolidin-1-yl)ethyl)piperidin-1-yl)-1,5-naphthyridin-3-yl)ethanone;
- 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(6-(2-(dimethylamino)ethylamino)pyridin-3-ylamino)-1,5-naphthyridin-3-yl)ethanone;
- 5 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(6-(2-(dimethylamino)ethylamino)-pyridin-3-ylamino)-1,5-naphthyridin-3-yl)ethanone;
- (S)-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)(cyclopropyl)methanone;
- 10 1-(4-(2-(3-aminopyrrolidin-1-yl)pyrimidin-5-ylamino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone;
- 1-(4-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-6-(1H-pyrazol-4-yl)-1,5-naphthyridin-3-yl)ethanone;
- 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-{*trans*-4-(hydroxymethyl)cyclohexyl]amino}-1,5-naphthyridin-3-yl)ethanone;
- 15 1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-{*trans*-4-[(dimethylamino)methyl]cyclohexyl-amino}-1,5-naphthyridin-3-yl]-2-hydroxyethanone;
- 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-[(1-methylpiperidin-4-yl)amino]-1,5-naphthyridin-3-yl)ethanone;
- 20 1-[6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-[(1-methylpiperidin-4-yl)amino]-1,5-naphthyridin-3-yl]ethanone;
- 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-{*trans*-4-(morpholinomethyl)cyclohexyl]-amino}-1,5-naphthyridin-3-yl)ethanone;
- 1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-(*trans*-4-{(2-hydroxyethyl)(methyl)amino]-methyl}cyclohexylamino)-1,5-naphthyridin-3-yl]-ethanone;
- 25 1-[6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(*trans*-4-{(2-hydroxyethyl)(methyl)amino]methyl}cyclohexylamino)-1,5-naphthyridin-3-yl]-ethanone;
- 1-(6-(3,5-difluoro-4-hydroxyphenyl)-4-{*trans*-4-

- [(dimethylamino)methyl]cyclohexyl-amino}-1,5-naphthyridin-3-yl)ethanone;
- 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-{6-[3-(dimethylamino)pyrrolidin-1-yl]pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone;
- 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-{6-[3-(dimethylamino)pyrrolidin-1-yl]-pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone;
- 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-{6-[3-(methylamino)pyrrolidin-1-yl]pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone;
- 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-{6-[3-(methylamino)-pyrrolidin-1-yl]-pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone;
- 1-(6-(1H-benzo[d]imidazol-5-yl)-4-{*trans*-4-[(dimethylamino)methyl]cyclohexyl-amino}-1,5-naphthyridin-3-yl)ethanone;
- 1-{4-[4-(*trans*-4-dimethylamino)methylcyclohexylamino]-6-(pyridin-4-yl)-1,5-naphthyridin-3-yl}ethanone;
- 5-(7-acetyl-8-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-2-yl)pyrimidine-2-carbonitrile;
- 1-(6-(3,5-dimethyl-1H-pyrazol-4-yl)-4-{*trans*-4-[(dimethylamino)-methyl]-cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone;
- 1-(4-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-6-(4-hydroxy-3,5-dimethyl-phenyl)-1,5-naphthyridin-3-yl)ethanone;
- 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-{6-[3-(dimethylamino)pyrrolidin-1-yl]pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone;
- 1-{6-(3,5-dichloro-4-hydroxyphenyl)-4-{*trans*-4-(pyrrolidin-1-ylmethyl)-cyclohexyl-amino}-1,5-naphthyridin-3-yl}ethanone;
- 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-{[*trans*-4-(pyrrolidin-1-ylmethyl)cyclo-hexyl]amino}-1,5-naphthyridin-3-yl)ethanone;
- 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-{*trans*-4-[(4-methylpiperazin-1-yl)-methyl]-cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone;
- 1-(4-{[6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino}-6-(3,5-dichloro-4-hydroxy-

phenyl)-1,5-naphthyridin-3-yl)ethanone;

1-(4-{{6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino}-6-(3-chloro-5-fluoro-4-hydroxy-phenyl)-1,5-naphthyridin-3-yl)ethanone;

1-(4-[*trans*-(4-aminocyclohexyl)amino]-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone;

1-(4-[*trans*-(4-aminocyclohexyl)amino]-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone;

1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-{{*trans*-4-[(4-methylpiperazin-1-yl)-methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone;

10 N-(*trans*-4-{{[3-acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl]-amino}cyclohexyl}-2-amino-3-methylbutanamide;

1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-[*trans*-4-(piperazin-1-ylmethyl)-cyclohexyl-amino]-1,5-naphthyridin-3-yl)ethanone;

(S)-1-(4-{{6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino}-6-(3,5-dichloro-4-hydroxy-phenyl)-1,5-naphthyridin-3-yl)ethanone;

(S)-1-(4-{{6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino}-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone;

N-(*trans*-4-[3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino]-cyclohexyl)-2-aminopropanamide;

20 N-(4-[3-acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-*trans*-4-yl-amino]cyclohexyl)-2-aminopropanamide;

(S)-N-(4-[3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-*trans*-4-yl-amino]cyclohexyl)pyrrolidine-2-carboxamide;

(S)-N-(4-[3-acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-*trans*-4-ylamino]cyclohexyl)pyrrolidine-2-carboxamide;

1-(6-(3-hydroxypyrrolidin-1-yl)-4-{{*trans*-4-[(3-hydroxypyrrolidin-1-yl)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone;

1-(6-(pyrrolidin-1-yl)-4-[*trans*-4-(pyrrolidin-1-ylmethyl)-cyclohexylamino]-1,5-

naphthyridin-3-yl} ethanone;

N-{*trans*-4-[3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino]-cyclohexyl}-2-amino-3-methylbutanamide;

cyclopropyl{6-(3,5-dichloro-4-hydroxyphenyl)-4-{*trans*-4-(dimethylamino)cyclohexyl- amino}-1,5-naphthyridin-3-yl} methanone;

1-[6-(3-chloro-5-fluoro-4-methoxyphenyl)-4-{*trans*-4-[(dimethylamino)methyl]-cyclohexylamino}-1,5-naphthyridin-3-yl]ethanone;

1-(4-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-6-(1H-pyrrolo[2,3-b]pyridin-5-yl)-1,5-naphthyridin-3-yl)ethanone;

10 (S)-{4-[6-(3-aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3-chloro-5-fluoro-4-hydroxy- phenyl)-1,5-naphthyridin-3-yl}(cyclopropyl)methanone;

1-(4-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-6-(4-methoxyphenyl)-1,5- naphthyridin-3-yl)ethanone;

1-[6-(3,5-dichloro-4-methoxyphenyl)-4-{*trans*-4-[(dimethylamino)methyl]cyclohexyl- amino}-1,5-naphthyridin-3-yl]ethanone;

1-(4-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-6-(6-hydroxypyridin-3-yl)- 1,5-naphthyridin-3-yl)ethanone;

5-(7-acetyl-8-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-2- yl)picolinonitrile;

20 1-(4-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-6-(4-hydroxyphenyl)-1,5- naphthyridin-3-yl)ethanone dihydrochloride;

1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-{[*trans*-4-(dimethylamino)cyclohexyl]methyl- amino}-1,5-naphthyridin-3-yl]ethanone;

1-[6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-{[*trans*-4-(dimethylamino)cyclohexyl]- methylamino}-1,5-naphthyridin-3-yl]ethanone;

25 1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-(*trans*-4-hydroxycyclohexylamino)-1,5-naphthyridin-3-yl]ethanone;

1-[6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(*trans*-4-hydroxycyclohexylamino)-

1,5-naphthyridin-3-yl]ethanone;

1-{6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-({*cis*-4-[(dimethylamino)methyl]-cyclohexyl}amino)-1,5-naphthyridin-3-yl}ethanone;

1-{6-(3,5-dichloro-4-hydroxyphenyl)-4-({*cis*-4-[(dimethylamino)methyl]-cyclohexyl}amino)-1,5-naphthyridin-3-yl}ethanone;

(R)-1-{4-[6-(3-aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}ethanone;

(R)-1-{4-[6-(3-aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}ethanone;

and pharmaceutically acceptable salts thereof.

According to another aspect of the invention, there is provided a compound represented by formula (I) or a pharmaceutically acceptable salt thereof, which is selected from the group consisting of the following compounds:

1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((4-(dimethylamino)cyclohexyl)amino)-1,5-naphthyridin-3-yl)ethanone;

cyclopropyl (6-(3,5-dichloro-4-hydroxyphenyl)-4-(4-((dimethylamino)methyl)-cyclohexylamino)-1,5-naphthyridin-3-yl) methanone;

(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(4-((dimethylamino)methyl)cyclohexylamino)-1,5-naphthyridin-3-yl) (cyclopropyl) methanone;

1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((4-((dimethylamino)methyl)cyclohexyl)amino)-1,5-naphthyridin-3-yl) ethanone;

1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-((4-((dimethylamino)methyl)cyclohexyl)- amino)-1,5-naphthyridin-3-yl) ethanone;

1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((4-(2-(dimethylamino)ethyl)cyclohexyl)- amino)-1,5-naphthyridin-3-yl) ethanone;

(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3,5-dichloro-4-hydroxyphenyl)- 1,5-naphthyridin-3-yl)(cyclopropyl)methanone;

1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-{*trans*-4-[(dimethylamino)methyl]cyclo-

hexylamino}-1,5-naphthyridin-3-yl]-2-hydroxyethanone;

1-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone;

1-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3-chloro-5-fluoro-4-hydroxy-phenyl)-1,5-naphthyridin-3-yl)ethanone;

1-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3,5-dichloro-4-hydroxy-phenyl)-1,5-naphthyridin-3-yl)ethanone;

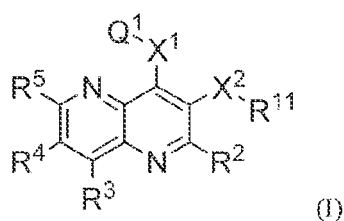
{4-[6-(3-aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3-chloro-5-fluoro-4-hydroxy-phenyl)-1,5-naphthyridin-3-yl} (cyclopropyl) methanone;

1-{4-[6-(3-aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3,5-dichloro-4-hydroxy-phenyl)-1,5-naphthyridin-3-yl} ethanone;

1-{4-[6-(3-aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl} ethanone;

and pharmaceutically acceptable salts thereof.

According to one aspect of the invention, there is provided a process for preparing a compound of formula (I):

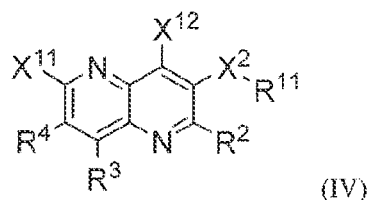


or a pharmaceutically acceptable salt thereof according to any one of above-mentioned (1)

to (12), wherein X¹ is -NH-; and X², R¹¹, R², R³, and R⁴ are the groups as defined in any one

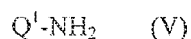
of above-mentioned (1) to (10) or in the other descriptions hereinbefore, which comprises:

reacting a compound represented by formula (IV):

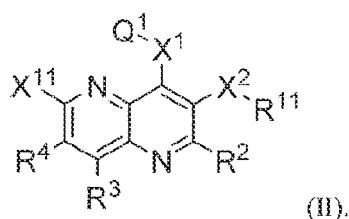


wherein X^2 , R^{11} , R^2 , R^3 , and R^4 are the groups as defined hereinbefore, with the proviso that the groups may have one or more protecting groups; and X^{11} and X^{12} are independently selected from a halogen atom such as a chlorine atom; with a compound

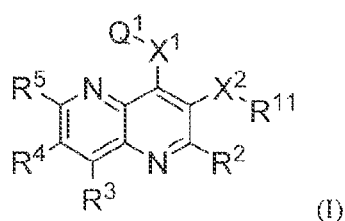
5 represented by formula (V):



wherein Q^1 is the group as defined above, with the proviso that the groups may have one or more protecting groups; to obtain a compound represented by formula (II):



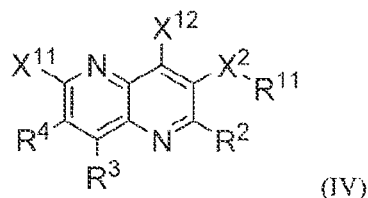
10 According to another aspect of the invention, there is provided a process for preparing a compound of formula (I):



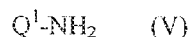
or a pharmaceutically acceptable salt thereof according to any one of above-mentioned (1) to (11), wherein X^1 is $-NH-$; R^5 is phenyl optionally substituted with one or more

15 substituents independently selected from A^3 ; and Q^1 , X^1 , X^2 , R^{11} , R^2 , R^3 , and R^4 are the groups as defined in one of above-mentioned (1) to (10) or in the other descriptions hereinbefore; which comprises:

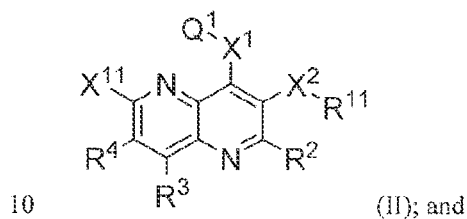
reacting a compound represented by formula (IV):



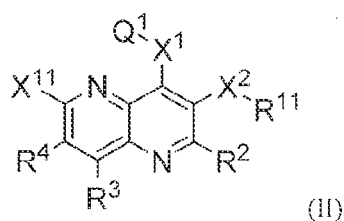
wherein X², R¹¹, R², R³, and R⁴ are the groups as defined hereinbefore, with the proviso that the groups may have one or more protecting groups, and X¹¹ and X¹² are
 5 independently selected from a halogen atom such as a chlorine atom; with a compound represented by formula (V):



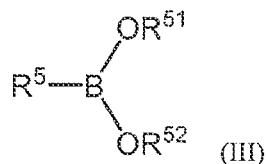
wherein Q¹ is the group as defined hereinbefore, with the proviso that the groups may have one or more protecting groups; to obtain a compound represented by formula (II):



reacting a compound represented by formula (II):



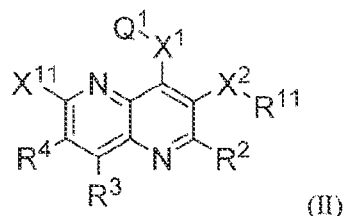
wherein Q¹, X¹, X², R¹¹, R², R³, and R⁴ are the groups as defined above, with the proviso that the groups may have one or more protecting groups, and X¹¹ is a halogen atom;
 15 with a compound represented by formula (III):



wherein R^5 is as defined above with the proviso that the group of R^5 may have one or more protecting groups; and R^{51} and R^{52} are independently selected from the group consisting of C_1 - C_6 alkyl, or R^{51} and R^{52} together with the boron atom to which they are
 5 attached forms 5- to 7-membered cyclic boronic acid ester optionally substituted with one or more substituents independently selected from the group consisting of C_1 - C_6 alkyl.

In one aspect, the protecting group to protect -NH- and/or - NH_2 is selected from the group consisting of C_1 - C_6 alkylcarbonyl (e.g. acetyl), C_1 - C_6 alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, and tert-butoxycarbonyl), phenyl(C_1 - C_6 alkoxy)carbonyl
 10 (e.g. benzyloxycarbonyl), (C_1 - C_6 alkoxy) C_1 - C_6 alkyl (e.g. methoxymethyl), phenyl(C_1 - C_6 alkoxy)methyl (e.g. benzyloxymethyl), and (phenyl) C_1 - C_6 alkyl (e.g. benzyl), and the protecting group to protect hydroxy is selected from the group consisting of C_1 - C_6 alkylcarbonyl (e.g. acetyl), C_1 - C_6 alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, and tert-butoxycarbonyl), phenyl(C_1 - C_6 alkoxy)carbonyl (e.g. benzyloxycarbonyl), (C_1 - C_6
 15 alkoxy) C_1 - C_6 alkyl (e.g. methoxymethyl), phenyl(C_1 - C_6 alkoxy)methyl (e.g. benzyloxymethyl), (phenyl) C_1 - C_6 alkyl (e.g. benzyl), tri(C_1 - C_6 alkyl)silyl (e.g. trimethylsilyl, and tert-butyl-dimethylsilyl), di(C_1 - C_6 alkyl)phenylsilyl, (C_1 - C_6 alkyl)diphenylsilyl, and triphenylsilyl. Further, the carboxy group may be protected with C_1 - C_6 alkyl (e.g. methyl and ethyl), (phenyl) C_1 - C_6 alkyl (e.g. benzyl), (C_1 - C_6 alkoxy) C_1 - C_6
 20 alkyl (e.g. methoxymethyl) or phenyl(C_1 - C_6 alkoxy) C_1 - C_6 alkyl (e.g. benzyloxymethyl) to form the corresponding ester.

According to one aspect of the invention, there is provided a compound represented by formula (II) or a pharmaceutically acceptable salt thereof:



wherein Q^1 , X^1 , X^2 , R^{11} , R^2 , R^3 , and R^4 are the groups as defined in one of above-mentioned (1) to (10) with the proviso that -NH- and/or -NH₂ containing in the groups may have one or more protecting groups selected from the group consisting of C₁-C₆

- 5 alkylcarbonyl (e.g. acetyl), C₁-C₆ alkoxy carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, and tert-butoxycarbonyl), phenyl(C₁-C₆ alkoxy)carbonyl (e.g. benzyloxycarbonyl), (C₁-C₆ alkoxy)C₁-C₆ alkyl (e.g. methoxymethyl), phenyl(C₁-C₆ alkoxy)methyl (e.g. benzyloxymethyl), and benzyl; and X^{11} is a halogen atom.

BRIEF DESCRIPTION OF DRAWINGS

- 10 Figure 1 is composed of a series of graphs, (a)-(e), depicting *In vitro* anti-proliferative activity of Compound Example 6. The graphs indicate growth inhibition curves of Compound Example 6 for various types of human cancer cell line; (a) A549 (lung cancer), (b) T47D (breast cancer), (c) DU4475 (breast cancer), and (d) 22Rv1 (prostate cancer) cells, in which MELK is highly expressed, as well as (e) HT1197 (bladder cancer)
- 15 cell line, in which MELK expression is hardly detectable.

- Figure 2 is composed of a series of graphs, (a)-(h), depicting mice xenograft models showing the effectiveness of Example 6 on the growth of various human cancer xenograft. Nude mice bearing (a,b) MDA-MB-231 (triple-negative breast cancer), (c,d) A549 (lung cancer), (e) DU145 (prostate cancer), or (f) MIA PaCa-2 (pancreatic cancer)
- 20 were treated with either vehicle control or Compound Example 6 of given concentrations for 14 days. The administration doses were (a) 20 mg/kg intravenously once every two days or (b) 10 mg/kg orally once a day for MDA-MB-231; (c) 1, 5, or 10 mg/kg intravenously once a day or (d) 5 or 10 mg/kg orally once a day for A549; (e) 10 mg/kg orally once a day for DU145; and (f) 10 mg/kg orally once a day for MIA PaCa-2. Mean

tumor volumes $\pm$ SD ($n = 6$ for each treatment group) are shown. (g) Lysates of tumor samples taken from A549 and PC-14 xenograft mice were immunoblotted with anti-MELK and anti-ACTB antibodies. (h) Compound Example 6 was administered to nude mice bearing PC-14 (MELK-negative bladder cancer cells) at a dose of 10 mg/kg orally once a day. Mean tumor volumes $\pm$ SD ($n = 3$ per group) are shown. i.v. q.2d; intravenously once every two days, i.v. q.d.; intravenously once a day, p.o. q.d.; orally once a day.

Figure 3 is composed of a series of graphs, (a)-(f), depicting the Effect of Example 6 on body weight for mice xenograft models. Nude mice bearing (a,b) MDA-MB-231 (MELK-positive, triple negative breast cancer), (c,d) A549 (lung cancer), (e) DU145 (prostate cancer), or (f) MIAPaCa-2 (pancreatic cancer) cells were administered either vehicle control or Compound Example 6 for 14 days. Mean relative body weights $\pm$ SD ($n = 6$ per each treatment group) in comparison with the mean body weight just before the administration (day 0) are shown. The mean relative body weights after 14 days of administration were: (a) 0.93 for 20 mg/kg intravenously once every two days, in MDA-MB-231; (b) 0.89 for 10 mg/kg orally once a day in MDA-MB-231; (c) 1.06 for 1 mg/kg intravenously once a day, 1.03 for 5 mg/kg intravenously once a day, and 1.00 for 10 mg/kg intravenously once a day in A549; (d) 0.99 for 5 mg/kg orally once a day, and 0.98 for 10 mg/kg orally once a day in A549; (e) 0.96 for 10 mg/kg orally once a day in DU145; (f) 0.97 for 10 mg/kg orally once a day in MIAPaCa-2. i.v. q.2d; intravenously once every two days, i.v. q.d.; intravenously once a day, p.o. q.d.; orally once a day.

DESCRIPTION OF EMBODIMENTS

An object of the present invention to provide a compound having inhibitory activity against MELK, which is useful for treating proliferative diseases such as cancer, and a pharmaceutical composition comprising the compound. Another object of the present invention is to provide a method for treating and/or preventing a proliferative disease. A further object is to provide a process for preparing the compound.

Hereinafter, a compound represented by formula (I) will be referred to as compound (I). The same applies to the compounds represented by the other formula

numbers. It must be noted that as used herein and in the appended claims, the singular forms “a”, “an”, and “the” include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to a “group” is a reference to one or more groups, unless otherwise noted.

5 In the definitions of each of the groups of formulas indicated above, the “C₁-C₆ alkyl”, and the C₁-C₆ alkyl portion of “C₁-C₆ alkoxy”, “C₁-C₆ alkylamino”, “di(C₁-C₆ alkyl)amino”, (C₁-C₆ alkyl)carbonyl and the like mean a straight-chain or branched-chain alkyl group having one to six carbon atoms. Specifically, examples of the “C₁-C₆ alkyl” and the “C₁-C₆ alkyl portion” include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-
10 butyl, tert-butyl, pentyl, 1-methylbutyl, 1-ethylpropyl, 2-methylbutyl, isopentyl, tert-pentyl, 1,2-dimethylpropyl, neopentyl, hexyl, 1-methylpentyl, 1-ethylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, isohexyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1-isopropylpropyl, 1-ethyl-1-methylpropyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 2-ethylbutyl, and 3-ethylbutyl, but are not limited thereto.

15 The “C₂-C₆ alkenyl”, and the C₂-C₆ alkenyl portion of “C₂-C₆ alkenyloxy” and the like mean a straight-chain or branched-chain alkenyl group having two to six carbon atoms and one to three double bonds. Specifically, examples of the “C₁-C₆ alkenyl” and the “C₁-C₆ alkenyl portion” include ethenyl (vinyl), 1-propen-1-yl, 2-propen-1-yl (allyl), propen-2-yl, 1-buten-1-yl, 2-buten-1-yl, and 1,3-but-dien-1-yl, but are not limited thereto.

20 The “C₂-C₆ alkynyl”, and the C₂-C₆ alkynyl portion of “C₂-C₆ alkynyloxy” and the like mean a straight-chain or branched-chain alkynyl group having two to six carbon atoms and one to three triple bonds. Specifically, examples of the “C₁-C₆ alkynyl” and the “C₁-C₆ alkynyl portion” include ethynyl, 1-propyn-1-yl, 2-propyn-1-yl (propargyl), propyn-2-yl, 1-butyne-1-yl, 2-butyne-1-yl, and 1,3-but-diyn-1-yl, but are not limited thereto.

25 In this specification, the C₁-C₆ alkyl portion in each group has the same definition as the aforementioned “C₁-C₆ alkyl portion” unless otherwise noted. In a case that a group contains plural C₁-C₆ alkyl portions, the C₁-C₆ alkyl portions may be same or different.

Specific examples of “C₁-C₆ alkoxy” include methoxy, ethoxy, propoxy,

isopropoxy, isobutyloxy, tert-butyloxy, butoxy, pentyloxy, and hexyloxy, but are not limited thereto.

The “C₁-C₆ alkoxy carbonyl” refers to a monovalent group represented by -C(=O)O-(C₁-C₆ alkyl). Specific examples of “C₁-C₆ alkoxy carbonyl” include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, isobutyloxy carbonyl, tert-butoxy carbonyl, butoxy carbonyl, pentyloxy carbonyl, and hexyloxy carbonyl, but are not limited thereto.

The “(C₁-C₆ alkyl) carbonyl” refers to a monovalent group represented by -C(=O)-(C₁-C₆ alkyl). Specific examples of “C₁-C₆ alkyl carbonyl” include methyl carbonyl (i.e. acetyl), ethyl carbonyl, propyl carbonyl, isopropyl carbonyl, isobutyl carbonyl, tert-butyl carbonyl, butyl carbonyl, pentyl carbonyl, and hexyl carbonyl, but are not limited thereto.

Specific examples of “C₁-C₆ alkyl amino” include methyl amino, ethyl amino, propyl amino, isopropyl amino, butyl amino, isobutyl amino, sec-butyl amino, and tert-butyl amino, pentyl amino, but are not limited thereto.

The alkyl portions of “di(C₁-C₆ alkyl) amino” may be same or different. Specific examples of “di(C₁-C₆ alkyl) amino” include dimethyl amino, diethyl amino, dipropyl amino, diisopropyl amino, dibutyl amino, diisobutyl amino, di(sec-butyl) amino, di(tert-butyl) amino, dipentyl amino, ethyl(methyl) amino, propyl(methyl) amino, isopropyl(methyl) amino, butyl(methyl) amino, isobutyl(methyl) amino, sec-butyl(methyl) amino, tert-butyl(methyl) amino, and pentyl(methyl) amino, but are not limited thereto.

The formula: -S(O)_nR¹⁹ represents -SR¹⁹ (n=0), -SOR¹⁹ (n=1), and -SO₂R¹⁹ (n=2), and the examples include “C₁-C₆ alkyl thio” such as methyl thio, ethyl thio, and isopropyl thio, “C₁-C₆ alkyl sulfonyl” such as methyl sulfonyl, ethyl sulfonyl, and isopropyl sulfonyl, and “C₁-C₆ alkyl sulfinyl” such as methyl sulfinyl, ethyl sulfinyl, and isopropyl sulfinyl, but are not limited thereto. This will apply to definitions of the formulae -S(O)_nR²⁷, and -S(O)_nR³⁷.

Specific examples of “a halogen atom” include a fluorine, a chlorine, a bromine, and an iodine atoms.

The term “C₃-C₁₀ cycloalkyl” refers to a saturated monocyclic hydrocarbon group

having three to ten carbon atoms, and a bridged cyclic hydrocarbon group having four to ten carbon atoms which is formed when two or more saturated monocyclic hydrocarbons share two or more carbon atoms. The term "C₃-C₁₀ cycloalkyl" also encompasses a cycloalkyl group condensed with an aromatic or non-aromatic carbocyclic ring to form a bicyclic group. Specifically, examples of "C₃-C₁₀ cycloalkyl" include saturated monocyclic hydrocarbon groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl, and bridged cyclic hydrocarbon groups such as adamantyl, but are not limited thereto.

The term "C₆-C₁₀ aryl" refers to an aromatic carbocyclic group having six to ten carbon atoms, and encompasses an aromatic carbocyclic group condensed with an aromatic or non-aromatic carbocyclic ring to form a bicyclic group. Specific examples include phenyl, 1-naphthyl, 2-naphthyl, and 2,3-dihydro-1H-indenyl, but are not limited thereto.

The term "5- to 10-membered heteroaryl" refers to an aromatic heterocyclic group having one or more heteroatoms, preferably one to three heteroatoms, selected from the group consisting of a nitrogen atom, an oxygen atom, and a sulfur atom. The term "5- to 10-membered heteroaryl" encompasses an aromatic heterocyclic group condensed with an aromatic or non-aromatic carbocyclic ring or an aromatic or non-aromatic heterocyclic ring to form a bicyclic group, and also encompasses an aromatic carbocyclic group condensed with an aromatic or non-aromatic heterocyclic ring to form a bicyclic group. Specific examples include furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, isoindolyl, indolyl, 1H-indazolyl, benzimidazolyl, benzotriazolyl, oxazolopyrimidinyl, thiazolopyrimidinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, imidazopyridinyl, purinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pyridopyrimidinyl, [1,2,4] triazolo[1,5-a]pyridyl, and pyrrolo[2,3-b]pyridyl, but are not limited thereto. Particularly, thienyl, pyrrolyl, imidazolyl, isoxazolyl, pyridyl, pyrimidinyl, pyrazolyl, 1H-indazolyl, benzimidazolyl,

[1,2,4]triazolo[1,5-a]pyridyl, or pyrrolo[2,3-b]pyridyl is preferred.

The term "3- to 10-membered non-aromatic heterocyclyl" refers to a non-aromatic heterocyclic group having one or more heteroatoms, preferably one to three heteroatoms, selected from the group consisting of a nitrogen atom, an oxygen atom, and a sulfur atom.

- 5 The term "3- to 10-membered non-aromatic heterocyclyl" encompasses a non-aromatic heterocyclic group condensed with an aromatic or non-aromatic carbocyclic ring or an aromatic or non-aromatic heterocyclic ring to form a bicyclic group, and also encompasses a non-aromatic carbocyclic group condensed with an aromatic or non-aromatic heterocyclic ring to form a bicyclic group. Specific examples include aziridinyl, azetidiny,
- 10 pyrrolidinyl, piperidyl (including piperidino), azepanyl, 1,2,5,6-tetrahydropyridyl, 1,2,3,6-tetrahydropyridyl, imidazolidinyl, pyrazolidinyl, piperazinyl, homopiperazinyl, pyrazolinyl, oxiranyl, tetrahydrofuranyl, tetrahydro-2H-pyranyl, 5,6-dihydro-2H-pyranyl, oxazolidinyl, morpholinyl (including morpholino), tetrahydrothiophenyl, tetrahydro-2H-thiopyranyl, thioxazolidinyl, thiomorpholinyl, 2H-oxazolyl, 2H-thioxazolyl, dihydroindolyl,
- 15 dihydroisoindolyl, dihydrobenzofuranyl, benzoimidazolidinyl, 2,3-dihydrobenzimidazolyl, 2,3-dihydrobenzoxazolyl, dihydrobenzothioxazolyl, benzodioxolinyl, tetrahydroquinolyl, tetrahydroisoquinolyl, dihydro-2H-chromanyl, dihydro-1H-chromanyl, dihydro-2H-thiochromanyl, dihydro-1H-thiochromanyl, tetrahydroquinoxaliny, tetrahydroquinazolinyl, dihydrobenzodioxanyl, oxetanyl, 1,2-dihydropyridyl, 1-azabicyclo[2.2.2]octan-3-yl, 2,5-
- 20 azabicyclo[2.2.1]heptyl, 8-azabicyclo[3.2.1]octyl, piperidin-4-spiro-3'-pyrrolidin-1-yl, and isoindolyl, but are not limited thereto. In particular, azetidiny, pyrrolidinyl, piperidino, piperidyl, piperazinyl, morpholino, morpholinyl, 1,2-dihydropyridyl, 1,2,5,6-tetrahydropyridyl, 1-azabicyclo[2.2.2]octan-3-yl, 2,5-azabicyclo[2.2.1]heptyl, 8-
- 25 azabicyclo[3.2.1]octyl, 2,3-dihydrobenzimidazolyl, or piperidin-4-spiro-3'-pyrrolidin-1-yl is preferred.

The term "3- to 10-membered nitrogen-containing heterocyclyl" refers to an aromatic or non-aromatic heterocyclic group having one nitrogen atom and one or more additional heteroatoms, preferably one to three heteroatoms, selected from the group

consisting of a nitrogen atom, an oxygen atom, and a sulfur atom. The term "3- to 10-membered nitrogen-containing heterocyclyl" encompasses a heterocyclic group condensed with an aromatic or non-aromatic carbocyclic ring or an aromatic or non-aromatic heterocyclic ring to form a bicyclic group. Specific examples include aziridinyl, azetidiny, pyrrolyl, pyrrolidinyl, piperidyl (including piperidino), azepanyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, piperazinyl, and morpholinyl.

Specific examples of "(C₃-C₁₀ cycloalkyl)-C₁-C₆ alkyl" include (C₃-C₁₀ cycloalkyl)-C₁-C₂ alkyl, namely (C₃-C₁₀ cycloalkyl)-methyl such as cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl and cyclooctylmethyl; 1-(C₃-C₁₀ cycloalkyl)-ethyl such as 1-cyclopropylethyl, 1-cyclobutylethyl, 1-cyclopentylethyl, 1-cyclohexylethyl, 1-cycloheptylethyl and 1-cyclooctylethyl; and 2-(C₃-C₁₀ cycloalkyl)-ethyl such as 2-cyclopropylethyl, 2-cyclobutylethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, 2-cycloheptylethyl and 2-cyclooctylethyl. Specific examples of "(C₆-C₁₀ aryl)-C₁-C₆ alkyl" include (C₆-C₁₀ aryl)-C₁-C₂ alkyl, namely (C₆-C₁₀ aryl)-methyl, such as benzyl, 2-phenylethyl and 1-phenylethyl. Specific examples of (5- to 10-membered heteroaryl)-C₁-C₆ alkyl include (5- to 10-membered heteroaryl)-C₁-C₂ alkyl, namely (5- to 10-membered heteroaryl)-methyl such as pyridylmethyl, namely pyridin-2-ylmethyl, pyridin-3-ylmethyl, and pyridin-4-ylmethyl. Specific examples of "(3- to 10-membered non-aromatic heterocyclyl)-C₁-C₆ alkyl" include namely (3- to 10-membered non-aromatic heterocyclyl)-C₁-C₂ alkyl, (3- to 10-membered non-aromatic heterocyclyl)-methyl such as piperidylmethyl, namely piperidin-1-ylmethyl (i.e. piperidinomethyl), piperidin-2-ylmethyl, piperidin-3-ylmethyl, and piperidin-4-ylmethyl; piperazinylmethyl, namely piperazin-1-ylmethyl, and piperazin-2-ylmethyl; and morpholinylmethyl, namely morpholin-2-ylmethyl, morpholin-3-ylmethyl, and morpholin-4-ylmethyl (i.e. morpholinomethyl).

Specific examples of amino-C₁-C₆ alkyl include aminomethyl, 1-aminoethyl, 2-aminoethyl, 1-aminopropyl, 2-aminopropyl, 3-aminopropyl. Specific examples of (C₁-C₆ alkylamino)-C₁-C₆ alkyl include (methylamino)-C₁-C₆ alkyl such as (methylamino)methyl, 1-(methylamino)ethyl, 2-(methylamino)ethyl, 1-(methylamino)propyl, 2-

(methylamino)propyl, 3-(methylamino)propyl, and (C₁-C₆ alkylamino)-methyl such as (methylamino)methyl, (ethylamino)methyl, (propylamino)methyl, (isopropylamino)methyl, (butylamino)methyl, (isobutylamino)methyl, (sec-butylamino)methyl, (tert-butylamino)methyl, and (pentylamino)methyl, but are not limited thereto. Specific

5 examples of di(C₁-C₆ alkyl)amino-C₁-C₆ alkyl include (dimethylamino)-C₁-C₆ alkyl such as (dimethylamino)methyl, 1-(dimethylamino)ethyl, 2-(dimethylamino)ethyl, 1-(dimethylamino)propyl, 2-(dimethylamino)propyl, 3-(dimethylamino)propyl, and di(C₁-C₆ alkyl)amino-methyl such as (dimethylamino)methyl, (diethylamino)methyl, (dipropylamino)methyl, (diisopropylamino)methyl, (dibutylamino)methyl, (diisobutylamino)methyl, [di(sec-butyl)amino]-methyl, [(tert-butyl)amino]methyl, (dipentylamino)methyl, [ethyl(methyl)amino]methyl, [propyl(methyl)amino]methyl, [isopropyl(methyl)amino]methyl, [butyl(methyl)amino]methyl, [isobutyl(methyl)amino]methyl, [sec-butyl(methyl)amino]methyl, [tert-butyl(methyl)amino]methyl, and [pentyl(methyl)amino]methyl, but are not limited thereto.

10 Specific examples of amino-C₁-C₆ alkoxy include aminomethoxy, 1-aminoethoxy, 2-aminoethoxy, 1-aminopropoxy, 2-aminopropoxy, 3-aminopropoxy. Specific examples of (C₁-C₆ alkylamino)-C₁-C₆ alkoxy include (methylamino)-C₁-C₆ alkoxy such as (methylamino)methoxy, 1-(methylamino)ethoxy, 2-(methylamino)ethoxy, 1-(methylamino)propoxy, 2-(methylamino)propoxy, 3-(methylamino)propoxy, and (C₁-C₆ alkylamino)-methoxy such as (methylamino)methoxy, (ethylamino)methoxy, (propylamino)methoxy, (isopropylamino)methoxy, (butylamino)methoxy, (isobutylamino)methoxy, (sec-butylamino)methoxy, (tert-butylamino)methoxy, and (pentylamino)methoxy, but are not limited thereto. Specific examples of di(C₁-C₆ alkyl)amino-C₁-C₆ alkoxy include (dimethylamino)-C₁-C₆ alkoxy such as

15 (dimethylamino)methoxy, 1-(dimethylamino)ethoxy, 2-(dimethylamino)ethoxy, 1-(dimethylamino)propoxy, 2-(dimethylamino)propoxy, 3-(dimethylamino)propoxy, and di(C₁-C₆ alkyl)amino-methoxy such as (dimethylamino)methoxy, (diethylamino)methoxy, (dipropylamino)methoxy, (diisopropylamino)methoxy, (dibutylamino)methoxy,

20 (dimethylamino)methoxy, 1-(dimethylamino)ethoxy, 2-(dimethylamino)ethoxy, 1-(dimethylamino)propoxy, 2-(dimethylamino)propoxy, 3-(dimethylamino)propoxy, and di(C₁-C₆ alkyl)amino-methoxy such as (dimethylamino)methoxy, (diethylamino)methoxy, (dipropylamino)methoxy, (diisopropylamino)methoxy, (dibutylamino)methoxy,

25 (dimethylamino)methoxy, 1-(dimethylamino)ethoxy, 2-(dimethylamino)ethoxy, 1-(dimethylamino)propoxy, 2-(dimethylamino)propoxy, 3-(dimethylamino)propoxy, and di(C₁-C₆ alkyl)amino-methoxy such as (dimethylamino)methoxy, (diethylamino)methoxy, (dipropylamino)methoxy, (diisopropylamino)methoxy, (dibutylamino)methoxy,

(diisobutylamino)methoxy, [di(sec-butyl)amino]-methoxy, [di(tert-butyl)amino]methoxy, (dipentylamino)methoxy, [ethyl(methyl)amino]methoxy, [propyl(methyl)amino]methoxy, [isopropyl(methyl)amino]methoxy, [butyl(methyl)amino]methoxy, [isobutyl(methyl)amino]methoxy, [sec-butyl(methyl)amino]methoxy, [tert-butyl(methyl)amino]methoxy, and [pentyl(methyl)amino]methoxy, but are not limited thereto.

Specific examples of hydroxy-C₁-C₆ alkyl include hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropyl, 2-hydroxypropyl, 3-hydroxypropyl. Specific examples of (C₁-C₆ alkoxy)-C₁-C₆ alkyl include methoxy-C₁-C₆ alkyl such as methoxymethyl, 1-(methoxy)ethyl, 2-(methoxy)ethyl, 1-(methoxy)propyl, 2-(methoxy)propyl, 3-(methoxy)propyl, and (C₁-C₆ alkoxy)-methyl such as (methoxy)methyl, (ethoxy)methyl, (propoxy)methyl, (isopropoxy)methyl, (butoxy)methyl, (isobutoxy)methyl, (sec-butoxy)methyl, (tert-butoxy)methyl, and (pentoxy)methyl; but are not limited thereto.

Specific examples of carboxy-C₁-C₆ alkyl include carboxymethyl, 1-carboxyethyl, 2-carboxyethyl, 1-carboxypropyl, 2-carboxypropyl, and 3-carboxypropyl, but are not limited thereto. Specific examples of [(C₁-C₆ alkoxy)carbonyl]-C₁-C₆ alkyl include methoxycarbonyl-C₁-C₆ alkyl such as methoxycarbonyl-methyl, 1-(methoxycarbonyl)ethyl, 2-(methoxycarbonyl)ethyl, 1-(methoxycarbonyl)propyl, 2-(methoxycarbonyl)propyl, and 3-(methoxycarbonyl)propyl; and [(C₁-C₆ alkoxy)carbonyl]-methyl such as (methoxycarbonyl)methyl, 1-(methoxycarbonyl)ethyl, 2-(methoxycarbonyl)ethyl, 1-(methoxycarbonyl)propyl, 2-(methoxycarbonyl)propyl, and 3-(methoxycarbonyl)propyl; but are not limited thereto.

Specific examples of carbamoyl-C₁-C₆ alkyl include carbamoylmethyl, 1-carbamoylethyl, 2-carbamoylethyl, 1-carbamoylpropyl, 2-carbamoylpropyl, and 3-carbamoylpropyl, but are not limited thereto. Specific examples of [N-(C₁-C₆ alkyl)carbamoyl]-C₁-C₆ alkyl include N-methylcarbamoyl-C₁-C₆ alkyl such as N-methylcarbamoyl-methyl, 1-(N-methylcarbamoyl)ethyl, 2-(N-methylcarbamoyl)ethyl, 1-(methylcarbamoyl)propyl, 2-(N-methylcarbamoyl)propyl, and 3-(N-

methylcarbamoyl)propyl; and [N-(C₁-C₆ alkyl)carbamoyl]-methyl such as (N-methylcarbamoyl)methyl, (N-ethylcarbamoyl)methyl, (N-propylcarbamoyl)methyl, (N-isopropylcarbamoyl)methyl, (N-butylcarbamoyl)methyl, [N-(tert-butyl)carbamoyl]methyl and [N-(sec-butyl)carbamoyl]methyl; but are not limited thereto. Specific examples of

5 [N,N-di(C₁-C₆ alkyl)carbamoyl]-C₁-C₆ alkyl include (N,N-dimethylcarbamoyl)-C₁-C₆ alkyl such as (N,N-dimethylcarbamoyl)methyl, 1-(N,N-dimethylcarbamoyl)ethyl, 2-(N,N-dimethylcarbamoyl)ethyl, 1-(N,N-dimethyl carbamoyl)propyl, 2-(N,N-dimethylcarbamoyl)propyl, and 3-(N,N-dimethylcarbamoyl)propyl; and [N,N-di(C₁-C₆ alkyl)carbamoyl]-methyl such as (N,N-dimethyl carbamoyl)methyl, (N,N-

10 diethylcarbamoyl)methyl, (N,N-dipropylcarbamoyl)methyl, (N,N-diisopropylcarbamoyl)methyl, (N,N-dibutylcarbamoyl)methyl, (N,N-diisobutylcarbamoyl)methyl, [N,N-di(sec-butyl)carbamoyl]methyl, [N,N-di(tert-butyl)carbamoyl]methyl, (N,N-dipentylcarbamoyl)methyl, [N-ethyl-N-

(methyl)carbamoyl]methyl, [N-propyl-N-(methyl)carbamoyl]methyl, [N-isopropyl-N-

15 (methyl)carbamoyl]methyl, [N-butyl-N-(methyl)carbamoyl]methyl, [N-isobutyl-N-(methyl)carbamoyl]methyl, [N-sec-butyl-N-(methyl)carbamoyl]methyl, [N-tert-butyl-N-(methyl)carbamoyl]methyl, and [N-pentyl-N-(methyl)carbamoyl]methyl; but are not limited thereto.

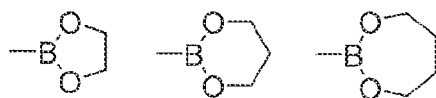
Specific examples of (C₁-C₆ alkyl)carbonylamino include methylcarbonylamino,

20 ethylcarbonylamino, propylcarbonylamino, isopropylcarbonylamino, butylcarbonylamino, isobutylcarbonylamino, sec-butylcarbonylamino, tert-butylcarbonylamino, and pentylcarbonylamino, but are not limited thereto. Specific examples of N-(C₁-C₆ alkyl)carbonyl-N-(C₁-C₆ alkyl)amino include N-acetyl-N-(C₁-C₆ alkyl)amino such as N-acetyl-N-methylamino, N-acetyl-N-ethylamino, N-acetyl-N-propylamino, N-acetyl-N-

25 isopropylamino, N-acetyl-N-butylamino, N-acetyl-N-isobutylamino, N-acetyl-N-sec-butylamino, N-acetyl-N-tert-butylamino, and N-acetyl-N-pentylamino; and N-(C₁-C₆ alkyl)carbonyl-N-(methyl)amino such as N-acetyl-N-(methyl)amino, N-ethylcarbonyl-N-(methyl)amino, N-propylcarbonyl-N-(methyl)amino, N-isopropylcarbonyl-N-

(methyl)amino, N-isobutylcarbonyl-N-(methyl)amino, N-tert-butylcarbonyl-N-(methyl)amino, N-butylcarbonyl-N-(methyl)amino, N-pentylcarbonyl-N-(methyl)amino, and N-hexylcarbonyl-N-(methyl)amino, but are not limited thereto.

Specific examples of 5- to 7-membered cyclic boronic acid ester are indicated by the following formulae:



Pharmaceutically acceptable salts of compound (I) mean, for example, pharmaceutically acceptable acid-added salts, amino acid-added salts, or such. Specific examples of the pharmaceutically acceptable acid-added salts of compound (I) include inorganic acid salts such as hydrochloride, sulfate, and phosphate, organic acid salts such as acetate, maleate, fumarate, citrate, and such, and examples of pharmaceutically acceptable amino acid-added salts include addition salts such as of lysine, glycine, phenylalanine, asparagine acid, or glutamic acid. Particularly, Pharmaceutically acceptable salts of compound (I) include hydrochloride salt, dihydrochloride salt, and trihydrochloride salt.

Examples of diseases involving overexpression of MELK, which may be treated and/or prevented by pharmaceutical compositions comprising as an active ingredient a compound or a pharmaceutically acceptable salt thereof of the present invention, include cancer, breast cancer, bladder cancer, cervical cancer, cholangiocellular carcinoma, chronic myeloid leukemia (CML), colorectal cancer, endometriosis, esophagus cancer, gastric cancer, liver cancer, non-small cell lung cancer (NSCLC), lymphoma, osteosarcoma, ovarian cancer, pancreatic cancer, prostate cancer, renal carcinoma and small cell lung cancer (SCC), but are not limited thereto. Examples of the cancer which may be treated and/or prevented include breast cancer, bladder cancer, cervical cancer, cholangiocellular carcinoma, CML, colorectal cancer, endometriosis, esophagus cancer, gastric cancer, liver cancer, NSCLC, lymphoma, osteosarcoma, ovarian cancer, pancreatic cancer, prostate cancer, renal carcinoma and SCC, but are not limited thereto.

Compound (I) includes compounds which may have stereoisomers such as regioisomers, geometrical isomers, optical isomers, and tautomers, and all possible isomers including them and mixtures thereof are included in the present invention.

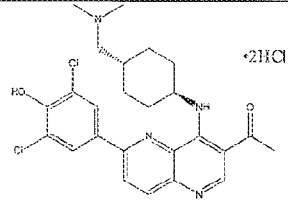
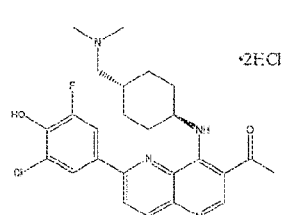
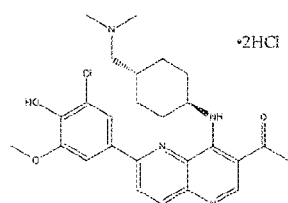
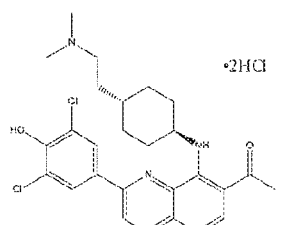
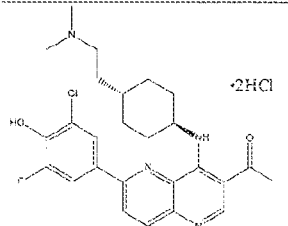
Compound (I) also includes compounds having one or more minor stable isotopes
5 or radio isotopes such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O and the like, which can be prepared in line with conventional procedures for preparing a compound with one or more isotopes indicated above.

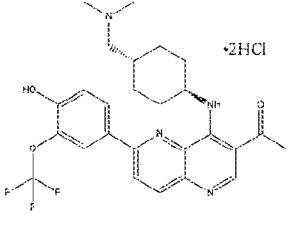
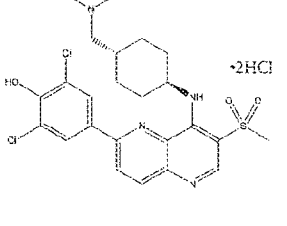
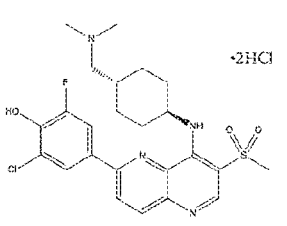
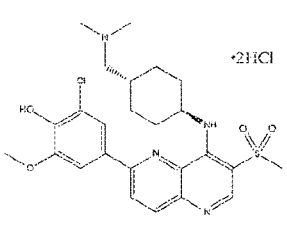
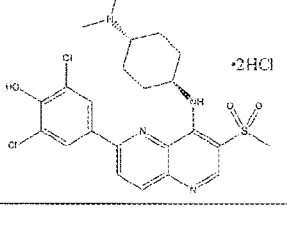
Furthermore, compound (I) and pharmaceutically acceptable salts thereof may exist in a form of solvate with water (hydrate) or various other solvents, and these solvates are
10 also included in the present invention.

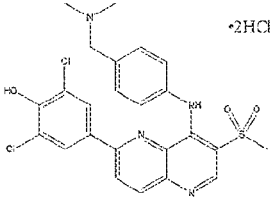
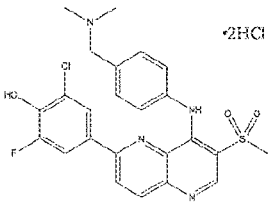
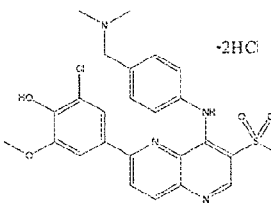
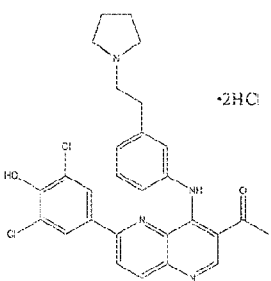
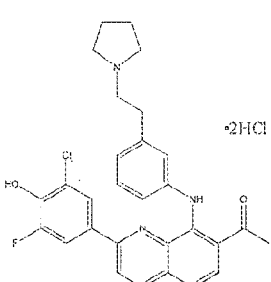
Specific examples of Compound (I) of the present invention are shown in Table 1. However, compounds of the present invention are not limited thereto.

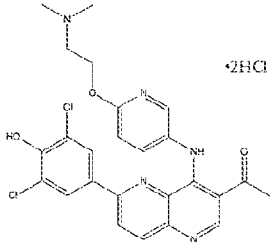
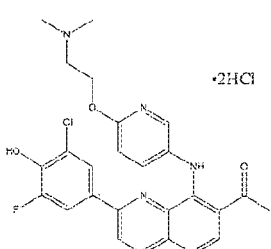
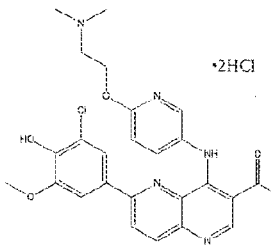
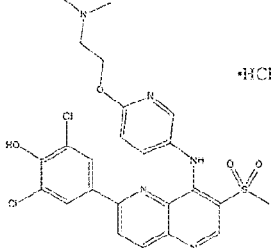
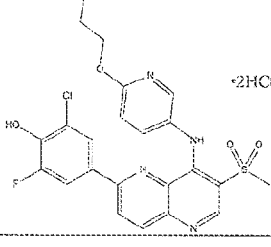
Table 1

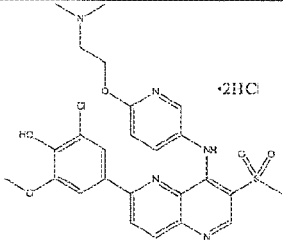
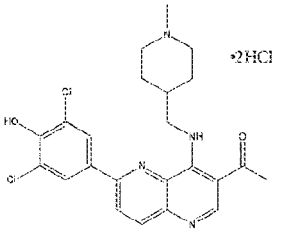
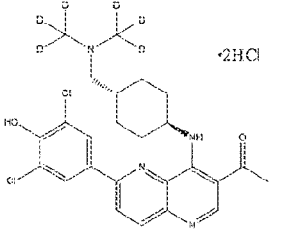
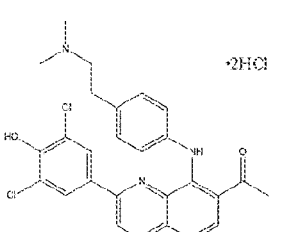
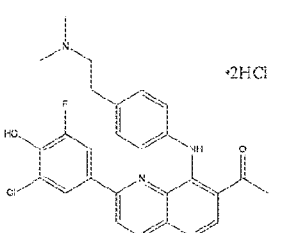
Example No.	Structure	Name	ESI MS (m/z)
1		1-(6-Chloro-4-{trans-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)-ethanone	361.1
2		1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-[(trans-4-(dimethylamino)cyclohexylamino]-1,5-naphthyridin-3-yl)ethanone dihydrochloride	473.1
3		1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-[(trans-4-(dimethylamino)cyclohexylamino]-1,5-naphthyridin-3-yl)ethanone dihydrochloride	457.1
4		Cyclopropyl(6-(3,5-dichloro-4-hydroxyphenyl)-4-[(trans-4-[(dimethylamino)methyl]cyclohexylamino]-1,5-naphthyridin-3-yl)methanone dihydrochloride	513.1
5		(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-[(trans-4-[(dimethylamino)methyl]cyclohexylamino]-1,5-naphthyridin-3-yl)(cyclopropyl)methanone dihydrochloride	497.1

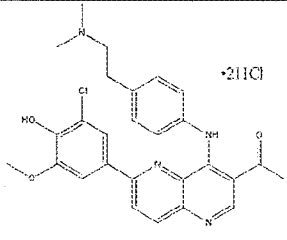
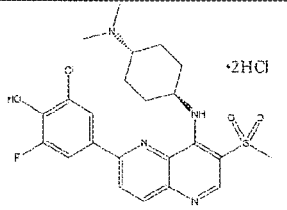
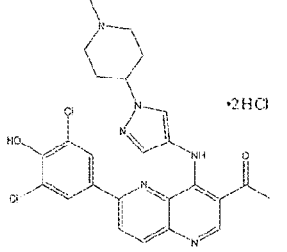
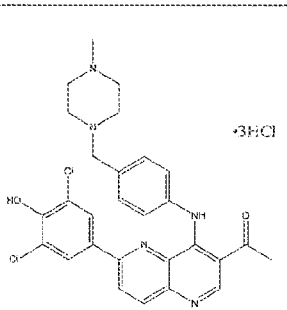
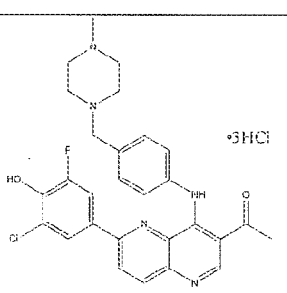
6		1-({6-(3,5-Dichloro-4-hydroxyphenyl)-4-((trans-4-[(dimethylamino)methyl]-cyclohexyl)amino)-1,5-naphthyridin-3-yl}ethanone dihydrochloride	487.1
7		1-({6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-((trans-4-[(dimethylamino)methyl]cyclohexyl)-amino)-1,5-naphthyridin-3-yl}ethanone dihydrochloride	471.2
8		1-({6-(3-Chloro-4-hydroxy-5-methoxyphenyl)-4-((trans-4-[(dimethylamino)methyl]cyclohexyl)-amino)-1,5-naphthyridin-3-yl}ethanone dihydrochloride	483.2
9		1-({6-(3,5-Dichloro-4-hydroxyphenyl)-4-((trans-4-[2-(dimethylamino)ethyl]-cyclohexyl)amino)-1,5-naphthyridin-3-yl}ethanone dihydrochloride	501.1
10		1-({6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-((trans-4-[2-(dimethylamino)-ethyl]cyclohexylamino)-1,5-naphthyridin-3-yl}ethanone dihydrochloride	485.1

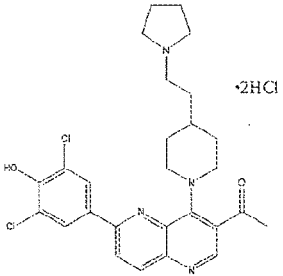
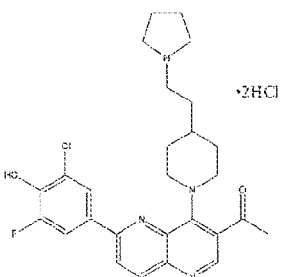
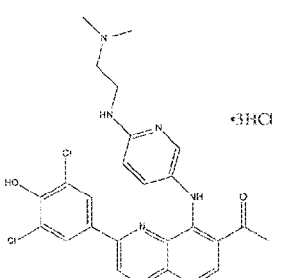
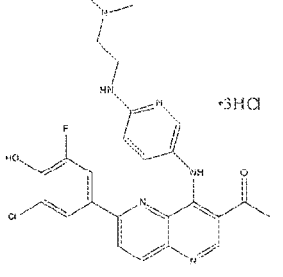
11		1-(4-{trans-4-[(dimethylamino)methyl]-cyclohexylamino}-6-{4-hydroxy-3-(trifluoromethoxy)-phenyl}-1,5-naphthyridin-3-yl)ethanone dihydrochloride	503.1
12		2,6-Dichloro-4-{8-[trans-4-[(dimethylamino)methyl]-cyclohexylamino]-7-(methylsulfonyl)-1,5-naphthyridin-2-yl}phenol dihydrochloride	523.1
13		6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-{trans-4-[(dimethylamino)methyl]cyclohexylamino}-3-methylsulfonyl-1,5-naphthyridine dihydrochloride	507.1
14		6-(3-Chloro-4-hydroxy-5-methoxyphenyl)-4-{trans-4-[(dimethylamino)methyl]cyclohexylamino}-3-methylsulfonyl-1,5-naphthyridine dihydrochloride	519.1
15		2,6-Dichloro-4-{8-[trans-4-(dimethylamino)cyclohexylamino]-7-(methylsulfonyl)-1,5-naphthyridin-2-yl}phenol dihydrochloride	509.1

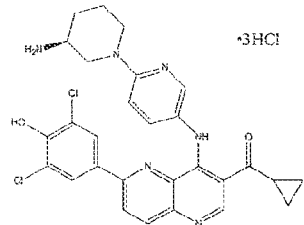
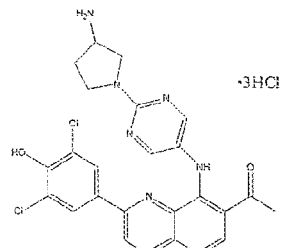
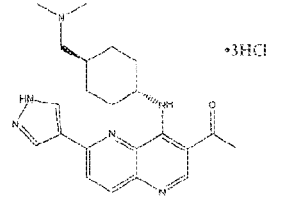
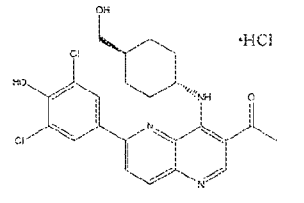
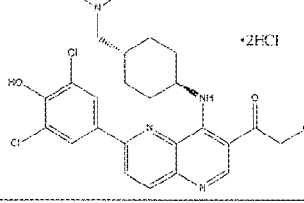
16		2,6-Dichloro-4-(8-((4-((dimethylamino)methyl)phenylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)phenol) dihydrochloride	517.1
17		2-Chloro-4-(8-((4-((dimethylamino)methyl)phenylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-fluorophenol) dihydrochloride	501.0
18		2-Chloro-4-(8-((4-((dimethylamino)methyl)phenylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-methoxyphenol) dihydrochloride	513.1
19		1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-(3-(2-(pyrrolidin-1-yl)ethyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	521.1
20		1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-(3-(2-(pyrrolidin-1-yl)ethyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	505.2

21		1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-(6-(2-(dimethylamino)ethoxy)pyridin-3-ylamino)-1,5-naphthyridin-3-yl) ethanone dihydrochloride	512.1
22		1-(6-(3-Chloro-5-fluoro-4-hydroxy-phenyl)-4-(6-(2-(dimethylamino)ethoxy)-pyridin-3-ylamino)-1,5-naphthyridin-3-yl) ethanone dihydrochloride	496.1
23		1-(6-(3-Chloro-4-hydroxy-5-methoxy-phenyl)-4-(6-(2-(dimethylamino)ethoxy)-pyridin-3-ylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	508.1
24		2,6-Dichloro-4-(8-(6-(2-(dimethylamino)ethoxy)pyridin-3-ylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-phenol hydrochloride	548.0
25		2-Chloro-4-(8-(6-(2-(dimethylamino)-ethoxy)pyridin-3-ylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-fluorophenol dihydrochloride	532.1

26		2-Chloro-4-(8-(6-(2-(dimethylamino)ethoxy)pyridin-3-ylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-methoxyphenol dihydrochloride	544.2
27		1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-((1-methylpiperidin-4-yl)methylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	459.2
28		1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-(trans-4-((dimethylamino-d ₆)methyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	493.2
29		1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-(4-(2-(dimethylamino)ethyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	495.1
30		1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(4-(2-(dimethylamino)ethyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	479.1

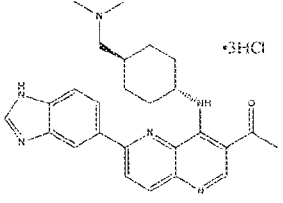
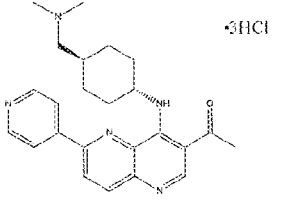
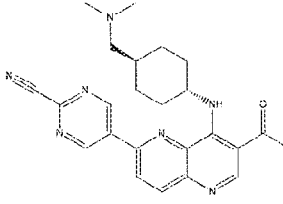
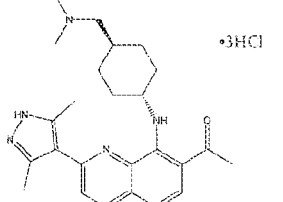
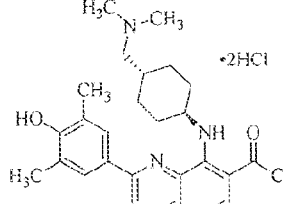
31		1-(6-(3-Chloro-4-hydroxy-5-methoxyphenyl)-4-(2-(dimethylamino)ethyl)phenylamino)-1,5-naphthyridin-3-yl ethanone dihydrochloride	491.1
32		2-Chloro-4-(8-(trans-4-(dimethylamino)cyclohexylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-fluorophenol dihydrochloride	493.0
33		1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-(1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-ylamino)-1,5-naphthyridin-3-yl) ethanone dihydrochloride	511.1
34		1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-(4-(4-methylpiperazin-1-yl)methyl)phenylamino)-1,5-naphthyridin-3-yl) ethanone trihydrochloride	536.1
35		1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-(4-(4-methylpiperazin-1-yl)methyl)phenylamino)-1,5-naphthyridin-3-yl) ethanone trihydrochloride	520.1

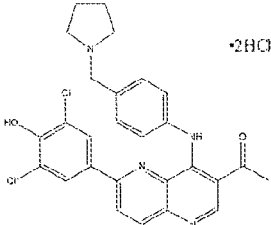
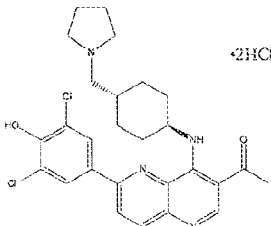
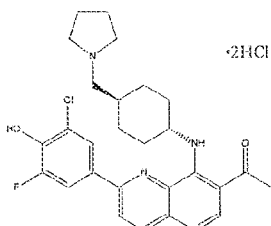
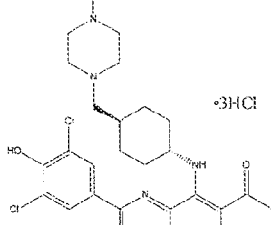
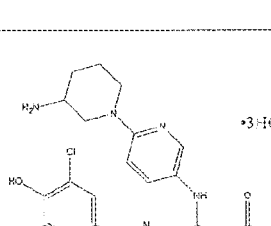
36		1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-(4-(2-(pyrrolidin-1-yl)ethyl)piperidin-1-yl)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	513.2
37		1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-(4-(2-(pyrrolidin-1-yl)ethyl)piperidin-1-yl)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	497.1
38		1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-(6-(2-(dimethylamino)ethylamino)pyridin-3-ylamino)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	511.1
39		1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-(6-(2-(dimethylamino)ethylamino)pyridin-3-ylamino)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	495.1

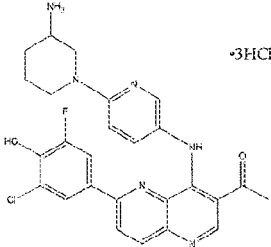
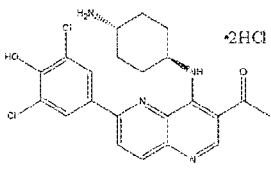
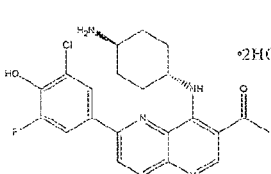
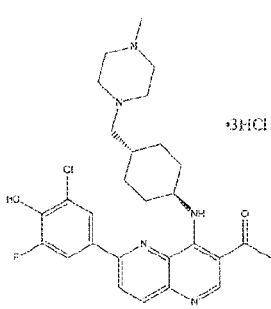
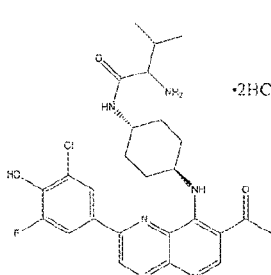
40		(S)-4-(6-(3-Aminopiperidin-1-yl)-pyridin-3-ylamino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl(cyclopropyl) methanone trihydrochloride	549.1
41		1-(4-(2-(3-Aminopyrrolidin-1-yl)-pyrimidin-5-ylamino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	510.1
42		1-(4-(trans-4-((Dimethylamino)methyl)-cyclohexylamino)-6-(1H-pyrazol-4-yl)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	393.2
43		1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-[trans-4-(hydroxymethyl)cyclohexyl]-amino)-1,5-naphthyridin-3-yl) ethanone hydrochloride	460.1
44		1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4-{trans-4-[(dimethylamino)methyl]-cyclohexylamino}-1,5-naphthyridin-3-yl]-2-hydroxyethanone dihydrochloride	503.1

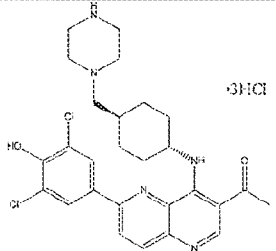
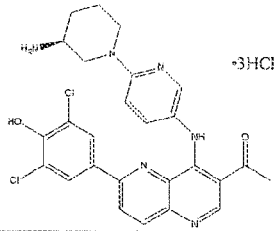
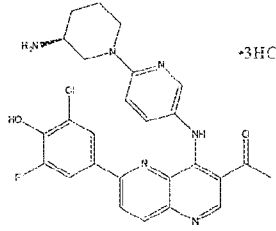
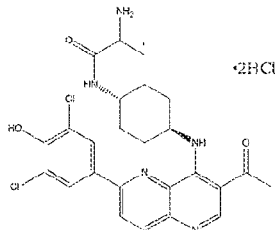
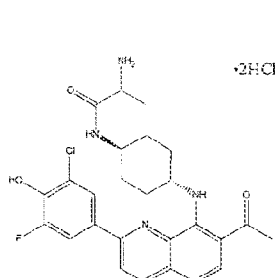
45		1-{6-(3,5-Dichloro-4-hydroxyphenyl)-4-[(1-methylpiperidin-4-yl)amino]-1,5-naphthyridin-3-yl}ethanone	445.1
46		1-{6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-[(1-methylpiperidin-4-yl)amino]-1,5-naphthyridin-3-yl}ethanone	429.0
47		1-{6-(3,5-Dichloro-4-hydroxyphenyl)-4-[[trans-4-(morpholinomethyl)-cyclohexyl]amino]-1,5-naphthyridin-3-yl}ethanone	529.1
48		1-{6-(3,5-Dichloro-4-hydroxyphenyl)-4-[(trans-4-{{(2-hydroxyethyl)-(methyl)amino}methyl)-cyclohexylamino]-1,5-naphthyridin-3-yl}ethanone dihydrochloride	517.1
49		1-{6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-[(trans-4-{{(2-hydroxyethyl)-(methyl)amino}methyl)-cyclohexylamino]-1,5-naphthyridin-3-yl}ethanone dihydrochloride	500.1

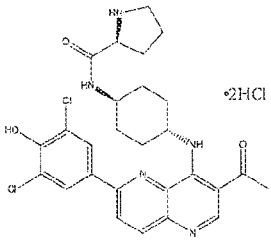
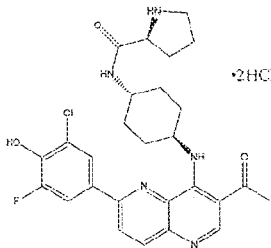
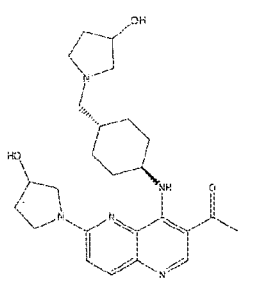
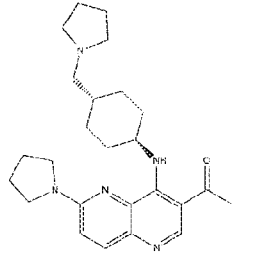
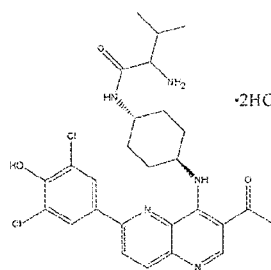
50		1-(6-(3,5-Difluoro-4-hydroxyphenyl)-4- {trans-4-[(dimethylamino)methyl]- cyclohexylamino}-1,5-naphthyridin-3- yl)ethanone dihydrochloride	455.1
51		1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4- {6-[3-(dimethylamino)pyrrolidin-1-yl]- pyridin-3-ylamino}-1,5-naphthyridin-3- yl) ethanone trihydrochloride	537.3
52		1-(6-(3-Chloro-5-fluoro-4-hydroxy- phenyl)-4-((6-[3-(dimethylamino)- pyrrolidin-1-yl]pyridin-3-ylamino)-1,5- naphthyridin-3-yl)ethanone trihydrochloride	521.3
53		1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4- {6-[3-(methylamino)pyrrolidin-1-yl]- pyridin-3-ylamino}-1,5-naphthyridin-3- yl) ethanone trihydrochloride	523.1
54		1-(6-(3-Chloro-5-fluoro-4-hydroxy- phenyl)-4-((6-[3-(methylamino)- pyrrolidin-1-yl]pyridin-3-ylamino)-1,5- naphthyridin-3-yl) ethanone trihydrochloride	507.0

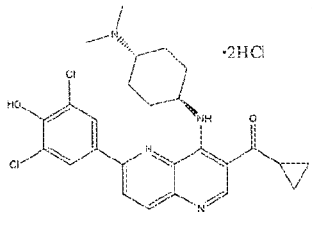
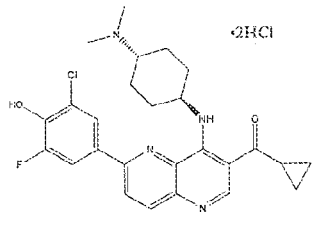
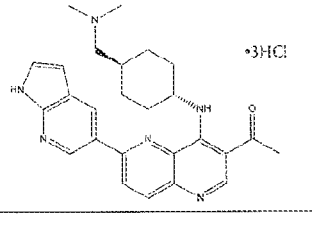
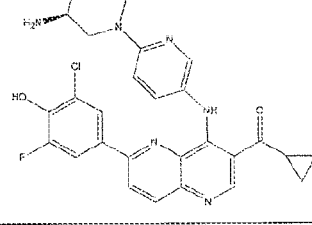
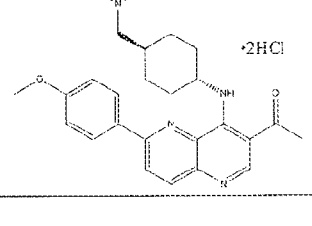
55		1-(6-(1H-Benzo[d]imidazol-5-yl)-4-{trans-4-[(dimethylamino)methyl]-cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone trihydrochloride	443.3
56		1-(4-[4-(trans-4-Dimethylamino)methylcyclohexylamino]-6-(pyridin-4-yl)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	404.2
57		5-(7-Acetyl-8-{trans-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-2-yl)pyrimidine-2-carbonitrile	430.2
58		1-(6-(3,5-Dimethyl-1H-pyrazol-4-yl)-4-{trans-4-[(dimethylamino)methyl]-cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone trihydrochloride	421.3
59		1-(4-{trans-4-[(Dimethylamino)methyl]-cyclohexylamino}-6-(4-hydroxy-3,5-dimethylphenyl)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	447.3

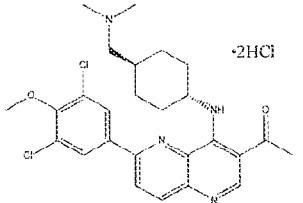
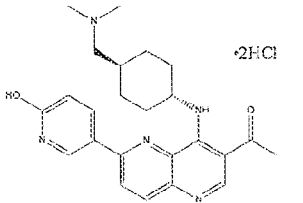
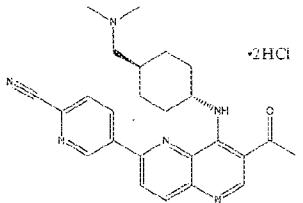
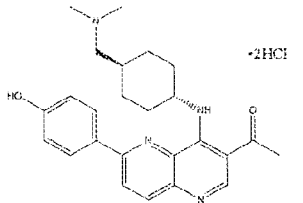
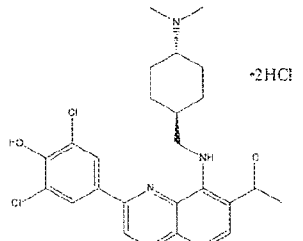
60		1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-{6-[3-(dimethylamino)pyrrolidin-1-yl]pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone dihydrochloride	507.2
61		1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-[trans-4-(pyrrolidin-1-ylmethyl)cyclohexylamino]-1,5-naphthyridin-3-yl)ethanone dihydrochloride	513.1
62		1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-{[trans-4-(pyrrolidin-1-ylmethyl)cyclohexyl]amino}-1,5-naphthyridin-3-yl)ethanone dihydrochloride	497.4
63		1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-{trans-4-[(4-methylpiperazin-1-yl)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone trihydrochloride	542.2
64		1-(4-{[6-(3-Aminopiperidin-1-yl)pyridin-3-yl]amino}-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	523.1

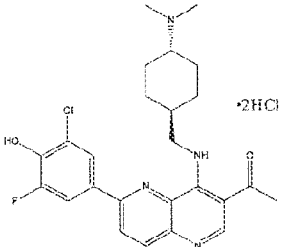
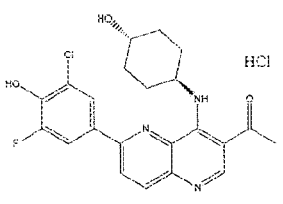
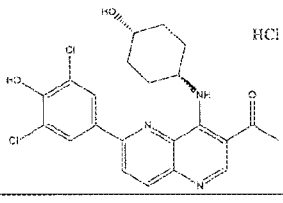
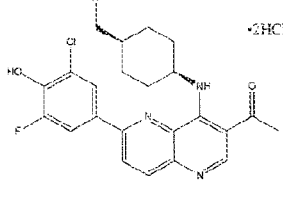
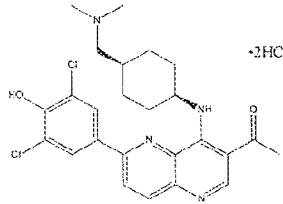
65		1-(4-([6-(3-Aminopiperidin-1-yl)pyridin-3-yl]amino)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	507.0
66		1-(4-[trans-(4-Aminocyclohexyl)amino]-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)-ethanone dihydrochloride	445.1
67		1-(4-[trans-(4-Aminocyclohexyl)amino]-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)-ethanone dihydrochloride	429.1
68		1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-([trans-4-[(4-methylpiperazin-1-yl)methyl]cyclohexylamino]-1,5-naphthyridin-3-yl)ethanone trihydrochloride	526.3
69		N-(trans-4-([3-Acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl]amino)-cyclohexyl)-2-amino-3-methylbutanamide dihydrochloride	528.2

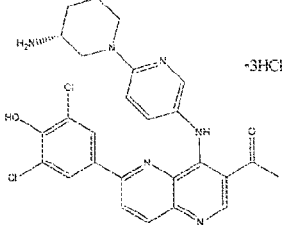
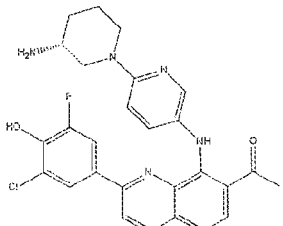
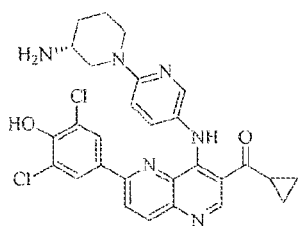
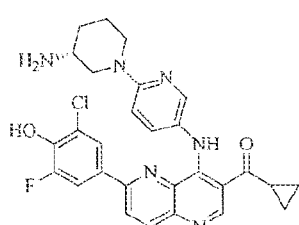
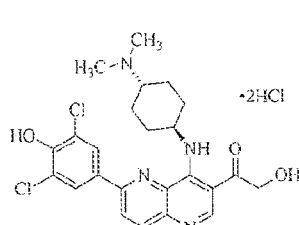
70		1-({6-(3,5-Dichloro-4-hydroxyphenyl)-4-[trans-4-(piperazin-1-ylmethyl)cyclohexylamino]-1,5-naphthyridin-3-yl}ethanone trihydrochloride	528.1
71		(S)-1-(4-({6-(3-Aminopiperidin-1-yl)pyridin-3-yl}amino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	523.1
72		(S)-1-(4-({6-(3-Aminopiperidin-1-yl)pyridin-3-yl}amino)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	507.1
73		N-({trans-4-[3-Acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino]-cyclohexyl}-2-aminopropanamide dihydrochloride	516.1
74		N-({4-[3-Acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino]-cyclohexyl}-2-aminopropanamide dihydrochloride	500.5

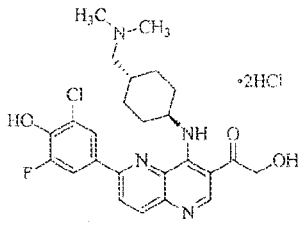
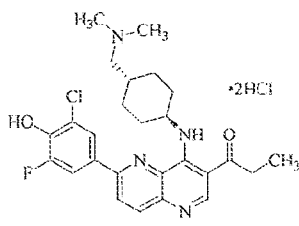
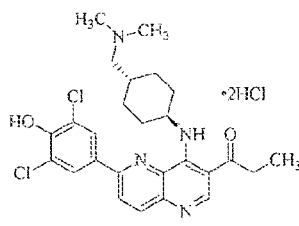
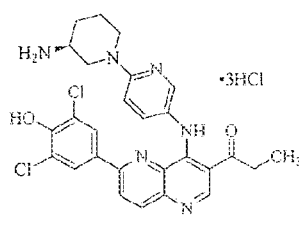
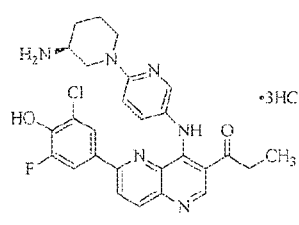
75		(S)-N-{4-[3-Acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-trans-4-ylamino]-cyclohexyl}pyrrolidine-2-carboxamide dihydrochloride	542.1
76		(S)-N-{4-[3-Acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-trans-4-ylamino]cyclohexyl}pyrrolidine-2-carboxamide dihydrochloride	527.1
77		1-(6-(3-Hydroxypyrrolidin-1-yl)-4-[(trans-4-[(3-hydroxypyrrolidin-1-yl)methyl]-cyclohexylamino)-1,5-naphthyridin-3-yl]ethanone	454.2
78		1-{6-(Pyrrolidin-1-yl)-4-[(trans-4-(pyrrolidin-1-ylmethyl)cyclohexylamino)-1,5-naphthyridin-3-yl]ethanone	422.2
79		N-{trans-4-[3-Acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino]-cyclohexyl}-2-amino-3-methylbutanamide dihydrochloride	544.1

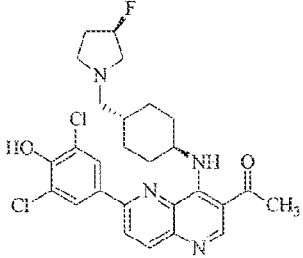
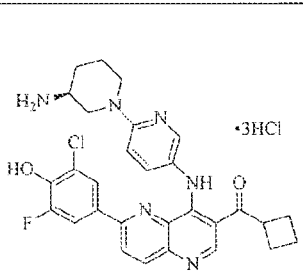
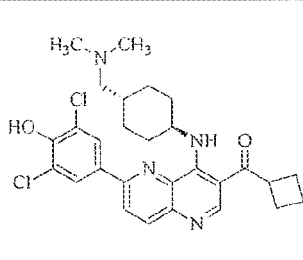
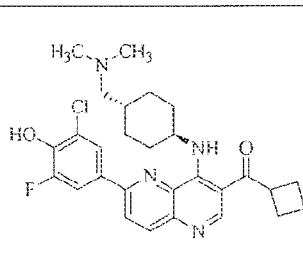
80		Cyclopropyl{6-(3,5-dichloro-4-hydroxyphenyl)-4-[trans-4-(dimethylamino)-cyclohexylamino]-1,5-naphthyridin-3-yl}methanone dihydrochloride	499.1
81		1-[6-(3-Chloro-5-fluoro-4-methoxyphenyl)-4-{trans-4-[(dimethylamino)methyl]-cyclohexylamino}-1,5-naphthyridin-3-yl]ethanone dihydrochloride	483.1
82		1-(4-{trans-4-[(Dimethylamino)methyl]-cyclohexylamino}-6-(1H-pyrrolo[2,3-b]pyridin-5-yl)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	443.2
83		(S)-{4-[6-(3-Aminopiperidin-1-yl)-pyridin-3-ylamino]-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}(cyclopropyl) methanone	533.1
84		1-(4-{trans-4-[(Dimethylamino)methyl]-cyclohexylamino}-6-(4-methoxyphenyl)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	433.2

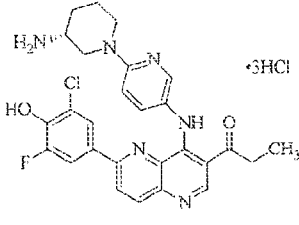
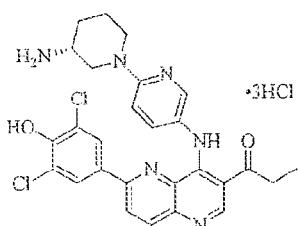
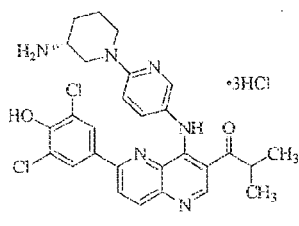
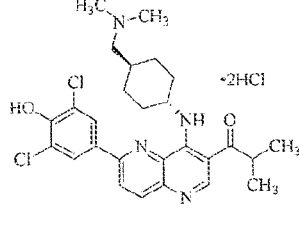
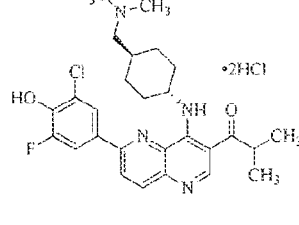
85		1-[6-(3,5-Dichloro-4-methoxyphenyl)-4-{trans-4-[(dimethylamino)methyl]-cyclohexylamino}-1,5-naphthyridin-3-yl]ethanone dihydrochloride	501.1
86		1-(4-{trans-4-[(Dimethylamino)methyl]-cyclohexylamino}-6-(6-hydroxypyridin-3-yl)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	420.2
87		5-(7-Acetyl-8-{trans-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-2-yl)picolinonitrile dihydrochloride	429.3
88		1-(4-{trans-4-[(Dimethylamino)methyl]-cyclohexylamino}-6-(4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	419.2
89		1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4-{[trans-4-(dimethylamino)cyclohexyl]-methylamino}-1,5-naphthyridin-3-yl]ethanone dihydrochloride	487.1

90		1-{6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-[(trans-4-(dimethylamino)cyclohexyl)methylamino]-1,5-naphthyridin-3-yl} ethanone dihydrochloride	471.1
91		1-{6-(3,5-Dichloro-4-hydroxyphenyl)-4-(trans-4-hydroxycyclohexylamino)-1,5-naphthyridin-3-yl} ethanone hydrochloride	430.1
92		1-{6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-(trans-4-hydroxycyclohexylamino)-1,5-naphthyridin-3-yl} ethanone hydrochloride	446.1
93		1-{6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-[(cis-4-[(dimethylamino)methyl]cyclohexyl)amino]-1,5-naphthyridin-3-yl} ethanone dihydrochloride	471.2
94		1-{6-(3,5-Dichloro-4-hydroxyphenyl)-4-[(cis-4-[(dimethylamino)methyl]cyclohexyl)amino]-1,5-naphthyridin-3-yl} ethanone dihydrochloride	487.1

95		(R)-1-{4-[6-(3-Aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}ethanone trihydrochloride	523.3
96		(R)-1-{4-[6-(3-Aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}ethanone	507.1
201		(R)-4-[[6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino]-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl (cyclopropyl)methanone	549.1
202		(R)-4-[[6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino]-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl (cyclopropyl)methanone	533.1
203		1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-[[trans-4-(dimethylamino)cyclohexyl]amino]-1,5-naphthyridin-3-yl]-2-hydroxyethanone dihydrochloride	489.1

204		1-[6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-((trans-4-[(dimethylamino)methyl]cyclohexyl)amino)-1,5-naphthyridin-3-yl]-2-hydroxyethanone dihydrochloride	487.2
205		1-[6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-((trans-4-[(dimethylamino)methyl]cyclohexyl)amino)-1,5-naphthyridin-3-yl]propan-1-one dihydrochloride	484.5
206		1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-((trans-4-[(dimethylamino)methyl]cyclohexyl)amino)-1,5-naphthyridin-3-yl]propan-1-one dihydrochloride	501.2
207		(S)-1-(4-({6-(3-aminopiperidin-1-yl)pyridin-3-yl}amino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)propan-1-one trihydrochloride	537.0
208		(S)-1-(4-({6-(3-aminopiperidin-1-yl)pyridin-3-yl}amino)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)propan-1-one trihydrochloride	521.0

209		1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-({4-[(R)-3-fluoropyrrolidin-1-yl)methyl] cyclohexyl}amino)-1,5-naphthyridin-3-yl]ethanone dihydrochloride	531.0
210		(S)-4-((6-(3-aminopiperidin-1-yl)pyridin-3-yl)amino)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl(cyclobutyl)methanone dihydrochloride	547.2
211		(6-(3,5-dichloro-4-hydroxyphenyl)-4-((4-((dimethylamino)methyl)cyclohexyl)amino)-1,5-naphthyridin-3-yl)(cyclobutyl)methanone dihydrochloride	527.1
212		(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-((4-((dimethylamino)methyl)cyclohexyl)amino)-1,5-naphthyridin-3-yl)(cyclobutyl)methanone dihydrochloride	511.1

213		(S)-4-({6-(3-aminopiperidin-1-yl)pyridin-3-yl}amino)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl(cyclobutyl)methanone	521.0
214		(R)-1-(4-((6-(3-aminopiperidin-1-yl)pyridin-3-yl)amino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)propan-1-one trihydrochloride	537.0
215		(R)-1-(4-({6-(3-aminopiperidin-1-yl)pyridin-3-yl}amino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)-2-methylpropan-1-one trihydrochloride	535.1
216		1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-({trans-4-[(dimethylamino)methyl]cyclohexyl}amino)-1,5-naphthyridin-3-yl]-2-methylpropan-1-one dihydrochloride	515.1
217		1-[6-chloro-4-({trans-4-[(dimethylamino)methyl]cyclohexyl}amino)-1,5-naphthyridin-3-yl]-2-methylpropan-1-one dihydrochloride	498.9

Compound (I) and pharmaceutically acceptable salts thereof may be administered singly as they are; however, ordinarily, they are desirably provided as various types of pharmaceutical formulations. Such pharmaceutical formulations are used for animals or humans.

5 Pharmaceutical formulations of the present invention may comprise as an active ingredient compound (I) or a pharmaceutically acceptable salt thereof alone, or a mixture with any other active ingredients for treatment. Furthermore, these pharmaceutical formulations are produced by any methods well known in the technical field of drug formulation by mixing the active ingredient together with one or more types of
10 pharmaceutically acceptable carriers (for example, diluents, solvents, and excipients).

Desirably, the route of administration most effective for the treatment is used, and examples include oral route, or parenteral route such as intravenous route.

The form of administration is, for example, tablets and injections.

Tablets are appropriate for oral administration and can be produced using
15 excipients such as lactose, disintegrants such as starch, lubricants such as magnesium stearate, and binders such as hydroxypropylcellulose.

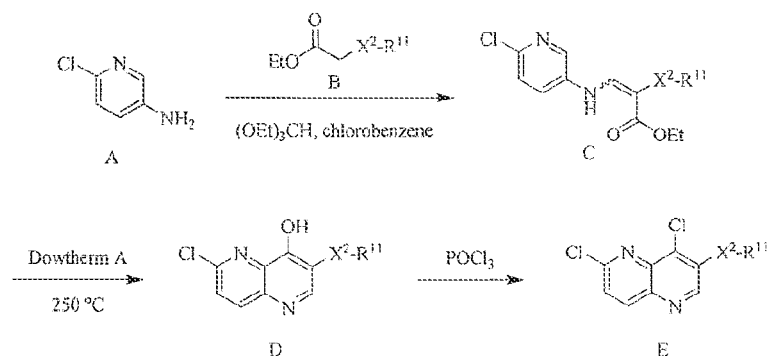
Injections are appropriate for parenteral administration, and can be produced using, for example, solvents or diluents such as salt solutions, glucose solutions, or a mixture of salt water and glucose solution.

20 The dose of compound (I) or a pharmaceutically acceptable salt thereof, and the number of doses differ depending on the form of administration, the age and body weight of the patient, the nature of the symptom to be treated or severity, and such, but ordinarily for oral administration, it is 0.01 mg to 1000 mg, preferably in the range of 0.05 mg to 100 mg for an adult, and it is administered once to several times a day. In the case of parenteral
25 administration such as intravenous administration, 0.001 mg to 1000 mg, or preferably 0.01 mg to 100 mg is administered to an adult once to several times a day. However, these doses and the number of doses vary depending on the various conditions mentioned above.

General methods for producing the above-mentioned compounds will be indicated

below.

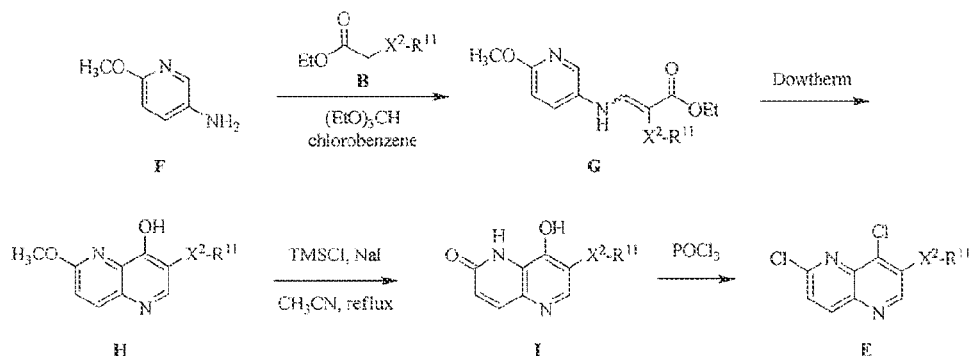
Scheme 1



The formula $-X^2-R^{11}$ is defined hereinbefore, such as (C₁-C₆ alkyl)carbonyl, (C₃-C₁₀ cycloalkyl)carbonyl, (C₁-C₆ alkyl)sulfonyl, and (C₃-C₁₀ cycloalkyl)sulfonyl, wherein the alkylcarbonyl, cycloalkyl)carbonyl, alkylsulfonyl, and cycloalkylsulfonyl are optionally substituted with one or more halogen atoms. Specific examples of $-X^2-R^{11}$ include acetyl, ethylcarbonyl, cyclopropylcarbonyl, methylsulfonyl, ethylsulfonyl, cyclopropylsulfonyl, chloroacetyl, 1-chloroethylcarbonyl, 2-chloroethylcarbonyl, chlorocyclopropylcarbonyl, chloromethylsulfonyl, 1-chloroethylsulfonyl, 2-chloroethylsulfonyl, and chlorocyclopropylsulfonyl.

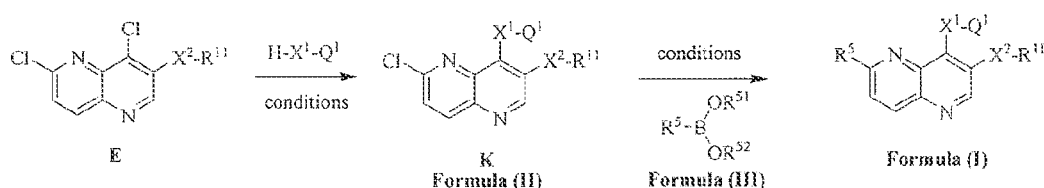
The 2-chloro-5-aminopyridine **A** is converted by heating in the presence of ester **B** and triethyl orthoformate to the condensation product **C** as a mixture of olefin isomers (Scheme 1). Various esters that are commercially available, known in the literature or prepared using known literature procedures are applicable to the reaction. Intermediate **C** is added to hot DowthermTM A to facilitate the ring closure and to afford the 1,5-naphthyridine **D**. Treatment of **D** with phosphorus oxychloride affords the key intermediate **E** (Scheme 1).

Scheme 2



An alternative synthetic sequence to obtain the key intermediate **E** is described in Scheme 2. Commercially available 2-methoxy-5-aminopyridine **F** is converted by heating in the presence of ester **B** and triethyl orthoformate to the condensation product **G** as a mixture of olefin isomers (Scheme 2). Intermediate **G** is added to hot Dowtherm™ **A** to facilitate the ring closure and to yield the 1,5-naphthyridine **H**. Demethylation at the 6-position of **H** is conducted by treatment with trimethylsilyl chloride and sodium iodide in refluxing acetonitrile to give intermediate **I**, which may be used, without purification, for the reaction with phosphorus oxychloride to provide the key intermediate **E** (Scheme 2).

Scheme 3



15

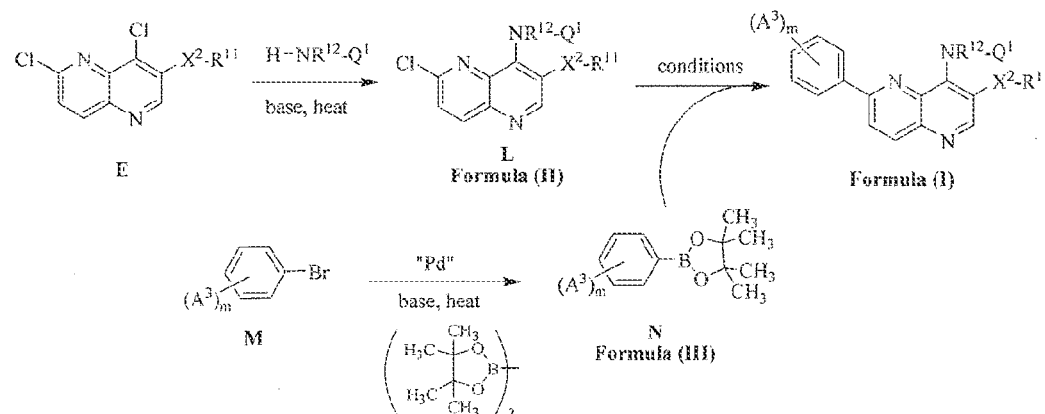
The formula $\text{-X}^1\text{-Q}^1$ is defined hereinbefore, such as $\text{C}_5\text{-C}_7$ cycloalkylamino, phenylamino, pyridylamino, pyrazolylamino, pyrimidinylamino, piperidyl amino, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, and morpholin-1-yl, which are optionally substituted with one or more substituents independently selected from A^1 as defined

hereinbefore.

The formula $-R^5$ as defined hereinbefore other than a halogen atom, such as C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein the cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A^3 as defined hereinbefore. Specific examples of R^5 include phenyl substituted with one or three substituents independently selected from A^3 , such as 3,5-dichloro-4-hydroxyphenyl, 3,5-difluoro-4-hydroxyphenyl, and 3-chloro-5-fluoro-4-hydroxyphenyl.

The preparation of the target compounds is described in Scheme 3. Intermediate **E** is reacted at the 4-position with a compound defined as $H-X^1-Q^1$ to introduce a substituent indicated as X^1-Q^1 . The resulting intermediate **L**, which belongs to compounds categorized by Formula (II), is reacted at the 6-position with $R^5-B(OR^{51})OR^{52}$, a compound categorized by Formula (III) to introduce a substituent indicated as R^5 .

Scheme 4



To introduce an amino group at the 4-position of the 1,5-naphthyridine ring, **E** is heated with an appropriate amine in the presence of base to afford intermediate **L**, belonging to Formula (II) (Scheme 4). Various amines that are commercially available, known in the literature or prepared using known literature procedures are applicable to the reaction. Intermediate **L** is subjected to a standard Suzuki cross-coupling reaction with a

boronate ester N to provide compounds belonging to Formula (1). Various boronate esters that are commercially available, known in the literature or prepared using known literature procedures are applicable to the reaction. In scheme 4, the boronate ester N is prepared by reacting an aryl bromide M with bis(pinacolato)diboron in the presence of an organopalladium to provide compounds belonging to Formula (1). If necessary, a protecting group removal is conducted after the Suzuki reaction to obtain the target compound.

In Scheme 4, A³ represents a optional substituent on the benzene ring as defined hereinbefore, and m represents an integer selected from 0 to 5, preferably selected from 1 to

10 3.

The intermediates and compounds of interest in the following Examples can be isolated and purified by subjecting them to separation and purification methods commonly used in synthetic organic chemistry unless otherwise specified, and examples include filtration, extraction, washing, drying, concentration, recrystallization, and various types of chromatographies. Alternatively, intermediates can be subjected to the next reaction without purification.

Hereinbelow, the present invention will be specifically described with reference to the Examples, but the scope of the present invention is not to be construed as being limited thereto.

Furthermore, in the Examples shown below, unless otherwise specified, if a defined group becomes altered under the conditions of the production method or is unsuitable for carrying out the method, the compound of interest can be produced by using the methods for introducing and removing protecting groups commonly used in synthetic organic chemistry (for example, "Protective Groups in Organic Synthesis", T. W. Greene, John Wiley & Sons Inc., 1999). Furthermore, the order of the reaction processes such as substituent introduction can be changed as necessary.

EXAMPLES

General procedure I (substitution at the 4-position)

To a suspension of intermediates **E** (1.0 equiv) in dioxane or a mixture of dioxane and DMF (2:1) was added the requisite amine (1.0 – 2.0 equiv), *N,N*-diisopropylethylamine (2.0–5.0 equiv) and finely ground K_2CO_3 (2.0–3.0 equiv) and the reaction mixture was stirred with heat between 60 – 100 °C for 16 h or until **E** was consumed (monitored by LCMS analysis). The reaction mixture was cooled, diluted with satd. aq. sodium bicarbonate and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated. The residue was purified by column chromatography (silica, methanol/dichloromethane) to afford the desired product **L**.

10 General procedure II (substitution at the 6-position)

To a suspension of intermediate **L** (1.0 equiv), the requisite boronic ester (1.5 – 2.0 equiv) and $Pd(dppf)Cl_2$ (0.1 – 0.2 equiv) in dioxane (0.1 – 0.2 M) was added Cs_2CO_3 (1.0 M in H_2O , 3.0 – 4.0 eq). The reaction mixture was degassed with nitrogen and stirred with heat at 80 °C for 2 – 24 h. The reaction mixture was cooled, poured onto satd. aq. sodium bicarbonate and extracted with 3:1 chloroform/isopropanol. The combined organic layers were dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated. The residue was purified by chromatography (normal phase silica using methanol/dichloromethane or reverse phase silica using water/acetonitrile containing 0.025% TFA) to afford the target compound. In some instances the product was diluted in methanol followed by the addition of excess HCl (2.0 – 5.0 equiv as a solution in ether, methanol, dioxane or water). After 5 min the mixture was concentrated to dryness to obtain the HCl salt of the target compound.

General procedure III (synthesis of boronic esters)

To a suspension of the appropriate aryl bromide (1.0 equiv), bis(pinacolato)diboron (1.5 – 2.0 equiv) and KOAc (2.0 – 3.0 equiv) in dioxane (0.1 – 0.2 M) was added $Pd(dppf)Cl_2$ (0.05 – 0.1 equiv). The reaction mixture was degassed with nitrogen followed by stirring with heat at 80 °C for 2 – 16 h. The reaction mixture was cooled, filtered, and the filtrate was concentrated. The residue was purified by

chromatography (silica, ethyl acetate/hexanes) to afford the desired product M.

General procedure IV-1 (Boc-deprotection protocol)

To a solution of Boc-protected compound in THF, methanol or methanol/methylene chloride (0.1 M) was added excess HCl (2.0 – 5.0 equiv as a solution in ether, methanol, dioxane or water). The reaction was stirred at room temperature or with heat (50 – 70 °C) and upon completion (monitored by LCMS analysis) the reaction mixture was concentrated to obtain the HCl salt of the target compound.

General procedure IV-2 (Boc-deprotection protocol)

To a solution of Boc-protected compound in THF was added excess TFA (2.0 – 10 equiv) and the reaction mixture was stirred at room temperature or with heat (50 – 70 °C) until the reaction was complete (monitored by LCMS analysis). The reaction mixture was concentrated and the residue was diluted in methanol followed by the addition of excess HCl (2.0 – 5.0 equiv as a solution in ether, methanol, dioxane or water). After 5 min the mixture was concentrated to dryness to obtain the HCl salt of the target compound.

General procedure V

To a solution of {4-[(3-acetyl-6-chloro-1,5-naphthyridin-4-yl)amino]cyclohexyl}methyl methanesulfonate (1.0 mmol) in a mixture of 1,4-dioxane and N,N-dimethylformamide (2:1) was added the requisite amine (2.0 – 4.0 equiv), triethyl amine or N,N-diisopropylethylamine (2.0 – 3.0 equiv) and potassium iodide (cat.) and the reaction mixture was stirring with heat at 85 °C for 18 h. The reaction mixture was cooled and diluted with water and ethyl acetate. The layers were separated and the ethyl acetate layer was dried over sodium sulfate, filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, hexanes or methylene chloride/ethyl acetate) to afford the desired product.

General procedure VI

To a solution of 1-(4-((4-aminocyclohexyl)amino)-6-chloro-1,5-naphthyridin-3-yl)ethanone hydrochloride (1.0 mmol) in DMF (0.1 M) was added the requisite amino acid (1.2 mmol), diisopropylethylamine (5.0 equiv) and HATU (2-(7-Aza-1H-benzotriazole-1-

yl)- 1,1,3,3-tetramethyluronium hexafluorophosphate) (1.2 equiv) and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with water and ethyl acetate. The layers were separated and the ethyl acetate layer was dried over sodium sulfate, filtered and the filtrate was concentrated. The residue was purified by
 5 chromatography (silica, hexanes or methylene chloride/ethyl acetate) to afford the desired product.

Regarding the retention time indicated as t_R , HPLC analysis was performed under the following condition:

Column: Gemini-NXTM C18 column 150 x 4.6mm, 5 micro 100 A (Phenomenex);

10 Mobile phase: [Eluent A] water w/0.05% CF₃COOH;

[Eluent B] acetonitrile w/0.05% CF₃COOH;

Flow rate: 1 mL/min

Temperature: ambient

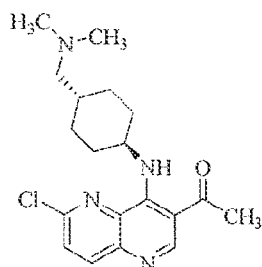
Detection wavelength: 223 nm or 254 nm

15 Gradient operation:

Time	H ₂ O w/0.05% CF ₃ COOH	Acetonitrile w/0.05% CF ₃ COOH
00 min	98 %	2 %
18 min	10%	90%
21 min	10%	90%
23 min	98 %	2 %

Example 1

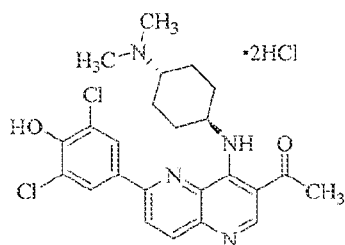
1-(6-Chloro-4-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-
 20 1,5-naphthyridin-3-yl)- ethanone



Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (360 mg, 1.5 mmol) was reacted with *trans*-4-[(dimethylamino)methyl]cyclohexylamine diacetic acid salt (500 mg, 1.8 mmol) to afford the desired product (340 mg, 63%) as a yellow solid: ^1H NMR (500 MHz, CDCl_3) δ 10.89 (s, 1H), 8.93 (s, 1H), 8.07 (d, J = 8.6 Hz, 1H), 7.51 (d, J = 8.6 Hz, 1H), 5.16 – 4.96 (m, 1H), 2.67 (s, 3H), 2.34 – 2.24 (m, 2H), 2.22 (s, 6H), 2.14 (d, J = 7.1 Hz, 2H), 1.98 – 1.89 (m, 2H), 1.56 – 1.47 (m, 1H), 1.41 – 1.32 (m, 2H), 1.28 – 1.10 (m, 2H); ESI MS m/z 361 $[\text{M} + \text{H}]^+$; HPLC 98.8% (AUC), t_R = 8.42 min.

Example 2

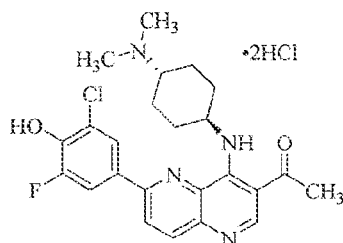
10 1-{6-(3,5-Dichloro-4-hydroxyphenyl)-4-[*trans*-4-(dimethylamino)cyclohexylamino]-1,5-naphthyridin-3-yl}ethanone dihydrochloride



Following general procedure II, 1-{6-chloro-4-[*trans*-4-(dimethylamino)cyclohexylamino]-1,5-naphthyridin-3-yl}ethanone (61 mg, 0.16 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (65 mg, 0.23 mmol) followed by formation of the dihydrochloride salt to afford the desired product (76 mg, 90%) as an off-white solid: ^1H NMR (500 MHz, CD_3OD) δ 9.17 (s, 1H), 8.47 (d, J = 9.0 Hz, 1H), 8.36 (d, J = 8.9 Hz, 1H), 8.10 (s, 2H), 5.65 – 5.55 (m, 1H), 3.52 – 3.43 (m, 1H), 2.91 (s, 6H), 2.76 (s, 3H), 2.66 – 2.56 (m, xH), 2.33 – 2.26 (m, 2H), 1.88 – 1.71 (m, 4H). ESI MS m/z 473 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), t_R = 9.51 min.

Example 3

1-{6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-[*trans*-4-(dimethylamino)cyclohexylamino]-1,5-naphthyridin-3-yl}ethanone dihydrochloride

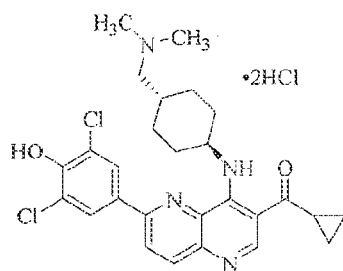


5

Following general procedure II, 1-{6-chloro-4-[*trans*-4-(dimethylamino)cyclohexyl amino]-1,5-naphthyridin-3-yl}ethanone (45 mg, 0.12 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (47 mg, 0.17 mmol) followed by formation of the dihydrochloride salt to afford the desired product (6.9 mg, 11%) as an off-white solid: ¹H NMR (500 MHz, CD₃OD) δ 9.17 (s, 1H), 8.47 (d, J = 9.0 Hz, 1H), 8.34 (d, J = 9.0 Hz, 1H), 8.00 (s, 1H), 7.91 (dd, J = 11.4, 2.2 Hz, 1H), 5.69 – 5.59 (m, 1H), 3.52 – 3.45 (m, 1H), 2.92 (s, 6H), 2.76 (s, 3H), 2.63 – 2.56 (m, 2H), 2.33 – 2.26 (m, 2H), 1.89 – 1.71 (m, 4H). ESI MS *m/z* 457 [M + H]⁺; HPLC >99% (AUC), *t_R* = 9.32 min.

Example 4

15 Cyclopropyl(6-(3,5-dichloro-4-hydroxyphenyl)-4-{*trans*-4-[(dimethylamino)methyl]-cyclohexylamino}-1,5-naphthyridin-3-yl)methanone dihydrochloride



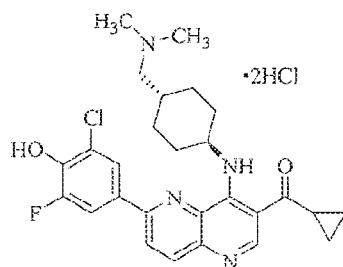
Following general procedure II, (6-chloro-4-{*trans*-4-[(dimethylamino)methyl]-cyclohexyl amino}-1,5-naphthyridin-3-yl)(cyclopropyl)methanone (60 mg, 0.16 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (65 mg,

20

0.23 mmol) followed by formation of the dihydrochloride salt to afford the desired product (66 mg, 73%) as a light yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 9.41 (s, 1H), 8.46 (d, $J = 8.9$ Hz, 1H), 8.34 (d, $J = 8.9$ Hz, 1H), 8.12 (s, 2H), 5.74 – 5.64 (m, 1H), 3.09 (d, $J = 6.6$ Hz, 2H), 2.93 (s, 6H), 2.92 – 2.85 (s, 1H), 2.47 – 2.40 (m, 2H), 2.08 – 1.96 (m, 3H), 1.72 – 1.60 (m, 2H), 1.47 – 1.34 (m, 2H), 1.32 – 1.18 (m, 4H). ESI MS m/z 513 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 9.67$ min.

Example 5

(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4- $\{trans$ -4-[(dimethylamino)methyl] cyclohexyl-amino}-1,5-naphthyridin-3-yl)(cyclopropyl)methanone dihydrochloride

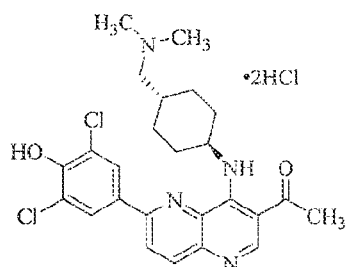


10

Following general procedure II, (6-chloro-4- $\{trans$ -4-[(dimethylamino)methyl]-cyclohexyl amino}-1,5-naphthyridin-3-yl)(cyclopropyl)methanone (60 mg, 0.16 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (61 mg, 0.23 mmol) followed by formation of the dihydrochloride salt to afford the desired product (54 mg, 61%) as a light yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 9.41 (s, 1H), 8.45 (d, $J = 8.9$ Hz, 1H), 8.34 (d, $J = 8.9$ Hz, 1H), 8.02 (t, $J = 1.9$ Hz, 1H), 7.88 (dd, $J = 11.6$, 2.2 Hz, 1H), 5.73 – 5.64 (m, 1H), 3.09 (d, $J = 6.6$ Hz, 2H), 2.94 (s, 6H), 2.93 – 2.83 (m, 1H), 2.48 – 2.40 (m, 2H), 2.10 – 1.96 (m, 3H), 1.73 – 1.61 (m, 2H), 1.46 – 1.34 (m, 2H), 1.34 – 1.18 (m, 4H). ESI MS m/z 497 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 10.26$ min.

Example 6

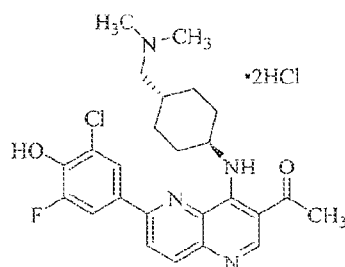
1- $\{6$ -(3,5-Dichloro-4-hydroxyphenyl)-4- $\{trans$ -4-[(dimethylamino)methyl]cyclohexyl-amino}-1,5-naphthyridin-3-yl} ethanone dihydrochloride



Following general procedure II, 1-(6-chloro-4-({*trans*-4-[(dimethylamino)methyl]cyclohexyl amino}-1,5-naphthyridin-3-yl)ethanone (20 mg, 0.055 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (29 mg, 0.10 mmol) followed by formation of the dihydrochloride salt to afford the desired product (18 mg, 58%) as an off-white solid: ^1H NMR (500 MHz, CD_3OD) δ 9.14 (s, 1H), 8.46 (d, J = 9.1 Hz, 1H), 8.33 (d, J = 9.1 Hz, 1H), 8.12 (s, 2H), 5.75 – 5.67 (m, 1H), 3.09 (d, J = 6.6 Hz, 2H), 2.94 (s, 6H), 2.76 (s, 3H), 2.48 – 2.41 (m, 2H), 2.09 – 1.98 (m, 1H), 1.75 – 1.63 (m, 1H), 1.48 – 1.36 (m, 2H). ESI MS m/z 487 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), t_R = 9.67 min.

10 Example 7

1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-({*trans*-4-[(dimethylamino)methyl]cyclohexyl} amino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride

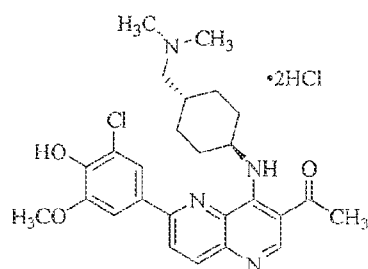


Following general procedure II, 1-(6-chloro-4-({*trans*-4-[(dimethylamino)methyl]cyclohexyl amino}-1,5-naphthyridin-3-yl)ethanone (20 mg, 0.055 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (27 mg, 0.10 mmol) followed by formation of the dihydrochloride salt to afford the desired product (16 mg, 52%) as a light yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 9.15 (s, 1H), 8.45 (d, J = 9.1 Hz, 1H), 8.33 (d, J = 9.0 Hz, 1H), 8.02 (t, J = 1.9 Hz, 1H), 7.88 (dd, J = 11.5, 2.2 Hz,

1H), 5.75 – 5.65 (m, 1H), 3.09 (d, $J = 6.6$ Hz, 2H), 2.94 (s, 6H), 2.76 (s, 3H), 2.45 (d, $J = 12.5$ Hz, 2H), 2.11 – 2.01 (m, 3H), 1.75 – 1.63 (m, 2H), 1.47 – 1.36 (m, 2H). ESI MS m/z 471 $[M + H]^+$; HPLC >99% (AUC), $t_R = 9.66$ min.

Example 8

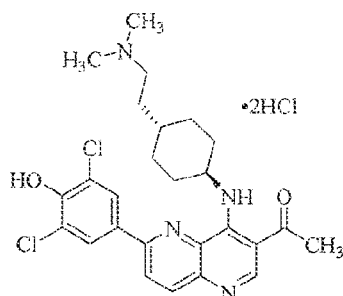
- 5 1-(6-(3-Chloro-4-hydroxy-5-methoxyphenyl)-4- $\{trans$ -4-
 [(dimethylamino)methyl]cyclohexyl-amino}-1,5-naphthyridin-3-yl)ethanone
 dihydrochloride



- Following general procedure II, 1-(6-chloro-4- $\{trans$ -4-[(dimethylamino)methyl]
 10 cyclohexyl amino}-1,5-naphthyridin-3-yl)ethanone (20 mg, 0.055 mmol) was reacted with
 2-chloro-6-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (28 mg, 1.0
 mmol) followed by formation of the dihydrochloride salt to afford the desired product (18
 mg, 59%) as a yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 9.13 (s, 1H), 8.49 (d, $J = 8.9$
 Hz, 1H), 8.32 (d, $J = 9.1$ Hz, 1H), 7.81 (d, $J = 2.1$ Hz, 1H), 7.58 (d, $J = 2.1$ Hz, 1H), 5.80 –
 15 5.70 (m, 1H), 4.03 (s, 3H), 3.08 (d, $J = 6.6$ Hz, 2H), 2.93 (s, 6H), 2.76 (s, 3H), 2.49 – 2.39
 (m, 2H), 2.08 – 1.96 (m, 3H), 1.72 – 1.62 (m, 2H), 1.47 – 1.35 (m, 2H). ESI MS m/z 483 $[M$
 + $H]^+$; HPLC >99% (AUC), $t_R = 9.62$ min.

Example 9

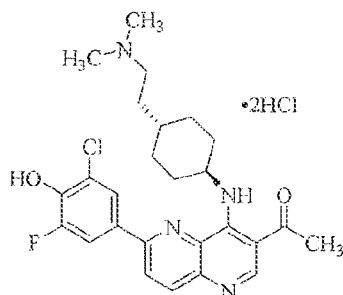
- 1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4- $\{trans$ -4-[2-
 20 (dimethylamino)ethyl]cyclohexyl} amino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride



Following general procedure II, 1-(6-chloro-4-{*trans*-4-[(dimethylamino)methyl]cyclohexyl amino}-1,5-naphthyridin-3-yl)ethanone (50 mg, 0.13 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (58 mg, 0.2 mmol) followed by formation of the dihydrochloride salt to afford the desired product (64 mg, 83%) as an off-white solid: ^1H NMR (500 MHz, CD_3OD) δ 9.13 (s, 1H), 8.46 (d, $J = 9.1$ Hz, 1H), 8.33 (d, $J = 9.0$ Hz, 1H), 8.13 (s, 1H), 5.74 – 5.64 (m, 1H), 3.27 – 3.18 (m, 2H), 2.91 (s, 6H), 2.75 (s, 3H), 2.45 – 2.35 (m, 2H), 2.05 – 1.98 (m, 2H), 1.78 – 1.70 (m, 2H), 1.66 – 1.52 (m, 3H), 1.45 – 1.35 (m, 2H). ESI MS m/z 501 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R =$ 10.22 min.

Example 10

1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-{*trans*-4-[2-(dimethylamino)ethyl]-cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone dihydrochloride

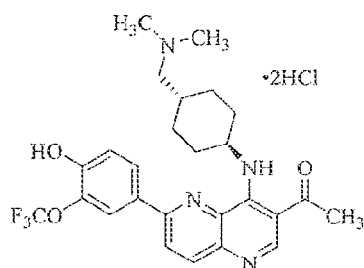


Following general procedure II, 1-(6-chloro-4-((*trans*-4-((dimethylamino)methyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone (50 mg, 0.13 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (55 mg, 0.2 mmol) followed by formation of the dihydrochloride salt to afford the desired product (58 mg,

78%) as an off-white solid: ^1H NMR (500 MHz, CD_3OD) δ 9.13 (s, 1H), 8.45 (d, $J = 8.9$ Hz, 1H), 8.32 (d, $J = 8.9$ Hz, 1H), 8.04 (t, $J = 1.8$ Hz, 1H), 7.89 (dd, $J = 11.6, 2.2$ Hz, 1H), 5.73 – 5.63 (m, 1H), 3.27 – 3.18 (m, 2H), 2.91 (s, 6H), 2.75 (s, 3H), 2.44 – 2.37 (m, 2H), 2.05 – 1.98 (m, 2H), 1.78 – 1.69 (m, 2H), 1.67 – 1.51 (m, 3H), 1.44 – 1.34 (m, 2H). ESI MS m/z 485 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 9.91$ min.

Example 11

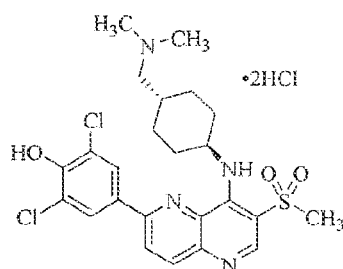
1-(4-{*trans*-4-[(Dimethylamino)methyl]cyclohexylamino}-6-[4-hydroxy-3-(trifluoromethoxy)phenyl]-1,5-naphthyridin-3-yl)ethanone dihydrochloride



Following general procedure II, 1-(6-chloro-4-{*trans*-4-[(dimethylamino)methyl]cyclohexyl amino}-1,5-naphthyridin-3-yl)ethanone (55 mg, 0.15 mmol) was reacted with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethoxy)phenol (68 mg, 0.23 mmol) followed by formation of the dihydrochloride salt to afford the desired product (71 mg, 79%) as an off-white solid: ^1H NMR (500 MHz, CD_3OD) δ 9.14 (s, 1H), 8.45 (d, $J = 8.9$ Hz, 1H), 8.32 (d, $J = 9.0$ Hz, 1H), 8.04 – 7.97 (m, 2H), 7.21 (d, $J = 8.6$ Hz, 1H), 5.70 – 5.60 (m, 1H), 3.07 (d, $J = 6.6$ Hz, 2H), 2.94 (s, 6H), 2.76 (s, 3H), 2.50 – 2.40 (m, 2H), 2.08 – 1.97 (m, 3H), 1.74 – 1.62 (m, 2H), 1.39 – 1.27 (m, 2H). ESI MS m/z 503 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 9.80$ min.

Example 12

2,6-Dichloro-4-(8-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)phenol dihydrochloride

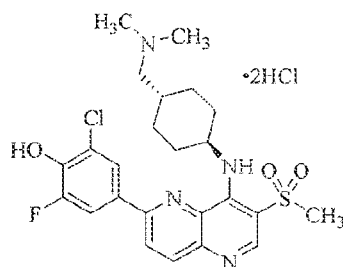


Following general procedure II, 6-chloro-N-({*trans*-4-[(dimethylamino)methyl]-cyclohexyl}-3-(methylsulfonyl)-1,5-naphthyridin-4-amine (56 mg, 0.14 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (61 mg, 0.21

5 mmol) followed by formation of the dihydrochloride salt to afford the desired product (43 mg, 51%) as a light yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 8.90 (s, 1H), 8.51 (d, J = 9.0 Hz, 1H), 8.35 (d, J = 9.0 Hz, 1H), 8.14 (s, 2H), 5.76 – 5.66 (m, 1H), 3.38 (s, 3H), 3.09 (d, J = 6.7 Hz, 2H), 2.94 (s, 6H), 2.50 – 2.43 (m, 2H), 2.08 – 1.96 (m, 3H), 1.74 – 1.64 (m, 2H), 1.47 – 1.35 (m, 2H). ESI MS m/z 523 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), t_R = 10.04 min.

10 Example 13

6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-({*trans*-4-[(dimethylamino)methyl]cyclohexyl}-amino)-3-methylsulfonyl-1,5-naphthyridine dihydrochloride

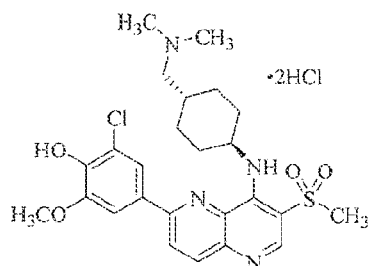


Following general procedure II, 6-chloro-N-({*trans*-4-[(dimethylamino)methyl]-cyclohexyl}-3-(methylsulfonyl)-1,5-naphthyridin-4-amine (61 mg, 0.15 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (63 mg, 0.23 mmol) followed by formation of the dihydrochloride salt to afford the desired product (52 mg, 59%) as a light yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 8.90 (s, 1H), 8.50 (d, J = 8.9 Hz, 1H), 8.35 (d, J = 9.0 Hz, 1H), 8.04 (t, J = 1.8 Hz, 1H), 7.90 (dd, J = 11.5, 2.2 Hz, 1H), 5.77 – 5.67 (m, 1H), 3.38 (s, 3H), 3.09 (d, J = 6.6 Hz, 2H), 2.94 (s, 6H), 2.51 – 2.44 (m,

2H), 2.08 – 1.97 (m, 3H), 1.76 – 1.64 (m, 2H), 1.46 – 1.34 (m, 2H). ESI MS m/z 507 $[M + H]^+$; HPLC 99.0% (AUC), t_R = 9.81 min.

Example 14

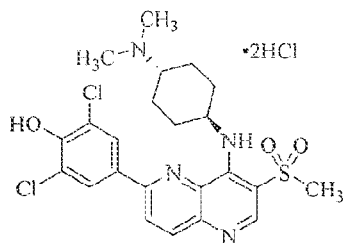
6-(3-Chloro-4-hydroxy-5-methoxyphenyl)-4-{*trans*-4-[(dimethylamino)methyl]-
5 cyclohexylamino}-3-methylsulfonyl-1,5-naphthyridine- dihydrochloride



Following general procedure II, 6-chloro-N-{*trans*-4-[(dimethylamino)methyl]-
cyclohexyl}-3-(methylsulfonyl)-1,5-naphthyridin-4-amine (24 mg, 0.061 mmol) was
reacted with 2-chloro-6-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (28
10 mg, 0.10 mmol) followed by formation of the dihydrochloride salt to afford the desired
product (23 mg, 64%) as a yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 8.89 (s, 1H), 8.54
(d, J = 9.1 Hz, 1H), 8.34 (d, J = 9.0 Hz, 1H), 7.83 (d, J = 2.0 Hz, 1H), 7.60 (d, J = 2.0 Hz,
1H), 5.83 – 5.73 (m, 1H), 4.04 (s, 3H), 3.38 (s, 3H), 3.08 (d, J = 6.6 Hz, 2H), 2.93 (s, 6H),
2.50 – 2.43 (m, 2H), 2.07 – 1.95 (m, 3H), 1.73 – 1.63 (m, 2H), 1.46 – 1.35 (m, 2H). ESI MS
15 m/z 519 $[M + H]^+$; HPLC >99% (AUC), t_R = 9.77 min.

Example 15

2,6-Dichloro-4-{8-[*trans*-4-(dimethylamino)cyclohexylamino]-7-(methylsulfonyl)-1,5-
naphthyridin-2-yl}phenol dihydrochloride

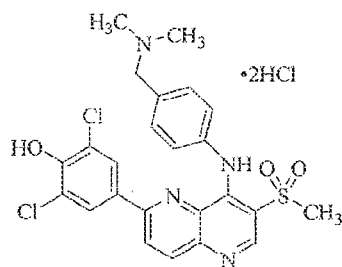


20 Following general procedure II, *trans*-N¹-[6-chloro-3-(methylsulfonyl)-1,5-

naphthyridin-4-yl]-N⁴,N⁴-dimethylcyclohexane-1,4-diamine (40 mg, 0.10 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (43 mg, 0.15 mmol) followed by formation of the dihydrochloride salt to afford the desired product (45 mg, 75%) as a light yellow solid: ¹H NMR (500 MHz, CD₃OD) δ 8.93 (s, 1H), 8.51 (d, J = 8.9 Hz, 1H), 8.37 (d, J = 8.9 Hz, 1H), 8.12 (s, 2H), 5.65 – 5.55 (m, 1H), 3.50 – 3.41 (m, 1H), 3.39 (s, 3H), 2.91 (s, 6H), 2.67 – 2.57 (m, 2H), 2.33 – 2.27 (m, 2H), 1.87 – 1.73 (m, 4H). ESI MS *m/z* 509 [M + H]⁺; HPLC 98.0% (AUC), *t_R* = 9.95 min.

Example 16

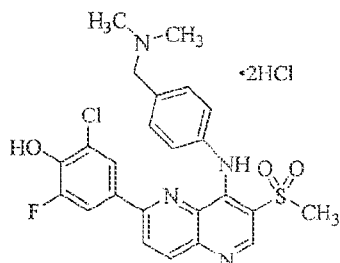
2,6-Dichloro-4-(8-{4-[(dimethylamino)methyl]phenylamino}-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)phenol dihydrochloride



Following general procedure II, 6-chloro-N-{4-[(dimethylamino)methyl]phenyl}-3-(methylsulfonyl)-1,5-naphthyridin-4-amine (50 mg, 0.14 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (61 mg, 0.21 mmol) followed by formation of the dihydrochloride salt to afford the desired product (35 mg, 42%) as an orange solid: ¹H NMR (500 MHz, CD₃OD) δ 9.12 (s, 1H), 8.47 (d, J = 9.1 Hz, 1H), 8.38 (d, J = 9.2 Hz, 1H), 7.63 (d, J = 9.0 Hz, 2H), 7.59 – 7.52 (m, 2H), 7.34 (s, 2H), 4.43 (s, 2H), 3.48 (s, 3H), 2.86 (s, 6H). ; ESI MS *m/z* 517 [M + H]⁺; HPLC >99% (AUC), *t_R* = 11.03 min.

Example 17

2-Chloro-4-(8-{4-[(dimethylamino)methyl]phenylamino}-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-fluorophenol dihydrochloride

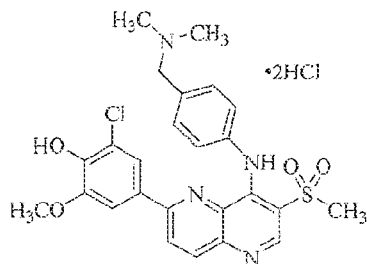


Following general procedure II, 6-chloro-*N*-{4-[(dimethylamino)methyl]phenyl}-3-(methylsulfonyl)-1,5-naphthyridin-4-amine (50 mg, 0.14 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (58 mg, 0.21 mmol)

- 5 followed by formation of the dihydrochloride salt to afford the desired product (51 mg, 63%) as a yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 9.12 (s, 1H), 8.46 (d, $J = 9.0$ Hz, 1H), 8.37 (d, $J = 9.1$ Hz, 1H), 7.68 – 7.61 (m, 2H), 7.60 – 7.53 (m, 2H), 7.22 (t, $J = 1.8$ Hz, 1H), 7.06 (dd, $J = 11.9, 2.2$ Hz, 1H), 4.43 (s, 2H), 3.48 (s, 3H), 2.88 (s, 6H).; ESI MS m/z 501 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 10.68$ min.

10 Example 18

2-Chloro-4-(8-{4-[(dimethylamino)methyl]phenylamino}-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-methoxyphenol dihydrochloride



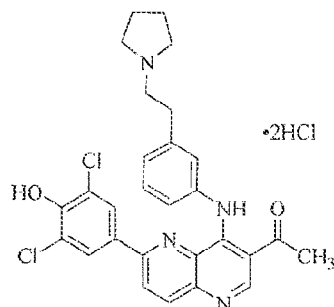
Following general procedure II, 6-chloro-*N*-{4-[(dimethylamino)methyl]phenyl}-3-

- 15 (methylsulfonyl)-1,5-naphthyridin-4-amine (50 mg, 0.14 mmol) was reacted with 2-chloro-6-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (60 mg, 0.21 mmol) followed by formation of the dihydrochloride salt to afford the desired product (44 mg, 54%) as an orange solid: ^1H NMR (500 MHz, CD_3OD) δ 9.11 (s, 1H), 8.50 (d, $J = 9.0$ Hz, 1H), 8.36 (d, $J = 9.0$ Hz, 1H), 7.62 – 7.50 (m, 4H), 7.34 (d, $J = 2.1$ Hz, 1H), 6.68 (d, $J = 2.0$ Hz, 1H), 4.40 (s, 2H), 3.92 (s, 3H), 3.47 (s, 3H), 2.83 (s, 6H); ESI MS m/z 513 $[\text{M} + \text{H}]^+$;
- 20

HPLC >99% (AUC), t_R = 10.56 min.

Example 19

1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4-{3-[2-(pyrrolidin-1-yl)ethyl]phenylamino}-1,5-naphthyridin-3-yl]ethanone dihydrochloride

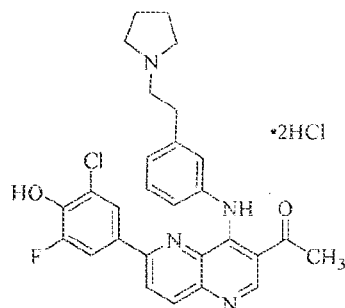


5

Following general procedure II, 1-(6-chloro-4-{3-[2-(pyrrolidin-1-yl)ethyl]phenylamino}-1,5-naphthyridin-3-yl)ethanone (59 mg, 0.15 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (65 mg, 0.23 mmol) followed by formation of the dihydrochloride salt to afford the desired product (67 mg, 75%) as a yellow solid: ^1H NMR (500 MHz, D_2O) δ 9.13 (s, 1H), 8.13 (d, J = 9.0 Hz, 1H), 8.01 (d, J = 9.1 Hz, 1H), 7.64 (t, J = 7.8 Hz, 1H), 7.41 (d, J = 7.4 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 6.79 (s, 1H), 6.66 (br s, 2H), 3.36 – 3.27 (m, 2H), 2.78 (s, 3H), 2.74 – 2.64 (m, 2H), 2.62 – 2.42 (m, 4H), 1.87 – 1.72 (m, 4H); ESI MS m/z 521 $[\text{M} + \text{H}]^+$; HPLC 98.9% (AUC), t_R = 10.34 min.

15 Example 20

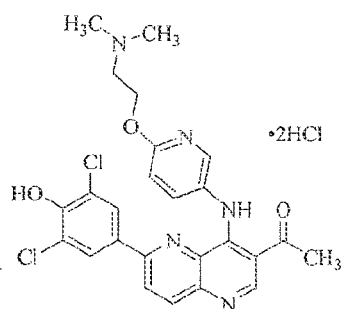
1-[6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-{3-[2-(pyrrolidin-1-yl)ethyl]phenylamino}-1,5-naphthyridin-3-yl]ethanone dihydrochloride



Following general procedure II, 1-(6-chloro-4-{3-[2-(pyrrolidin-1-yl)ethyl]phenylamino}-1,5-naphthyridin-3-yl)ethanone (59 mg, 0.15 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (61 mg, 0.23 mmol) followed by formation of the dihydrochloride salt to afford the desired product (63 mg, 72%) as a yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 9.30 (s, 1H), 8.43 (d, $J = 9.0$ Hz, 1H), 8.34 (d, $J = 8.9$ Hz, 1H), 7.54 – 7.30 (m, 4H), 7.23 (br s, 1H), 7.13 (br s, 1H), 3.68 – 3.60 (m, 2H), 3.35 – 3.23 (m, 2H), 3.11 – 2.99 (m, 4H), 2.80 (br s, 3H), 2.19 – 2.07 (m, 2H), 2.05 – 1.96 (m, 2H); ESI MS m/z 505 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 10.17$ min.

Example 21

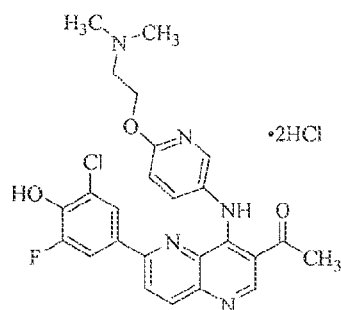
10 1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4-{6-[2-(dimethylamino)ethoxy]pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone dihydrochloride



Following general procedure II, 1-(6-chloro-4-{6-[2-(dimethylamino)ethoxy]pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone (50 mg, 0.13 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (56 mg, 0.20 mmol) followed by formation of the dihydrochloride salt to afford the desired product (63 mg, 83%) as a yellow-orange solid: ^1H NMR (500 MHz, CD_3OD) δ 9.35 (s, 1H), 8.46 (d, $J = 9.0$ Hz, 1H), 8.37 (d, $J = 9.0$ Hz, 1H), 8.24 (d, $J = 2.7$ Hz, 1H), 7.78 (dd, $J = 8.8, 2.7$ Hz, 1H), 7.44 (br s, 2H), 7.02 (d, $J = 8.8$ Hz, 1H), 4.72 – 4.66 (m, 2H), 3.64 – 3.58 (m, 2H), 3.00 (s, 6H), 2.84 (s, 3H); ESI MS m/z 512 $[\text{M} + \text{H}]^+$; HPLC 99% (AUC), $t_R = 9.73$ min.

Example 22

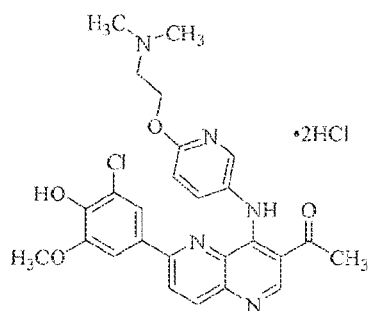
1-[6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-{6-[2-(dimethylamino)ethoxy]pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone dihydrochloride



Following general procedure II, 1-(6-chloro-4-{6-[2-(dimethylamino)ethoxy]pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone (50 mg, 0.13 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (53 mg, 0.20 mmol) followed by formation of the dihydrochloride salt to afford the desired product (40 mg, 54%) as an orange solid: ^1H NMR (500 MHz, CD_3OD) δ 9.35 (br s, 1H), 8.45 (d, $J = 9.0$ Hz, 1H), 8.37 (d, $J = 8.9$ Hz, 1H), 8.28 (d, $J = 2.6$ Hz, 1H), 7.76 (dd, $J = 8.8, 2.7$ Hz, 1H), 7.35 (br s, 1H), 7.10 (br s, 1H), 7.01 (d, $J = 8.8$ Hz, 1H), 4.74 – 4.68 (m, 2H), 3.66 – 3.60 (m, 2H), 3.02 (s, 6H), 2.84 (s, 3H). ; ESI MS m/z 496 $[\text{M} + \text{H}]^+$; HPLC 98.3% (AUC), $t_R = 9.47$ min.

Example 23

1-[6-(3-Chloro-4-hydroxy-5-methoxyphenyl)-4-{6-[2-(dimethylamino)ethoxy]pyridin-3-ylamino}-1,5-naphthyridin-3-yl]ethanone dihydrochloride

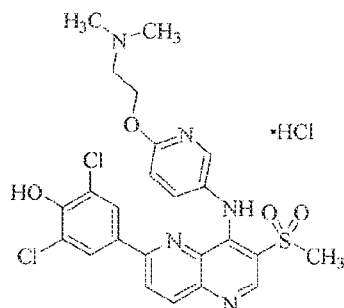


Following general procedure II, 1-(6-chloro-4-{6-[2-(dimethylamino)ethoxy]pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone (20 mg, 0.052 mmol) was reacted with 2-chloro-6-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (28 mg, 0.10 mmol) followed by formation of the dihydrochloride salt to afford the desired product (22 mg, 74%) as an orange solid: ^1H NMR (500 MHz, CD_3OD) δ 9.33 (s, 1H), 8.47 (d, $J = 9.0$ Hz,

1H), 8.35 (d, J = 9.0 Hz, 1H), 8.26 (d, J = 2.7 Hz, 1H), 7.74 (dd, J = 8.8, 2.7 Hz, 1H), 7.29 (br s, 1H), 6.96 (d, J = 8.8 Hz, 1H), 6.85 (br s, 1H), 4.70 – 4.64 (m, 2H), 3.95 (s, 3H), 3.62 – 3.56 (m, 2H), 2.99 (s, 6H), 2.83 (s, 3H). ; ESI MS m/z 508 $[M + H]^+$; HPLC >99% (AUC), t_R = 9.36 min.

5 Example 24

2,6-Dichloro-4-(8-{6-[2-(dimethylamino)ethoxy]pyridin-3-ylamino}-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)phenol hydrochloride

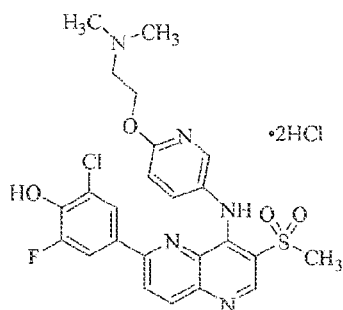


10

Following general procedure II, 1-[6-(3-chloro-4-hydroxy-5-methoxyphenyl)-4-{6-[2-(dimethylamino)ethoxy]pyridin-3-ylamino}-1,5-naphthyridin-3-yl]ethanone (60 mg, 0.14 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (65 mg, 0.23 mmol) followed by formation of the dihydrochloride salt to afford the desired product (70 mg, 79%) as a yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 9.11 (s, 1H), 8.49 (d, J = 9.1 Hz, 1H), 8.39 (d, J = 9.0 Hz, 1H), 8.28 (d, J = 2.7 Hz, 1H), 7.83 (dd, J = 8.8, 2.8 Hz, 1H), 7.46 (s, 2H), 7.03 (d, J = 8.8 Hz, 1H), 4.71 – 4.65 (m, 2H), 3.63 – 3.57 (m, 2H), 3.49 (s, 3H), 3.00 (s, 6H); ESI MS m/z 548 $[M + H]^+$; HPLC >99% (AUC), t_R = 10.87 min.

15 Example 25

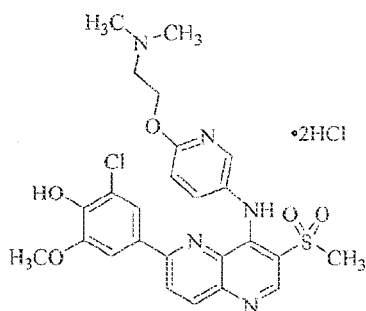
20 2-Chloro-4-(8-{6-[2-(dimethylamino)ethoxy]pyridin-3-ylamino}-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-fluorophenol dihydrochloride



Following general procedure II, 1-[6-(3-chloro-4-hydroxy-5-methoxyphenyl)-4-{6-[2-(dimethylamino)ethoxy]pyridin-3-ylamino}-1,5-naphthyridin-3-yl]ethanone (50 mg, 0.16 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (61 mg, 0.23 mmol) followed by formation of the dihydrochloride salt to afford the desired product (58 mg, 80%) as a yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 9.11 (s, 1H), 8.48 (d, $J = 9.1$ Hz, 1H), 8.38 (d, $J = 9.0$ Hz, 1H), 8.32 (d, $J = 2.7$ Hz, 1H), 7.81 (dd, $J = 8.8, 2.7$ Hz, 1H), 7.38 (t, $J = 1.8$ Hz, 1H), 7.11 (dd, $J = 11.8, 2.2$ Hz, 1H), 7.02 (d, $J = 8.7$ Hz, 1H), 4.74 – 4.68 (m, 2H), 3.66 – 3.60 (m, 2H), 3.49 (s, 3H), 3.02 (s, 6H). ; ESI MS m/z 532 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 10.51$ min.

Example 26

2-Chloro-4-(8-{6-[2-(dimethylamino)ethoxy]pyridin-3-ylamino}-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-methoxyphenol

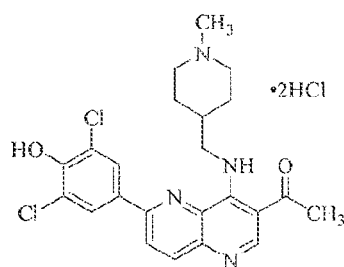


Following general procedure II, 1-[6-(3-chloro-4-hydroxy-5-methoxyphenyl)-4-{6-[2-(dimethylamino)ethoxy]pyridin-3-ylamino}-1,5-naphthyridin-3-yl]ethanone (49 mg, 0.12

mmol) was reacted with 2-chloro-6-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (50 mg, 0.18 mmol) followed by formation of the dihydrochloride salt to afford the desired product (56 mg, 78%) as an orange solid: ^1H NMR (500 MHz, CD_3OD) δ 9.09 (s, 1H), 8.49 (d, $J = 9.0$ Hz, 1H), 8.37 (d, $J = 9.0$ Hz, 1H), 8.30 (d, $J = 2.6$ Hz, 1H), 7.78 (dd, $J = 8.8, 2.8$ Hz, 1H), 7.28 (d, $J = 2.1$ Hz, 1H), 6.96 (d, $J = 8.8$ Hz, 1H), 6.88 (d, $J = 2.0$ Hz, 1H), 4.68 – 4.62 (m, 2H), 3.96 (s, 3H), 3.62 – 3.54 (m, 2H), 3.49 (s, 3H), 2.98 (s, 6H). ; ESI MS m/z 544 $[\text{M} + \text{H}]^+$; HPLC 99% (AUC), $t_R = 10.23$ min.

Example 27

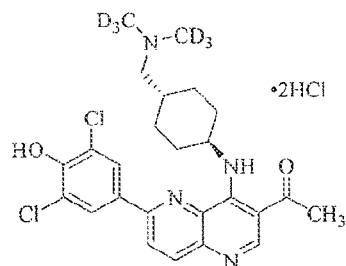
1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-((1-methylpiperidin-4-yl)methylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride



Following general procedure II, 61-{6-chloro-4-[(1-methylpiperidin-4-yl)methylamino]-1,5-naphthyridin-3-yl}ethanone (60 mg, 0.18 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (78 mg, 0.27 mmol) followed by formation of the dihydrochloride salt to afford the desired product (7.3 mg, 7.6%) as an off-white solid: ^1H NMR (500 MHz, CD_3OD) δ 9.18 (s, 1H), 8.48 (d, $J = 9.0$ Hz, 1H), 8.35 (d, $J = 8.9$ Hz, 1H), 8.11 (s, 2H), 4.60 (d, $J = 7.1$ Hz, 2H), 3.65 – 3.59 (m, 2H), 3.09 (td, $J = 13.0, 2.8$ Hz, 2H), 2.88 (s, 3H), 2.77 (s, 3H), 2.34 (br s, 1H), 2.27 (d, $J = 14.7$ Hz, 2H), 1.80 – 1.67 (m, 2H); ESI MS m/z 459 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 9.39$ min.

Example 28

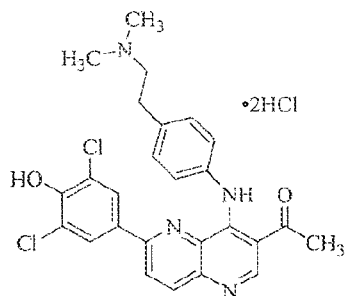
1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl]ethanone dihydrochloride



Following general procedure II, 1-(6-chloro-4-{*trans*-4-
 [(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone (153 mg, 0.42
 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol
 5 (180 mg, 0.63 mmol) followed by formation of the dihydrochloride salt to afford the desired
 product (164 mg, 69%) as an off-white solid: ^1H NMR (500 MHz, CD_3OD) δ 9.15 (s, 1H),
 8.46 (d, $J = 9.0$ Hz, 1H), 8.33 (d, $J = 9.0$ Hz, 1H), 8.12 (s, 2H), 5.76 – 5.71 (m, 1H), 3.09 (d,
 $J = 6.6$ Hz, 2H), 2.76 (s, 3H), 2.50 – 2.40 (m, 2H), 2.08 – 1.98 (m, 3H), 1.74 – 1.64 (m,
 2H), 1.47 – 1.37 (m, 2H). ; ESI MS m/z 493 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 9.83$ min.

10 Example 29

1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4-{4-[2-(dimethylamino)ethyl]phenylamino}-1,5-
 naphthyridin-3-yl)ethanone dihydrochloride

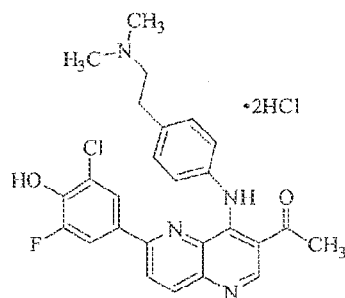


Following general procedure II, 1-(6-chloro-4-{4-[2-
 (dimethylamino)ethyl]phenylamino}-1,5-naphthyridin-3-yl)ethanone (40 mg, 0.11 mmol)
 15 was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (43
 mg, 0.15 mmol) followed by formation of the dihydrochloride salt to afford the desired
 product (17 mg, 28%) as an orange solid: ^1H NMR (500 MHz, CD_3OD) δ 9.30 (s, 1H), 8.43
 (d, $J = 9.0$ Hz, 1H), 8.33 (d, $J = 9.0$ Hz, 1H), 7.52 (br s, 2H), 7.42 (d, $J = 8.5$ Hz, 2 H),

7.37 (d, $J = 8.5$ Hz, 2H), 3.40 – 3.32 (m, 2H), 3.22 – 3.13 (m, 2H), 2.96 (s, 6H), 2.79 (s, 3H). ; ESI MS m/z 495 $[M + H]^+$; HPLC >99% (AUC), $t_R = 9.91$ min.

Example 30

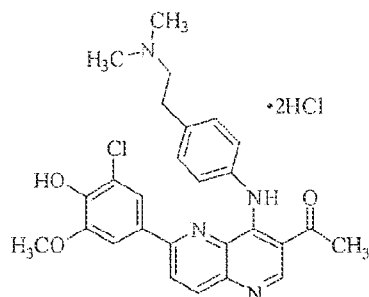
1-[6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-{4-[2-(dimethylamino)ethyl]phenylamino}-
5 1,5-naphthyridin-3-yl)ethanone dihydrochloride



Following general procedure II, 1-(6-chloro-4-{4-[2-(dimethylamino)ethyl]phenylamino}-1,5-naphthyridin-3-yl)ethanone (40 mg, 0.11 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (41 mg, 0.15 mmol) followed by formation of the dihydrochloride salt to afford the desired product (13 mg, 22%) as an orange solid: ^1H NMR (500 MHz, CD_3OD) δ 9.29 (s, 1H), 8.42 (d, $J = 9.1$ Hz, 1H), 8.32 (d, $J = 9.0$ Hz, 1H), 7.44 (d, $J = 8.5$ Hz, 2H), 7.41 – 7.35 (m, 3H), 7.11 (br s, 1H), 3.43 – 3.36 (m, 2H), 3.23–3.13 (m, 2H), 2.98 (s, 6H), 2.80 (s, 3H). ; ESI MS m/z 479 $[M + H]^+$; HPLC >99% (AUC), $t_R = 9.67$ min.

Example 31

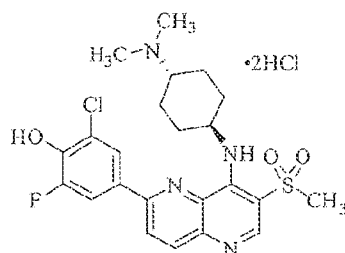
1-[6-(3-Chloro-4-phenol-5-methoxyphenyl)-4-{4-[2-(dimethylamino)ethyl]phenylamino}-
1,5-naphthyridin-3-yl)ethanone dihydrochloride



Following general procedure II, 1-(6-chloro-4-{4-[2-(dimethylamino)ethyl]phenylamino}-1,5-naphthyridin-3-yl)ethanone (40 mg, 0.11 mmol) was reacted with 2-chloro-6-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (57 mg, 0.20 mmol) followed by formation of the dihydrochloride salt to afford the desired product (40 mg, 66%) as an orange solid: ^1H NMR (500 MHz, CD_3OD) δ 9.30 (s, 1H), 8.47 (d, $J = 9.1$ Hz, 1H), 8.35 (d, $J = 9.1$ Hz, 1H), 7.41 (d, $J = 8.6$ Hz, 2H), 7.38 (d, $J = 8.6$ Hz, 2H), 7.33 (br s, 1H), 6.88 (br s, 1H), 3.95 (s, 3H), 3.35 – 3.30 (m, 2H), 3.20 – 3.12 (m, 2H), 2.98 (s, 6H), 2.81 (s, 3H). ; ESI MS m/z 491 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 9.62$ min.

10 Example 32

2-Chloro-4-{8-[*trans*-4-(dimethylamino)cyclohexylamino]-7-(methylsulfonyl)-1,5-naphthyridin-2-yl}-6-fluorophenol



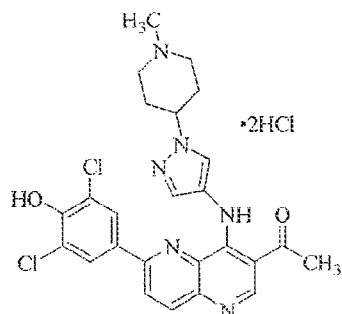
Following general procedure II, *trans*- N^1,N^1 -(6-chloro-3-(methylsulfonyl)-1,5-naphthyridin-4-yl)- N^1,N^1 -dimethylcyclohexane-1,4-diamine (28 mg, 0.073 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (41 mg, 0.15 mmol) followed by formation of the dihydrochloride salt to afford the desired product (30 mg, 72%) as an off-white solid: ^1H NMR (500 MHz, CD_3OD) δ 8.92 (s, 1H), 8.51 (d, $J = 9.0$ Hz, 1H), 8.37 (d, $J = 8.9$ Hz, 1H), 8.02 (t, $J = 1.7$ Hz, 1H), 7.92 (dd, $J = 11.5$, 2.2 Hz, 1H), 5.64 (br s, 1H), 3.52 – 3.42 (m, 1H), 3.39 (s, 3H), 2.91 (s, 6H), 2.65 – 2.55 (m, 2H), 2.33 – 2.26 (m, 2H), 1.88 – 1.72 (m, 4H). ; ESI MS m/z 493 $[\text{M} + \text{H}]^+$; HPLC 98.3% (AUC), $t_R = 9.62$ min.

Example 33

1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4-[1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-

ylamino}-

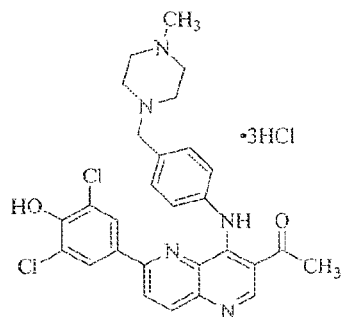
1,5-naphthyridin-3-yl]ethanone dihydrochloride



Following general procedure II, 1-(6-chloro-4-[(1-methylpiperidin-4-yl)-1H-pyrazol-4-ylamino]-1,5-naphthyridin-3-yl]ethanone (77 mg, 0.21 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (87 mg, 0.30 mmol) followed by formation of the dihydrochloride salt to afford the desired product (67 mg, 57%) as a yellow solid: ^1H NMR (500 MHz, D_2O) δ 9.14 (s, 1H), 8.15 (d, J = 9.0 Hz, 1H), 7.99 (d, J = 8.9 Hz, 1H), 7.73 (d, J = 2.8 Hz, 1H), 7.51 (br s, 1H), 6.97 (br s, 2H), 4.44 – 4.32 (m, 1H), 3.50 (d, J = 12.5 Hz, 2H), 3.07 (t, J = 13.0 Hz, 2H), 2.80 (s, 3H), 2.78 (s, 3H), 2.15 – 1.92 (m, 4H). ; ESI MS m/z 511 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), t_R = 9.37 min.

Example 34

1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-((4-methylpiperazin-1-yl)methyl)-phenylamino)-1,5-naphthyridin-3-yl]ethanone trihydrochloride



15

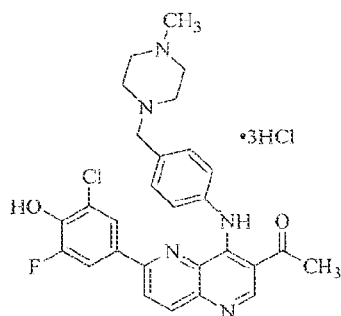
Following general procedure II, 1-(6-chloro-4-((4-methylpiperazin-1-yl)methyl)-phenylamino)-1,5-naphthyridin-3-yl]ethanone (74 mg, 0.18 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (78 mg, 0.27

mmol) followed by formation of the dihydrochloride salt to afford the desired product (84 mg, 77%) as a yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 9.33 (s, 1H), 8.45 (d, $J = 9.1$ Hz, 1H), 8.36 (d, $J = 9.0$ Hz, 1H), 7.70 (d, $J = 8.1$ Hz, 2H), 7.49 (d, $J = 8.1$ Hz, 2H), 7.38 (br s, 2H), 4.45 (s, 2H), 3.55 (br s, 8H), 2.99 (s, 3H), 2.81 (s, 3H). ; ESI MS m/z 536 $[\text{M} + \text{H}]^+$;

5 HPLC >99% (AUC), $t_R = 9.57$ min.

Example 35

1-[6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-{4-[(4-methylpiperazin-1-yl)methyl]phenylamino}-1,5-naphthyridin-3-yl]ethanone trihydrochloride

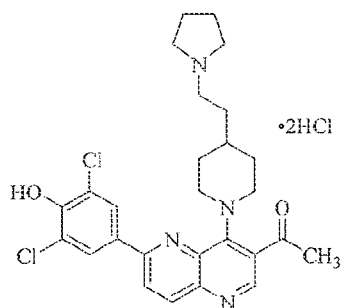


10 Following general procedure II, 1-(6-chloro-4-{4-[(4-methylpiperazin-1-yl)methyl]phenyl amino}-1,5-naphthyridin-3-yl)ethanone (74 mg, 0.18 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (74 mg, 0.27 mmol) followed by formation of the dihydrochloride salt to afford the desired product (96 mg, 93%) as a yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 9.32 (s, 1H), 8.44 (d, $J = 9.1$ Hz, 1H), 8.34 (d, $J = 9.1$ Hz, 1H), 7.65 (d, $J = 7.6$ Hz, 2H), 7.48 (d, $J = 8.0$ Hz, 2H), 7.31 (br s, 1H), 7.12 (br s, 1H), 4.26 (br s, 2H), 3.45 (br s, 8H), 2.97 (s, 3H), 2.80 (s, 3H); ESI MS m/z 520 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 9.37$ min.

Example 36

1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4-{4-[2-(pyrrolidin-1-yl)ethyl]piperidin-1-yl}-1,5-naphthyridin-3-yl]ethanone dihydrochloride

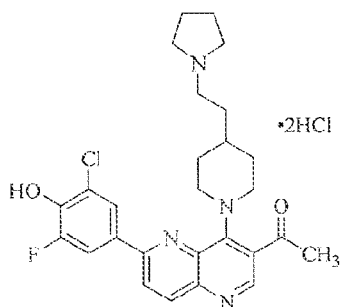
20



Following general procedure II, 1-(6-chloro-4-{4-[2-(pyrrolidin-1-yl)ethyl]piperidin-1-yl}-1,5-naphthyridin-3-yl)ethanone (60 mg, 0.16 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (65 mg, 0.23 mmol) followed by formation of the dihydrochloride salt to afford the desired product (54 mg, 60%) as a yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 8.91 (s, 1H), 8.46 (d, $J = 9.1$ Hz, 1H), 8.35 (d, $J = 8.9$ Hz, 1H), 8.16 (s, 2H), 4.63 (br s, 2H), 3.70 – 3.54 (m, 4H), 3.32 – 3.24 (m, 2H), 3.13 – 3.03 (m, 2H), 2.67 (s, 3H), 2.22 – 1.96 (m, 7H), 1.82 – 1.69 (m, 4H). ; ESI MS m/z $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 9.75$ min.

Example 37

1-[6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-{4-[2-(pyrrolidin-1-yl)ethyl]piperidin-1-yl}-1,5-naphthyridin-3-yl]ethanone dihydrochloride

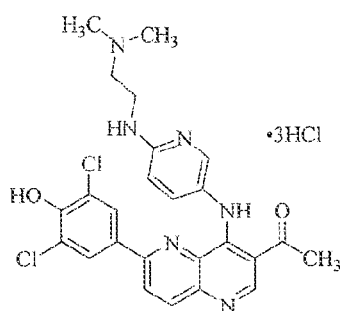


Following general procedure II, 1-(6-chloro-4-{4-[2-(pyrrolidin-1-yl)ethyl]piperidin-1-yl}-1,5-naphthyridin-3-yl)ethanone (60 mg, 0.16 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (61 mg, 0.23 mmol) followed by formation of the dihydrochloride salt to afford the desired product (73 mg, 83%) as a yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 8.91 (s, 1H), 8.45 (d, $J = 9.0$ Hz, 1H), 8.35 (d, $J = 8.9$

Hz, 1H), 8.04 (t, $J = 1.8$ Hz, 1H), 7.89 (dd, $J = 11.7, 2.2$ Hz, 1H), 4.66 (br s, 2H), 3.69 – 3.54 (m, 4H), 3.33 – 3.23 (m, 2H), 3.13 – 3.03 (m, 2H), 2.67 (s, 3H), 2.22 – 1.96 (m, 7H), 1.81 – 1.68 (m, 4H). ; ESI MS m/z 497 $[M + H]^+$; HPLC >99% (AUC), $t_R = 9.65$ min.

Example 38

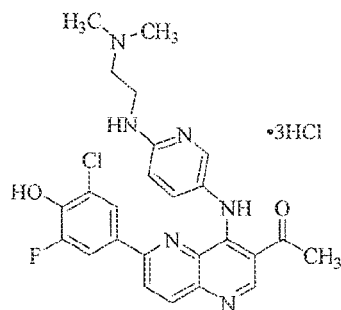
- 5 1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4-{6-[2-(dimethylamino)ethylamino]pyridin-3-ylamino}-1,5-naphthyridin-3-yl]ethanone trihydrochloride



- Following general procedure II, 1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-{6-[2-(dimethylamino)ethylamino]pyridin-3-ylamino}-1,5-naphthyridin-3-yl]ethanone (69 mg, 0.18 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (78 mg, 0.27 mmol) followed by formation of the trihydrochloride salt to afford the desired product (87 mg, 78%) as a yellow-orange solid: ^1H NMR (500 MHz, D_2O) δ 9.22 (s, 1H), 8.22 (d, $J = 8.9$ Hz, 1H), 8.02 (d, $J = 9.1$ Hz, 1H), 7.92 (d, $J = 2.5$ Hz, 1H), 7.59 – 7.53 (m, 1H), 6.98 (s, 2H), 6.79 (d, $J = 9.4$ Hz, 1H), 3.67 (t, $J = 6.4$ Hz, 2H), 3.23 (t, $J = 6.4$ Hz, 2H), 2.82 (s, 6 H), 2.80 (s, 3H). ; ESI MS m/z 511 $[M + H]^+$; HPLC >99% (AUC), $t_R = 9.13$ min.

Example 39

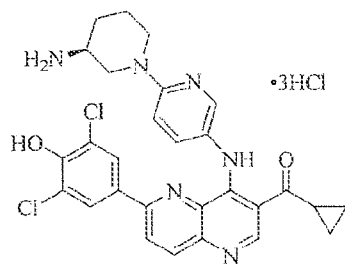
1-[6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-{6-[2-(dimethylamino)ethylamino]pyridin-3-ylamino}-1,5-naphthyridin-3-yl]ethanone trihydrochloride



Following general procedure II, 1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-{6-[2-(dimethylamino) ethylamino]pyridin-3-ylamino}-1,5-naphthyridin-3-yl]ethanone (69 mg, 0.18 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (74 mg, 0.27 mmol) followed by formation of the trihydrochloride salt to afford the desired product (71 mg, 66%) as a yellow-orange solid: ^1H NMR (500 MHz, CD_3OD) δ 9.40 (s, 1H), 8.49 (d, $J = 9.0$ Hz, 1H), 8.41 (d, $J = 9.1$ Hz, 1H), 8.23 (d, $J = 2.5$ Hz, 1H), 7.87 (dd, $J = 9.4, 2.5$ Hz, 1H), 7.42 (br s, 2H), 7.06 (d, $J = 9.4$ Hz, 1H), 3.91 (t, $J = 6.4$ Hz, 2H), 3.47 (t, $J = 6.4$ Hz, 2H), 2.99 (s, 6H), 2.85 (s, 3H); ESI MS m/z 495 $[\text{M} + \text{H}]^+$; HPLC 98.9% (AUC), $t_R = 8.97$ min.

Example 40

(*S*)-{4-[6-(3-Aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}(cyclopropyl)methanone trihydrochloride

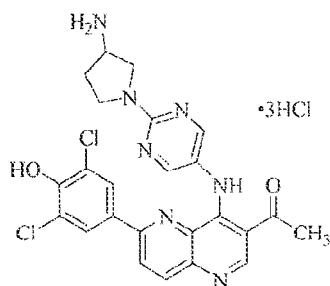


Following general procedure IV-2, (*S*)-tert-butyl 1-[5-[3-(cyclopropanecarbonyl)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino]pyridin-2-yl]piperidin-3-ylcarbamate (73 mg, 0.11 mmol) was reacted with TFA (3 mL) followed by formation of the trihydrochloride salt to afford the desired product (31 mg, 42%) as an orange solid: ^1H NMR (500 MHz, CD_3OD) δ 9.52 (br s, 1H), 8.51 (d, $J = 9.0$ Hz, 1H), 8.42 (d, $J = 9.0$ Hz,

1H), 8.23 (d, J = 2.6 Hz, 1H), 7.88 (dd, J = 9.4, 2.7 Hz, 1H), 7.69 (br s, 2H), 7.24 (d, J = 9.5 Hz, 1H), 4.37 (d, J = 10.9 Hz, 1H), 4.05 – 3.95 (m, 1H), 3.50 – 3.33 (m, 3H), 2.90 (br s, 1H), 2.27 – 2.17 (m, 1H), 2.06 – 1.96 (m, 1H), 1.86 – 1.74 (m, 2H), 1.37 – 1.18 (m, 4H). ; ESI MS m/z 549 [M + H]⁺; HPLC 95.4% (AUC), t_R = 10.09 min.

5 Example 41

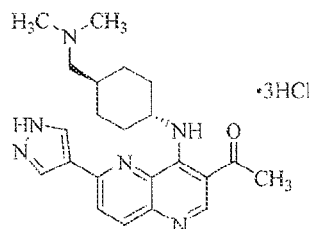
1-{4-[2-(3-Aminopyrrolidin-1-yl)pyrimidin-5-ylamino]-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}ethanone trihydrochloride



Following general procedure IV-1, *tert*-butyl 1-{5-[3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino]pyrimidin-2-yl}pyrrolidin-3-ylcarbamate (123 mg, 0.20 mmol) was reacted with 6 N HCl (2 mL) followed by formation of the trihydrochloride salt to afford the desired product (62 mg, 50%) as a light orange solid: ¹H NMR (500 MHz, CD₃OD) δ 9.36 (br s, 1H), 8.51 – 8.35 (m, 3H), 7.51 (br s, 2H), 4.12 – 3.97 (m, 2H), 3.89 – 3.84 (m, 1H), 3.80 – 3.69 (m, 2H), 2.84 (br s, 3H), 2.58 – 2.48 (m, 1H), 2.28 – 2.17 (m, 1H). ; ESI MS m/z 510 [M + H]⁺; HPLC 95.6% (AUC), t_R = 9.18 min.

Example 42

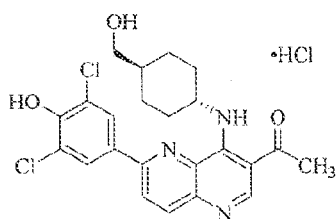
1-(4-{*trans*-4-[(Dimethylamino)methyl]cyclohexylamino}-6-(1H-pyrazol-4-yl)-1,5-naphthyridin-3-yl)ethanone trihydrochloride



Following general procedure II, 1-(6-chloro-4-{4-[(dimethylamino)methyl]-cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone (55 mg, 0.15 mmol) was reacted with *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (66 mg, 0.225 mmol) followed by formation of the trihydrochloride salt to afford the desired product (32 mg, 42%) as a yellow solid: ¹H NMR (300 MHz, CD₃OD) δ 9.10 (s, 1H), 8.34 (s, 2H) 8.30 – 8.23 (m, 2H), 5.64 (m, 1H), 3.14 (d, *J* = 6.7 Hz, 2H), 2.94 (s, 6H), 2.75 (s, 3H), 2.47 (d, *J* = 13.0 Hz, 2H), 2.09 – 1.97 (m, 3H), 1.73 – 1.61 (m, 2H), 1.45 – 1.33 (m, 2H); ESI MS *m/z* 393 [M + H]⁺; HPLC 98.3% (AUC), *t_R* = 8.60 min.

Example 43

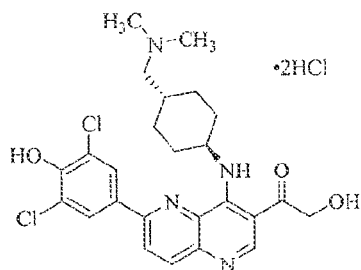
1-(6-{3,5-Dichloro-4-hydroxyphenyl}-4-[*trans*-4-(hydroxymethyl)cyclohexyl]amino}-1,5-naphthyridin-3-yl)ethanone hydrochloride



Following general procedure II, 1-{6-chloro-4-(hydroxymethyl)cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone (34 mg, 0.10 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (44 mg, 0.15 mmol) followed by formation of the hydrochloride salt to afford the desired product (40 mg, 80%) as an orange solid: ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.83 (d, *J* = 8.0 Hz, 1H), 10.91 (s, 1H), 9.22 (s, 1H), 8.61 (d, *J* = 8.9 Hz, 1H), 8.50 (d, *J* = 9.0 Hz, 1H), 8.16 (s, 2H), 5.55 – 5.45 (m, 1H), 3.28 (d, *J* = 6.5 Hz, 2H), 2.76 (s, 3H), 2.25 – 2.23 (m, 2H), 1.96 – 1.88 (m, 2H), 1.50 – 1.42 (m, 3H), 1.17 – 1.12 (m, 2H); ESI MS *m/z* 460 [M + H]⁺; HPLC 96.8% (AUC), *t_R* = 11.64 min.

Example 44

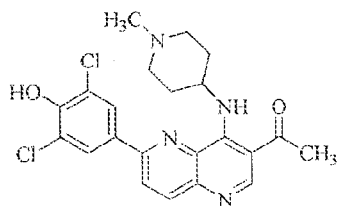
1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl]-2-hydroxyethanone dihydrochloride



Following general procedure II, 1-(6-chloro-4-*trans*-4-[(dimethylamino)methyl]-cyclohexylamino)-1,5-naphthyridin-3-yl)-2-hydroxyethanone (18 mg, 0.048 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (18 mg, 0.062 mmol) followed by formation of the dihydrochloride salt to afford the desired product (9.1 mg, 33%) as an off-white solid. ^1H NMR (500 MHz, CD_3OD) δ 9.13 (s, 1H), 8.47 (d, $J = 8.9$ Hz, 1H), 8.33 (d, $J = 8.9$ Hz, 1H), 8.13 (s, 2H), 5.78 – 5.68 (m, 1H), 4.91 (s, 2H), 3.10 (d, $J = 6.7$ Hz, 2H), 2.94 (s, 6H), 2.49 – 2.42 (m, 2H), 2.10 – 2.00 (m, 3H), 1.76 – 1.66 (m, 2H), 1.48 – 1.36 (m, 2H); ESI MS m/z 503 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R =$ 9.40 min.

Example 45

1-{6-(3,5-Dichloro-4-hydroxyphenyl)-4-[(1-methylpiperidin-4-yl)amino]-1,5-naphthyridin-3-yl}ethanone

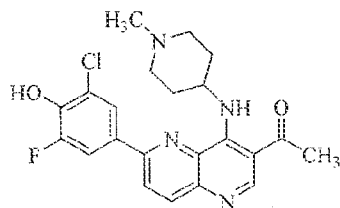


Following general procedure II, 1-(6-chloro-4-[(1-methylpiperidin-4-yl)amino]-1,5-naphthyridin-3-yl)ethanone (70 mg, 0.22 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (95 mg, 0.33 mmol) to afford the desired product (52 mg, 53%) as a yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 8.85 (s, 1H), 8.09 – 8.01 (m, 2H), 7.94 (s, 2H), 5.74 – 5.70 (m, 1H), 2.95 – 2.92 (m, 2H), 2.68 (s, 3H), 2.51 (t, $J = 11.7$ Hz, 2H), 2.37 (s, 3H), 2.33 – 2.25 (m, 2H), 1.73 – 1.71 (m, 2H); ESI MS m/z 445

$[M + H]^+$; HPLC >99% (AUC), $t_R = 9.03$ min.

Example 46

1-{6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-[(1-methylpiperidin-4-yl)amino]-
1,5-naphthyridin-3-yl}ethanone

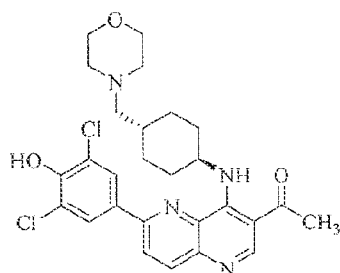


5

Following general procedure II, 1-{6-chloro-4-[(1-methylpiperidin-4-yl)amino]-
1,5-naphthyridin-3-yl}ethanone (69 mg, 0.22 mmol) was reacted with 2-chloro-6-fluoro-4-
(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (88 mg, 0.32 mmol) to afford the
desired product (44 mg, 47%) as a yellow solid: ^1H NMR (500 MHz, $CD_3OD + D_2O$) δ 8.94
10 (s, 1H), 8.15 (s, 2H), 7.92 (s, 1H), 7.74 (dd, $J = 12.0, 2.2$ Hz, 1H), 5.70 – 5.62 (m, 1H), 3.17
– 3.12 (m, 2H), 2.71 (s, 3H), 2.69 – 2.64 (m, 2H), 2.53 (s, 3H), 2.37 – 2.35 (m, 2H), 1.85 –
1.82 (m, 2H); ESI MS m/z 429 $[M + H]^+$; HPLC >99% (AUC), $t_R = 8.80$ min.

Example 47

1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4-[[*trans*-4-(morpholinomethyl)cyclohexyl]amino]-
15 1,5-naphthyridin-3-yl]ethanone

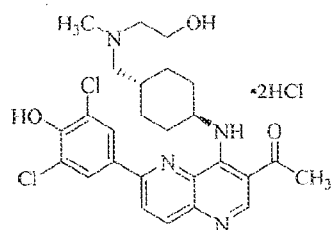


Following general procedure II, 1-(6-chloro-4-[[4-(morpholinomethyl)cyclohexyl]-
amino]-1,5-naphthyridin-3-yl)ethanone (85 mg, 0.21 mmol) was reacted with 2,6-dichloro-
4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (91 mg, 0.31 mmol) to afford the
20 desired product (59 mg, 53%) as an orange solid: ^1H NMR (500 MHz, $CDCl_3$) δ 11.18 –

11.16 (m, 1H), 8.95 (s, 1H), 8.21 (d, $J = 8.8$ Hz, 1H), 7.99 (s, 2H), 7.94 (d, $J = 8.8$ Hz, 1H), 5.51 – 5.42 (m, 1H), 3.71 (t, $J = 4.7$ Hz, 4H), 2.70 (s, 3H), 2.41 – 2.43 (m, 4H), 2.34 – 2.32 (m, 2H), 2.23 – 2.22 (m, 2H), 2.02 – 1.95 (m, 2H), 1.62 – 1.58 (m, 1H), 1.46 – 1.39 (m, 2H), 1.28 – 1.15 (m, 2H); ESI MS m/z 529 $[M + H]^+$; HPLC 98.2% (AUC), $t_R = 9.93$ min.

5 Example 48

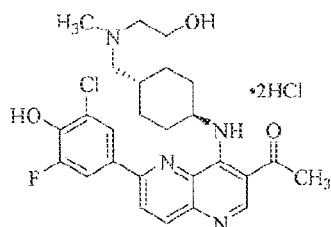
1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4-(*trans*-4-{[(2-hydroxyethyl)(methyl)amino]methyl}-cyclohexylamino)-1,5-naphthyridin-3-yl]ethanone dihydrochloride



10 Following general procedure II, 1-[6-chloro-4-(4-{[(2-hydroxyethyl)(methyl)amino]methyl}cyclohexylamino)-1,5-naphthyridin-3-yl]ethanone (70 mg, 0.18 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (76 mg, 0.27 mmol) followed by formation of the dihydrochloride salt to afford the desired product (68 mg, 64%) as a light yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 9.15 (s, 1H), 8.46 (d, $J = 9.0$ Hz, 1H), 8.34 (d, $J = 9.0$ Hz, 1H), 8.12 (s, 2H), 5.74 – 5.71 (m, 1H), 3.90 (t, $J = 5.0$ Hz, 2H), 3.39 – 3.37 (m, 1H), 3.28 – 3.26 (m, 2H), 3.06 – 3.02 (m, 1H), 2.97 (s, 3H), 2.76 (m, 3H), 2.46 – 2.43 (m, 2H), 2.13 – 2.03 (m, 3H), 1.69 – 1.66 (m, 2H), 1.44 – 1.42 (m, 2H); ESI MS m/z 517 $[M + H]^+$; HPLC >99% (AUC), $t_R = 9.74$ min.

Example 49

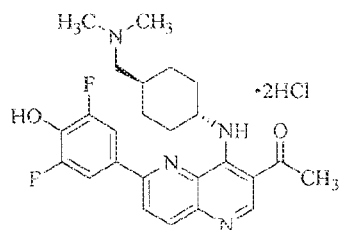
20 1-[6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-(*trans*-4-{[(2-hydroxyethyl)(methyl)amino]methyl}cyclohexylamino)-1,5-naphthyridin-3-yl]ethanone dihydrochloride



Following general procedure II, 1-[6-chloro-4-((2-hydroxyethyl)(methyl)amino)-methyl]cyclohexylamino)-1,5-naphthyridin-3-yl]ethanone (30 mg, 0.076 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (31 mg, 0.11 mmol) followed by formation of the dihydrochloride salt to afford the desired product (32 mg, 73%) as a light yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 9.14 (s, 1H), 8.45 (d, $J = 9.0$ Hz, 1H), 8.33 (d, $J = 9.0$ Hz, 1H), 8.03 (s, 1H), 7.89 (d, $J = 11.5$ Hz, 1H), 5.74 – 5.71 (m, 1H), 3.90 (t, $J = 5.1$ Hz, 2H), 3.45 – 3.32 (m, 1H), 3.30 – 3.26 (m, 2H), 3.07 – 3.04 (m, 1H), 2.97 (s, 3H), 2.76 (s, 3H), 2.45 (s, 2H), 2.17 – 2.02 (m, 3H), 1.70 – 1.62 (m, 2H), 1.48 – 1.36 (m, 2H); ESI MS m/z 501 $[\text{M} + \text{H}]^+$; HPLC 98.2% (AUC), $t_R = 9.54$ min.

Example 50

1-[6-(3,5-Difluoro-4-hydroxyphenyl)-4-*trans*-4-[(dimethylamino)methyl]cyclohexylamino)-1,5-naphthyridin-3-yl]ethanone dihydrochloride

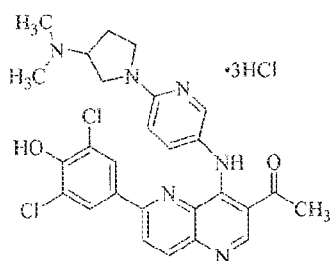


Following general procedure II, 1-(6-chloro-4-4-[(dimethylamino)methyl]cyclohexylamino)-1,5-naphthyridin-3-yl]ethanone (65 mg, 0.18 mmol) was reacted with 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (69 mg, 0.27 mmol) followed by formation of the dihydrochloride salt to afford

the desired product (87 mg, 90%) as an off-white solid: ^1H NMR (500 MHz, CD_3OD) δ 9.13 (s, 1H), 8.44 (d, $J = 9.0$ Hz, 1H), 8.35 (d, $J = 9.0$ Hz, 1H), 7.78 (dd, $J = 7.8, 1.7$ Hz, 2H), 5.66 – 5.62 (m, 1H), 3.09 (d, $J = 6.6$ Hz, 2H), 2.94 (s, 6H), 2.76 (s, 3H), 2.47 – 2.44 (m, 2H), 2.08 – 2.04 (m, 3H), 1.72 – 1.68 (m, 2H), 1.37 – 1.28 (m, 2H); ESI MS m/z 455 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 9.49$ min.

Example 51

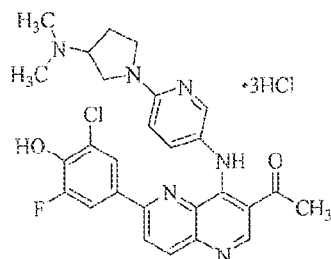
1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4-{6-[3-(dimethylamino)pyrrolidin-1-yl]pyridin-3-ylamino}-1,5-naphthyridin-3-yl]ethanone trihydrochloride



Following general procedure II, 1-(6-chloro-4-{6-[3-(dimethylamino)pyrrolidin-1-yl]-pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone (55 mg, 0.134 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (58 mg, 0.20 mmol) followed by formation of the trihydrochloride salt to afford the desired product (75 mg, 86%) as an orange solid: ^1H NMR (300 MHz, CD_3OD) δ 9.41 (s, 1H), 8.55 – 8.38 (m, 2H), 8.30 (d, $J = 2.4$ Hz, 1H), 7.97 (dd, $J = 9.5, 2.4$ Hz, 1H), 7.54 (s, 2H), 7.05 (d, $J = 9.5$ Hz, 1H), 4.20 – 4.16 (m, 2H), 4.02 – 3.86 (m, 2H), 3.80 – 3.70 (m, 1H), 3.03 (s, 6H), 2.85 (s, 3H), 2.82 – 2.68 (m, 1H), 2.39 – 2.52 (m, 1H); ESI MS m/z 537 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 9.08$ min.

Example 52

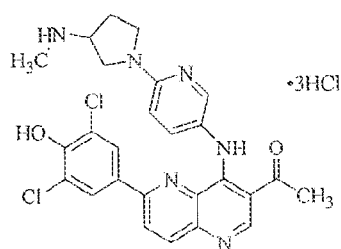
1-[6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-{6-[3-(dimethylamino)pyrrolidin-1-yl]pyridin-3-ylamino}-1,5-naphthyridin-3-yl]ethanone trihydrochloride



Following general procedure II, 1-(6-chloro-4-{6-[3-(dimethylamino)pyrrolidin-1-yl]pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone (55 mg, 0.134 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (55 mg, 0.20 mmol) followed by formation of the trihydrochloride salt to afford the desired product (85 mg, 99%) as a yellow solid: ^1H NMR (300 MHz, CD_3OD) δ 9.41 (s, 1H), 8.54 – 8.37 (m, 2H), 8.29 (d, J = 2.3 Hz, 1H), 7.99 (dd, J = 9.5, 2.3 Hz, 1H), 7.39 – 7.35 (m, 2H), 7.10 (d, J = 9.5 Hz, 1H), 4.29 – 4.11 (m, 2H), 4.03 – 3.85 (m, 2H), 3.75 – 3.71 (m, 1H), 3.03 (s, 6H), 2.85 (s, 3H), 2.71 – 2.82 (s, 1H); ESI MS m/z 521 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), t_R = 8.90 min.

Example 53

1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-{6-[3-(methylamino)pyrrolidin-1-yl]pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone trihydrochloride

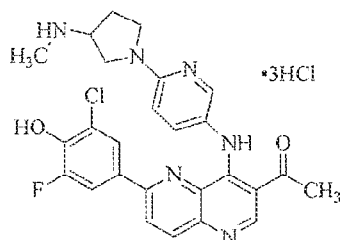


Following general procedure D-1, *tert*-butyl 1-{5-[3-acetyl-6-(3,5-dichloro-4-hydroxy-phenyl)-1,5-naphthyridin-4-ylamino]pyridin-2-yl}pyrrolidin-3-yl(methyl)carbamate (0.183 mmol) was reacted with TFA (2 mL) followed by formation of the trihydrochloride salt to afford the desired product (57 mg, 49% over two steps) as an orange-yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 9.37 (s, 1H), 8.49 (d, J = 8.9 Hz, 1H),

8.40 (d, $J = 8.9$ Hz, 1H), 8.24 (d, $J = 2.5$ Hz, 1H), 7.88 (dd, $J = 9.4, 2.5$ Hz, 1H), 7.57 (s, 2H), 6.96 (d, $J = 9.4$ Hz, 1H), 4.13 – 4.00 (m, 2H), 3.92 – 3.79 (m, 2H), 3.66 – 3.73 (m, 1H), 2.83 (s, 6H), 2.72 – 2.60 (m, 1H), 2.45 – 2.34 (m, 1H); ESI MS m/z 523 $[M + H]^+$; HPLC >99% (AUC), $t_R = 8.97$ min.

5 Example 54

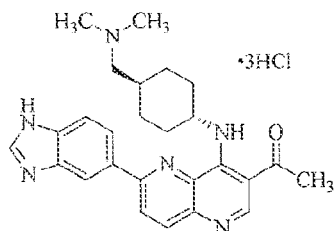
1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-{6-[3-(methylamino)pyrrolidin-1-yl]pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone trihydrochloride



Following general procedure D-1, *tert*-butyl 1-{5-[3-acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino]pyridin-2-yl}pyrrolidin-3-yl(methyl) carbamate (0.189 mmol) was reacted with TFA (2 mL) followed by formation of the trihydrochloride salt to afford the desired product (73 mg, 63% over two steps) as an orange solid: ^1H NMR (500 MHz, CD_3OD) δ 9.34 (s, 1H), 8.46 (d, $J = 9.0$ Hz, 1H), 8.38 (d, $J = 9.0$ Hz, 1H), 8.22 (d, $J = 2.5$ Hz, 1H), 7.82 (dd, $J = 9.4, 2.5$ Hz, 1H), 7.40 (s, 1H), 7.32 (d, $J = 11.8$ Hz, 1H), 6.92 (d, $J = 9.4$ Hz, 1H), 4.16 – 3.97 (m, 2H), 3.90 – 3.78 (m, 2H), 3.75 – 3.65 (m, 1H), 2.83 (s, 6H), 2.72 – 2.60 (m, 1H), 2.42 – 3.34 (m, 1H); ESI MS m/z 507 $[M + H]^+$; HPLC >99% (AUC), $t_R = 8.72$ min.

Example 55

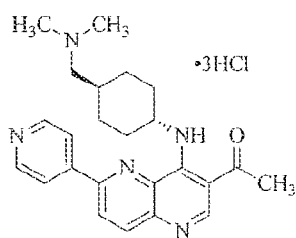
1-(6-(1H-Benzo[d]imidazol-5-yl)-4-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone trihydrochloride



Following general procedure II, 1-(6-chloro-4-*trans*-4-
 [(dimethylamino)methyl]cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone (68 mg, 0.188
 mmol) was reacted with 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-
 5 benzo[d]imidazole (69 mg, 0.282 mmol) followed by formation of the trihydrochloride salt
 to afford the desired product (76 mg, 73%) as a yellow-brown solid: ¹H NMR (500 MHz,
 CD₃OD) δ 9.49 (s, 1H), 9.19 (s, 1H), 8.63 (d, *J* = 8.9 Hz, 1H), 8.56 (s, 1H), 8.46 (d, *J* = 8.9
 Hz, 1H), 8.37 (d, *J* = 8.5 Hz, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 5.65 – 5.55 (m, 1H), 3.15 (d, *J* =
 6.9 Hz, 2H), 2.93 (s, 6H), 2.78 (s, 3H), 2.52 – 2.48 (m, 2H), 2.07 – 1.95 (m, 3H), 1.76 –
 10 1.64 (m, 2H), 1.43 – 1.31 (m, 2H); ESI MS *m/z* 443 [M + H]⁺; HPLC 97.7% (AUC), *t_R* =
 8.20 min.

Example 56

1-[4-[4-(*trans*-4-Dimethylamino)methylcyclohexylamino]-6-(pyridin-4-yl)-
 1,5-naphthyridin-3-yl]ethanone trihydrochloride



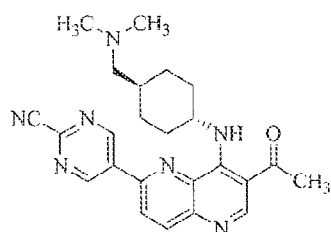
15

Following general procedure II, 1-(6-chloro-4-(*trans*-4-
 ((dimethylamino)methyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone (89 mg, 0.247
 mmol) was reacted with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (45 mg,
 0.370 mmol) followed by formation of the trihydrochloride salt to afford the desired product
 20 (108 mg, 85%) as a yellow solid: ¹H NMR (500 MHz, CD₃OD) δ 9.28 – 9.20 (m, 3H), 8.81

(d, $J = 8.9$ Hz, 1H), 8.74 – 8.69 (m, 2H), 8.57 (d, $J = 8.9$ Hz, 1H), 5.51 – 5.43 (m, 1H), 3.17 (d, $J = 6.7$ Hz, 2H), 2.94 (s, 6H), 2.78 (s, 3H), 2.52 – 2.44 (m, 2H), 2.08 – 1.97 (m, 3H), 1.77 – 1.65 (m, 2H), 1.42 – 1.33 (m, 2H); ESI MS m/z 404 $[M + H]^+$; HPLC 95.6% (AUC), $t_R = 7.62$ min.

5 Example 57

5-(7-Acetyl-8-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-2-yl)pyrimidine-2-carbonitrile



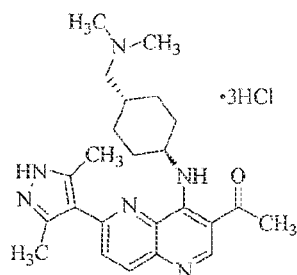
Following general procedure II, 1-(6-chloro-4-{*trans*-4-

- 10 [(dimethylamino)methyl]cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone (87 mg, 0.24 mmol) was reacted with 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine-2-carbonitrile (83 mg, 0.36 mmol) to afford the desired product (24 mg, 23%) as a yellow solid: ^1H NMR (500 MHz, $\text{CD}_3\text{OD} + \text{TFA}-d$) δ 9.62 (s, 2H), 9.23 (s, 1H), 8.68 (d, $J = 8.9$ Hz, 1H), 8.51 (d, $J = 8.9$ Hz, 1H), 5.52 – 5.41 (m, 1H), 3.12 (d, $J = 6.8$ Hz, 2H), 2.94 (s, 6H), 2.77 (s, 3H), 2.51 – 2.42 (m, 2H), 2.08 – 1.94 (m, 3H), 1.88 – 1.65 (m, 2H), 1.37 – 1.25 (m, 2H); ESI MS m/z 430 $[M + H]^+$; HPLC >99% (AUC), $t_R = 8.73$ min.
- 15

Example 58

1-(6-(3,5-Dimethyl-1H-pyrazol-4-yl)-4-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone

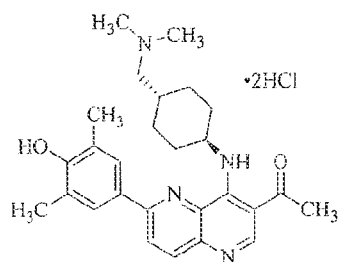
- 20 trihydrochloride



Following general procedure D-1, *tert*-butyl 4-(7-acetyl-8-*{trans*-4-
 [(dimethylamino)-methyl]cyclohexyl}amino)-1,5-naphthyridin-2-yl)-3,5-dimethyl-1H-
 pyrazole-1-carboxylate (0.25 mmol) was reacted with TFA (2 mL) followed by formation
 5 of the trihydrochloride salt to afford the desired product (96 mg, 72% over two steps) as a
 yellow foam: $^1\text{H NMR}$ (500 MHz, CD_3OD) δ 9.17 (s, 1H), 8.36 (d, $J = 8.8$ Hz, 1H), 8.08 (d,
 $J = 8.8$ Hz, 1H), 5.64–5.52 (m, 1H), 3.05 (d, $J = 6.7$ Hz, 2H), 2.90 (s, 6H), 2.76 (s, 3H),
 2.47 (s, 6H), 2.38–2.29 (m, 2H), 1.99–1.87 (m, 3H), 1.68–1.52 (m, 2H), 1.21–1.07 (m,
 2H); ESI MS m/z 421 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 8.45$ min.

10 Example 59

1-(4-*{trans*-4-[(Dimethylamino)methyl]cyclohexylamino}-6-(4-hydroxy-3,5-
 dimethylphenyl)-
 1,5-naphthyridin-3-yl)ethanone dichloride

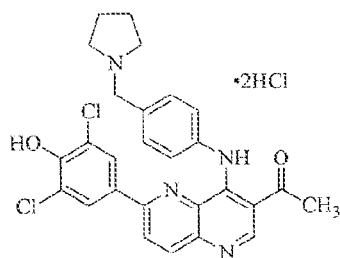


15 Following general procedure II, 1-(6-chloro-4-*{trans*-4-
 [(dimethylamino)methyl]cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone (60 mg, 0.166
 mmol) was reacted with 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-
 yl)phenol (62 mg, 0.25 mmol) followed by formation of the trihydrochloride salt to afford
 the desired product (41 mg, 48%) as a yellow solid: $^1\text{H NMR}$ (500 MHz, CD_3OD) δ 9.10 (s,

1H), 8.39 (d, $J = 9.0$ Hz, 1H), 8.26 (d, $J = 9.0$ Hz, 1H), 7.72 (s, 2H), 5.82 – 5.73 (m, 1H), 3.06 (d, $J = 6.6$ Hz, 2H), 2.93 (s, 6H), 2.75 (s, 3H), 2.49 – 2.42 (m, 2H), 2.35 (s, 6H), 2.09 – 1.98 (m, 3H), 1.73 – 1.60 (m, 2H), 1.40 – 1.27 (m, 2H); ESI MS m/z 447 $[M + H]^+$; HPLC 98.4% (AUC), $t_R = 9.81$ min.

5 Example 60

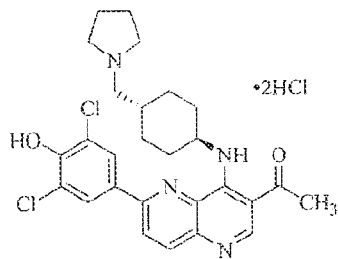
1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-{6-[3-(dimethylamino)pyrrolidin-1-yl]pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone dihydrochloride



Following general procedure II, 1-{6-chloro-4-[4-(pyrrolidin-1-ylmethyl)phenylamino]-1,5-naphthyridin-3-yl} ethanone (72 mg, 0.189 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (82 mg, 0.284 mmol) followed by formation of the dihydrochloride salt to afford the desired product (50 mg, 45%) as a yellow solid: $^1\text{H NMR}$ (500 MHz, CD_3OD) δ 9.34 (s, 1H), 8.44 (d, $J = 8.9$ Hz, 1H), 8.36 (d, $J = 8.9$ Hz, 1H), 7.68 – 7.62 (m, 2H), 7.54 – 7.47 (m, 2H), 7.40 (br s, 2H), 4.49 (s, 2H), 3.53 – 3.44 (m, 2H), 3.25 – 3.17 (m, 2H), 2.81 (s, 3H), 2.24 – 2.14 (m, 2H), 1.92 – 2.05 (m, 2H); ESI MS m/z 507 $[M + H]^+$; HPLC >99% (AUC), $t_R = 10.07$ min.

Example 61

1-{6-(3,5-Dichloro-4-hydroxyphenyl)-4-{*trans*-4-(pyrrolidin-1-ylmethyl)cyclohexylamino}-1,5-naphthyridin-3-yl} ethanone dihydrochloride

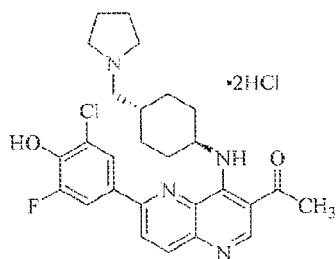


20

Following general procedure II, 1-(6-chloro-4-*trans*-4-(pyrrolidin-1-ylmethyl)-cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone (67 mg, 0.17 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (58 mg, 0.21 mmol) followed by formation of the dihydrochloride salt to afford the desired product (36 mg, 36%) as an off-white solid: ^1H NMR (300 MHz, CD_3OD) δ 9.15 (s, 1H), 8.47 (d, $J = 9.0$ Hz, 1H), 8.34 (d, $J = 9.0$ Hz, 1H), 8.12 (s, 2H), 5.75 – 5.67 (m, 1H), 3.72 – 3.65 (m, 2H), 3.17 – 3.06 (m, 4H), 2.76 (s, 3H), 2.48 – 2.40 (m, 2H), 2.20–1.99 (m, 6H), 1.73 – 1.61 (m, 2H), 1.47 – 1.36 (m, 2H); ESI MS m/z 513 $[\text{M} + \text{H}]^+$; HPLC 95.7% (AUC), $t_R = 10.21$ min.

Example 62

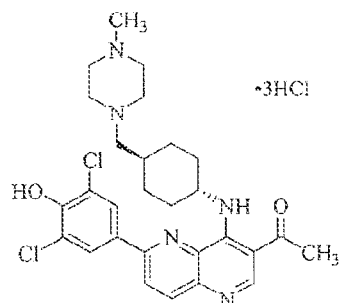
1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-*trans*-4-(pyrrolidin-1-ylmethyl)-cyclohexyl amino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride



Following general procedure II, 1-(6-chloro-4-*trans*-4-(pyrrolidin-1-ylmethyl)-cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone (86 mg, 0.22 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (90 mg, 0.33 mmol) followed by formation of the dihydrochloride salt to afford the desired product (75 mg, 69%) as a light brown solid: ^1H NMR (500 MHz, CD_3OD) δ 9.14 (s, 1H), 8.45 (d, $J = 9.0$ Hz, 1H), 8.34 (d, $J = 9.0$ Hz, 1H), 8.02 (s, 1H), 7.88 (dd, $J = 11.5, 2.0$ Hz, 1H), 5.74 – 5.64 (m, 1H), 3.74 – 3.68 (m, 2H), 3.18 – 3.10 (m, 4H), 2.76 (s, 3H), 2.47 – 2.41 (m, 2H), 2.22 – 1.98 (m, 7H), 1.74 – 1.62 (m, 2H), 1.47 – 1.34 (m, 2H); ESI MS m/z 497 $[\text{M} + \text{H}]^+$; HPLC 96.6% (AUC), $t_R = 9.90$ min.

Example 63

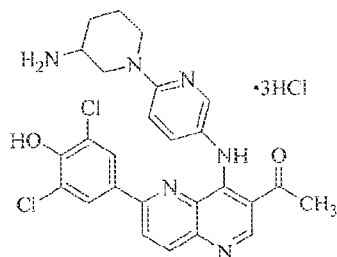
1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-*trans*-4-[(4-methylpiperazin-1-yl)methyl]cyclohexyl amino)-1,5-naphthyridin-3-yl)ethanone trihydrochloride



Following general procedure II, 1-(6-chloro-4-((4-methylpiperazin-1-yl)methyl)-cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone (32 mg, 0.076 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (26 mg, 0.092 mmol) followed by formation of the trihydrochloride salt to afford the desired product (31 mg, 67%) as a yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 9.14 (s, 1H), 8.46 (d, J = 8.9 Hz, 1H), 8.33 (d, J = 8.9 Hz, 1H), 8.10 (s, 2H), 5.73 – 5.68 (m, 1H), 3.75 (br s, 8H), 3.16 (br s, 2H), 3.02 (s, 3H), 2.76 (s, 3H), 2.46 – 2.42 (m, 2H), 2.22 – 2.14 (m, 2H), 2.10 – 2.00 (m, 1H), 1.72–1.63 (m, 2H), 1.46 – 1.37 (m, 2H); ESI MS m/z 542 $[\text{M} + \text{H}]^+$; HPLC 96.7% (AUC), t_R = 9.37 min.

Example 64

1-(4-([6-(3-Aminopiperidin-1-yl)pyridin-3-yl]amino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone trihydrochloride

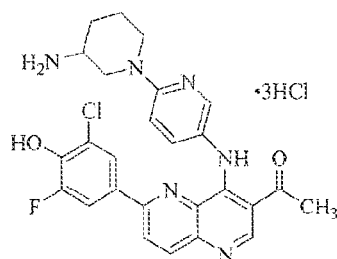


Following general procedure IV-2, *tert*-butyl [1-(5-([3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl]amino)pyridin-2-yl)piperidin-3-yl]carbamate (0.20 mmol) was reacted with TFA (2 mL) followed by formation of the trihydrochloride salt to afford the desired product (31 mg, 30% over two steps) as an orange solid: ^1H NMR (500 MHz, CD_3OD) δ 9.38 (s, 1H), 8.49 (d, J = 9.0 Hz, 1H), 8.41 (d, J = 9.0 Hz, 1H), 8.25 (d, J

= 2.6 Hz, 1H), 7.92 – 7.86 (m, 1H), 7.58 (s, 2H), 7.24 (d, $J = 9.5$ Hz, 1H), 4.41 – 4.34 (m, 1H), 4.03 – 3.96 (m, 1H), 3.53 – 3.32 (m, 4H), 2.84 (s, 3H), 2.24 – 2.21 (m, 1H), 2.05 – 1.97 (m, 1H), 1.84 – 1.76 (m, 2H); ESI MS m/z 523 $[M + H]^+$; HPLC 98.0% (AUC), t_R = 9.48 min.

5 Example 65

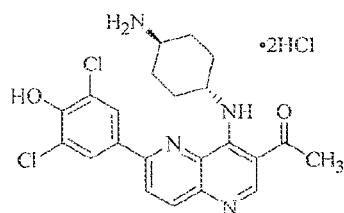
1-(4-{{6-(3-Aminopiperidin-1-yl)pyridin-3-yl}amino}-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}ethanone trihydrochloride



Following general procedure IV-2, *tert*-butyl [1-(5-{{3-acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl}amino}pyridin-2-yl)piperidin-3-yl]carbamate (0.20 mmol) was reacted with TFA (2 mL) followed by formation of the trihydrochloride salt to afford the desired product (33 mg, 33% over two steps) as an orange solid: ^1H NMR (500 MHz, CD_3OD) δ 9.38 (s, 1H), 8.48 (d, $J = 9.5$ Hz, 1H), 8.41 (d, $J = 9.5$ Hz), 8.25 (d, $J = 2.5$ Hz, 1H), 7.91 (dd, $J = 9.5, 2.5$ Hz, 1H), 7.41 – 7.37 (m, 2H), 7.28 (d, $J = 9.5$ Hz, 1H), 4.37 (d, $J = 10.7$ Hz, 1H), 4.03 – 3.99 (m, 1H), 3.52 – 3.32 (m, 3H), 2.84 (s, 3H), 2.28 – 2.20 (m, 1H), 2.08 – 1.98 (m, 1H), 1.84-1.78 (m, 2H); ESI MS m/z 507 $[M + H]^+$; HPLC >99% (AUC), t_R = 9.38 min.

Example 66

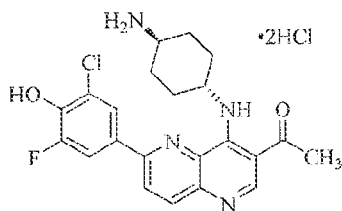
1-(4-[[*trans*-(4-Aminocyclohexyl)amino]-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl]-ethanone dihydrochloride



Following general procedure IV-2, *tert*-butyl (4-([3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl]amino)cyclohexyl)carbamate (0.23 mmol) was reacted with TFA (2 mL) followed by formation of the dihydrochloride salt to afford the desired product (32 mg, 27% over two steps) as a gray solid: ^1H NMR (300 MHz, D_2O) δ 8.96 (s, 1H), 8.18–8.00 (m, 2H), 7.53 (s, 2H), 3.28–3.23 (m, 1H), 2.68 (s, 3H), 2.28–2.24 (m, 2H), 2.16–2.13 (m, 2H), 1.76–1.64 (m, 2H), 1.57–1.45 (m, 2H); ESI MS m/z 445 $[\text{M} + \text{H}]^+$; HPLC 98.4% (AUC), $t_R = 9.34$ min.

Example 67

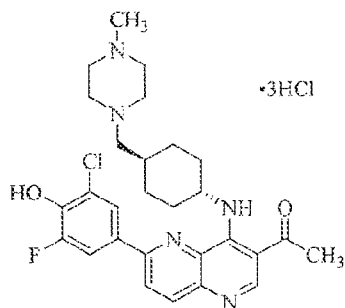
1-{4-[*trans*-(4-Aminocyclohexyl)amino]-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}ethanone dihydrochloride



Following general procedure IV-2, *tert*-butyl (4-([3-acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl]amino)cyclohexyl)carbamate (0.20 mmol) was reacted with TFA (2 mL) followed by formation of the dihydrochloride salt to afford the desired product (45 mg, 45% over two steps) as a white solid: ^1H NMR (500 MHz, D_2O) δ 8.99 (s, 1H), 8.13 (d, $J = 9.0$ Hz, 1H), 8.03 (d, $J = 9.0$ Hz, 1H), 7.40–7.34 (m, 2H), 4.91–4.94 (m, 1H), 3.35–3.28 (m, 1H), 2.72 (s, 3H), 2.30–2.22 (m, 2H), 2.21–2.14 (m, 2H), 1.75–1.68 (m, 2H), 1.56–1.48 (m, 2H); ESI MS m/z 429 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 9.10$ min.

Example 68

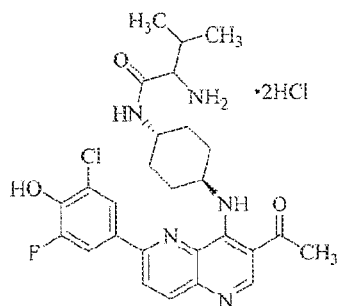
1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-{*trans*-4-[(4-methylpiperazin-1-yl)methyl]-cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone trihydrochloride



Following general procedure II, 1-(6-chloro-4-((4-methylpiperazin-1-yl)methyl)-cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone (53 mg, 0.13 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (41 mg, 0.152 mmol) followed by formation of the trihydrochloride salt to afford the desired product (11 mg, 14%) as a yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 9.14 (s, 1H), 8.45 (d, $J=9.0$ Hz, 1H), 8.32 (d, $J=9.0$ Hz, 1H), 8.02 (s, 1H), 7.88 (dd, $J=11.4, 2.2$ Hz, 1H), 5.75–5.65 (m, 1H), 3.70 (br s, 8H), 3.10 (br s, 2H), 3.01 (s, 3H), 2.75 (s, 3H), 2.46–2.42 (m, 2H), 2.16–2.13 (m, 2H), 2.05–2.02 (m, 1H), 1.73–1.61 (m, 2H), 1.46–1.35 (m, 2H); ESI MS m/z 526 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 9.14$ min.

Example 69

N-(*trans*-4-([3-Acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl]amino)-cyclohexyl)-2-amino-3-methylbutanamide dihydrochloride

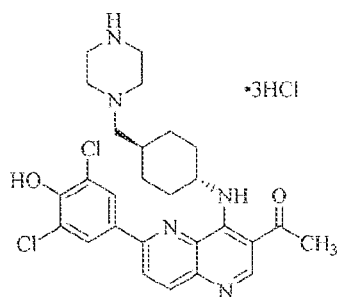


Following general procedure IV-2, *tert*-butyl [1-(*trans*-4-([3-acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl]amino)-cyclohexylamino)-3-methyl-1-oxobutan-2-yl]carbamate (0.19 mmol) was reacted with TFA (2 mL) followed by formation of the dihydrochloride salt to afford the desired product (35 mg, 30% over two steps) as an off-

white solid: ^1H NMR (500 MHz, CD_3OD) δ 9.14 (s, 1H), 8.44 (d, $J = 9.0$ Hz, 1H), 8.33 (d, $J = 9.0$ Hz, 1H), 8.00 (s, 1H), 7.87 (dd, $J = 11.4, 2.2$ Hz, 1H), 5.63 – 5.57 (m, 1H), 3.88 – 3.83 (m, 1H), 3.62 (d, $J = 6.0$ Hz, 1H), 2.76 (s, 3H), 2.51 – 2.40 (m, 2H), 2.10 – 2.12 (m, 3H), 1.81 – 1.53 (m, 4H), 1.08 (t, $J = 7.4$ Hz, 6H); ESI MS m/z 528 $[\text{M} + \text{H}]^+$; HPLC 98.9% (AUC), $t_R = 9.99$ min.

Example 70

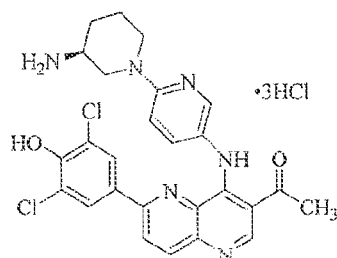
1-{6-(3,5-Dichloro-4-hydroxyphenyl)-4-[*trans*-4-(piperazin-1-ylmethyl)cyclohexylamino]-1,5-naphthyridin-3-yl} ethanone trihydrochloride



Following general procedure IV-2, *tert*-butyl 4-((4-((3-acetyl-6-(3,5-dichloro-4-hydroxy-phenyl)-1,5-naphthyridin-4-yl)amino)cyclohexyl)methyl)piperazine-1-carboxylate (0.298 mmol) was reacted with TFA (2 mL) followed by formation of the trihydrochloride salt to afford the desired product (84 mg, 47% over two steps) as a yellow solid: ^1H NMR (500 MHz, D_2O) δ 9.00 (s, 1H), 8.22 – 8.11 (m, 2H), 7.59 (s, 2H), 5.06 (m, 1H), 4.76 – 4.71 (m, 1H), 4.66 (s, 1H), 3.60 (s, 8H), 3.15 (d, $J = 6.7$ Hz, 2H), 2.74 (s, 3H), 2.25 – 2.23 (m, 2H), 2.02 – 1.97 (m, 2H), 1.60 – 1.58 (m, 2H), 1.24 – 1.20 (m, 2H); ESI MS m/z 528 $[\text{M} + \text{H}]^+$; HPLC 98.0% (AUC), $t_R = 9.29$ min.

Example 71

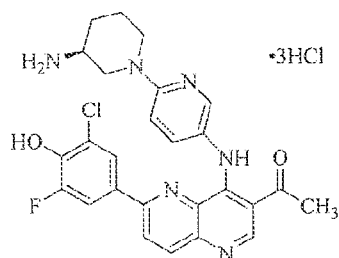
(S)-1-(4-{{6-(3-Aminopiperidin-1-yl)pyridin-3-yl}amino}-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone trihydrochloride



Following general procedure IV-2, (S)-tert-butyl [1-(5-{[3-acetyl-6-(3,5-dichloro-4-hydroxy-phenyl)-1,5-naphthyridin-4-yl]amino}pyridin-2-yl)piperidin-3-yl]carbamate (0.197 mmol) was reacted with TFA (2 mL) followed by formation of the trihydrochloride salt to afford the desired product (42 mg, 33% over two steps) as a yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 9.39 (s, 1H), 8.49 (d, $J = 9.0$ Hz, 1H), 8.41 (d, $J = 9.0$ Hz, 1H), 8.25 (d, $J = 2.6$ Hz, 1H), 7.92 (dd, $J = 9.5, 2.6$ Hz, 1H), 7.57 (s, 2H), 7.27 (d, $J = 9.5$ Hz, 1H), 4.37 (d, $J = 10.9$ Hz, 1H), 4.02 – 3.99 (m, 1H), 3.52 – 3.32 (m, 3H), 2.84 (s, 3H), 2.24 – 2.22 (m, 1H), 2.07 – 1.95 (m, 1H), 1.82 – 1.77 (m, 2H); ESI MS m/z 523 $[\text{M} + \text{H}]^+$; HPLC 97.5% (AUC), $t_R = 9.56$ min.

Example 72

(S)-1-(4-{[6-(3-Aminopiperidin-1-yl)pyridin-3-yl]amino}-6-(3-chloro-5-fluoro-4-hydroxy-phenyl)-1,5-naphthyridin-3-yl)ethanone trihydrochloride

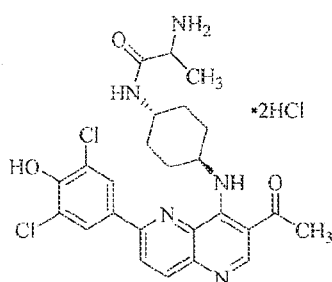


Following general procedure IV-2, (S)-tert-butyl [1-(5-{[3-acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl]amino}pyridin-2-yl)piperidin-3-yl]carbamate (0.20 mmol) was reacted with TFA (2 mL) followed by formation of the trihydrochloride salt to afford the desired product (42 mg, 34% over two steps) as an orange-yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 9.30 (s, 1H), 8.45 (d, $J = 9.0$ Hz, 1H), 8.35 (d, $J = 9.0$ Hz, 1H), 8.19 (d, $J = 2.6$ Hz, 1H), 7.68 (dd, $J = 9.2, 2.6$ Hz, 1H), 7.45 (br s, 1H), 7.27 (br s, 1H), 7.05 (d, J

= 9.2 Hz, 1H), 4.43 – 4.36 (m, 1H), 3.94 – 3.92 (m, 1H), 3.44 – 3.32 (m, 3H), 2.81 (s, 3H), 2.23 – 2.15 (m, 1H), 2.05 – 1.91 (m, 1H), 1.77 – 1.73 (m, 2H); ESI MS m/z 507 $[M + H]^+$; HPLC >99% (AUC), t_R = 9.57 min.

Example 73

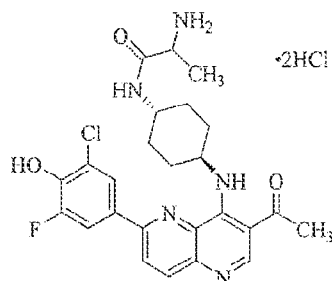
- 5 N-{*trans*-4-[3-Acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino]-cyclohexyl}-2-aminopropanamide dihydrochloride



- Following general procedure IV-1, crude *tert*-butyl 1-{*trans*-4-[3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino]cyclohexylamino}-1-oxopropan-2-ylcarbamate (0.13 mmol) was reacted with HCl (5 mL, 2 M in ether) to afford the desired product (32 mg, 41% over two steps) as a brown solid: ^1H NMR (500 MHz, CD_3OD) δ 9.14 (s, 1H), 8.45 (d, J = 8.5 Hz, 1H), 8.34 (d, J = 8.5 Hz, 1H), 8.10 (s, 2H), 5.65 – 5.55 (m, 1H), 3.90 (q, J = 6.9 Hz, 1H), 3.85 – 3.76 (m, 1H), 2.76 (s, 3H), 2.50 – 2.39 (m, 2H), 2.21 – 2.10 (m, 2H), 1.78 – 1.69 (m, 2H), 1.65 – 1.52 (m, 2H), 1.51 (d, J = 6.9 Hz, 3H); ESI MS m/z 516 $[M + H]^+$; HPLC >99% (AUC), t_R = 9.65 min.

Example 74

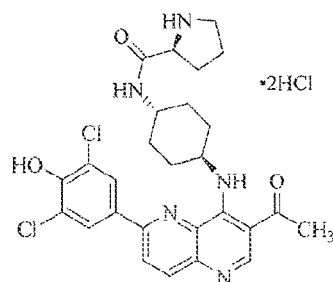
N-{4-[3-Acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-*trans*-4-ylamino]-cyclohexyl}-2-aminopropanamide dihydrochloride



Following general procedure IV-1, *tert*-butyl 1-([4-[3-acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-*trans*-4-ylamino]cyclohexylamino]-1-oxopropan-2-ylcarbamate (0.13 mmol) was reacted with HCl (5 mL, 2 M in ether) to afford the desired product (6.0 mg, 8% over two steps) as a white solid: ^1H NMR (500 MHz, CD_3OD) δ 9.14 (s, 1H), 8.44 (d, $J = 8.9$ Hz, 1H), 8.33 (d, $J = 8.9$ Hz, 1H), 8.00 (t, $J = 1.8$ Hz, 1H), 7.87 (dd, $J = 11.6, 1.8$ Hz, 1H), 5.65 – 5.57 (m, 2H), 3.94 – 3.77 (m, 2H), 2.76 (s, 3H), 2.50 – 2.40 (s, 2H), 2.20 – 2.12 (m, 2H), 1.78 – 1.58 (m, 2H), 1.61 – 1.52 (m, 2H), 1.51 (d, $J = 7.1$ Hz, 3H); ESI MS m/z 500 $[\text{M} + \text{H}]^+$; HPLC 99.0% (AUC), $t_R = 9.59$ min.

10 Example 75

(S)-N-([4-[3-Acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-*trans*-4-ylamino]cyclohexyl]pyrrolidine-2-carboxamide dihydrochloride

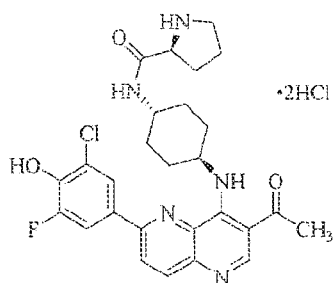


15 Following general procedure IV-1, (S)-*tert*-butyl 2-([4-[3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-*trans*-4-ylamino]cyclohexylcarbamoyl]pyrrolidine-1-carboxylate (0.19 mmol) was reacted with HCl (5 mL, 2 M in ether) to afford the desired product (70 mg, 58% over two steps) as an off-white solid: ^1H NMR (500 MHz,

CD₃OD) δ 9.14 (s, 1H), 8.45 (d, J = 9.0 Hz, 1H), 8.34 (d, J = 9.0 Hz, 1H), 8.09 (s, 2H), 5.66 – 5.53 (m, 1H), 4.24 (dd, J = 8.5, 6.9 Hz, 1H), 3.90 – 3.77 (m, 1H), 3.46 – 3.30 (m, 2H), 2.76 (s, 3H), 2.51 – 2.40 (m, 3H), 2.22 – 1.94 (m, 5H), 1.80 – 1.53 (m, 4H); ESI MS m/z 542 [M + H]⁺; HPLC 98.9% (AUC), t_R = 9.88 min.

5 Example 76

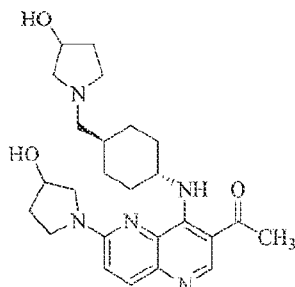
(S)-N-{4-[3-Acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-*trans*-4-ylamino]-cyclohexyl}pyrrolidine-2-carboxamide dihydrochloride



Following general procedure IV-1, *tert*-butyl 1-{4-[3-acetyl-6-(3-chloro-5-fluoro-4-hydroxy-phenyl)-1,5-naphthyridin-4-ylamino]cyclohexylamino}-1-oxopropan-2-ylcarbamate (0.19 mmol) was reacted with HCl (5 mL, 2 M in ether) to afford the desired product (46 mg, 45% over two steps) as an off-white solid: ¹H NMR (500 MHz, CD₃OD) δ 9.14 (s, 1H), 8.44 (d, J = 8.9 Hz, 1H), 8.33 (d, J = 8.9 Hz, 1H), 8.00 (t, J = 1.8 Hz, 1H), 7.87 (dd, J = 11.4, 1.8 Hz, 1H), 5.69 – 5.52 (m, 1H), 4.23 (dd, J = 8.5, 6.9 Hz, 1H), 3.80 – 3.88 (m, 1H), 3.47 – 3.32 (m, 2H), 2.75 (s, 3H), 2.51 – 2.39 (m, 3H), 2.20 – 2.13 (m, 2H), 2.12 – 1.95 (m, 3H), 1.81 – 1.68 (m, 2H), 1.67 – 1.52 (m, 2H); ESI MS m/z 527 [M + H]⁺; HPLC >99% (AUC), t_R = 9.69 min.

Example 77

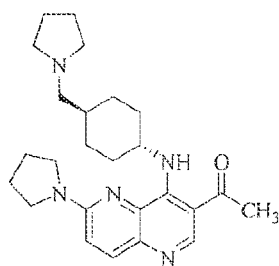
1-(6-(3-Hydroxypyrrolidin-1-yl)-4-{*trans*-4-[(3-hydroxypyrrolidin-1-yl)methyl]-cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone



Following general procedure V, {4-[(3-acetyl-6-chloro-1,5-naphthyridin-*trans*-4-yl)-amino]cyclohexylmethyl methanesulfonate (170 mg, 0.41 mmol) was reacted with pyrrolidin-3-ol (680 mg, 7.8 mmol) to afford the product (33 mg, 17%) as an orange-brown solid: ^1H NMR (500 MHz, CD_3OD) δ 8.64 (s, 1H), 7.85 (d, $J=9.2$ Hz, 1H), 7.04 (d, $J=9.2$ Hz, 1H), 5.63 – 5.55 (m, 1H), 4.61 – 4.54 (m, 1H), 4.40 – 4.30 (m, 1H), 3.79 – 3.65 (m, 3H), 3.60 – 3.52 (m, 1H), 2.88 – 2.80 (m, 1H), 2.79 – 2.70 (m, 1H), 2.63 (s, 2H), 2.63 – 2.53 (m, 1H), 2.53 – 2.48 (m, 1H), 2.47 – 2.35 (m, 2H), 2.30 – 2.05 (m, 6H), 2.00 – 1.89 (m, 2H), 1.75 – 1.70 (m, 1H), 1.62 – 1.52 (m, 1H), 1.40 – 1.31 (m, 2H), 1.21 – 1.10 (m, 2H); ESI MS m/z 454 $[\text{M} + \text{H}]^+$; HPLC 98.1% (AUC), $t_R = 8.66$ min.

Example 78

1-{6-(Pyrrolidin-1-yl)-4-[*trans*-4-(pyrrolidin-1-ylmethyl)cyclohexylamino]-1,5-naphthyridin-3-yl}ethanone

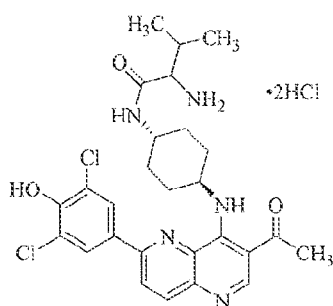


Following general procedure V, {4-[(3-acetyl-6-chloro-1,5-naphthyridin-4-yl)amino]-cyclohexyl}methyl methanesulfonate (180 mg, 0.437 mmol) was reacted with pyrrolidine (34 mg, 0.48 mmol) to afford the desired product (34 mg, 18%) as a brown solid: ^1H NMR (500 MHz, CD_3OD) δ 8.63 (s, 1H), 7.83 (d, $J=9.2$ Hz, 1H), 7.02 (d, $J=9.2$

Hz, 1H), 5.57 (br s, 1H), 3.61 – 3.53 (m, 4H), 2.63 (s, 6H), 2.45 (d, $J = 7.0$ Hz, 2H), 2.30 – 2.18 (m, 2H), 2.14 – 2.04 (m, 4H), 1.98 – 1.91 (m, 2H), 1.89 – 1.80 (m, 4H), 1.68 – 1.55 (m, 1H), 1.40 – 1.28 (m, 2H), 1.18 – 1.08 (m, 2H); ESI MS m/z 422 $[M + H]^+$; HPLC 97.5% (AUC), $t_R = 9.68$ min.

5 Example 79

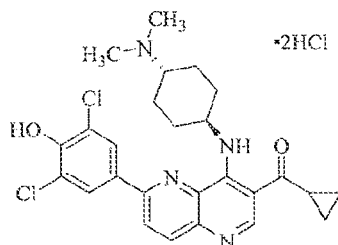
N-{*trans*-4-[3-Acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino]-cyclohexyl}-2-amino-3-methylbutanamide dihydrochloride



Following general procedure IV-2, *tert*-butyl 1-(4-(3-acetyl-6-(3,5-dichloro-4-hydroxy-phenyl)-1,5-naphthyridin-4-ylamino) cyclohexylamino)-3-methyl-1-oxobutan-2-ylcarbamate (0.19 mmol) was reacted with HCl (5 mL, 2 M in ether) to afford the desired product (55 mg, 47% over two steps) as an off-white solid: ^1H NMR (500 MHz, CD_3OD) δ 9.14 (s, 1H), 8.45 (d, $J = 9.0$ Hz, 1H), 8.33 (d, $J = 9.0$ Hz, 1H), 8.10 (s, 2H), 5.67 – 5.53 (m, 1H), 3.91 – 3.80 (m, 1H), 3.62 (d, $J = 6.0$ Hz, 1H), 2.76 (s, 3H), 2.49 – 2.40 (m, 2H), 2.25 – 2.10 (m, 3H), 1.81 – 1.54 (m, 4H), 1.07 (dd, $J = 9.0, 6.9$ Hz, 6H); ESI MS m/z 544 $[M + H]^+$; HPLC 99.0% (AUC), $t_R = 10.15$ min.

Example 80

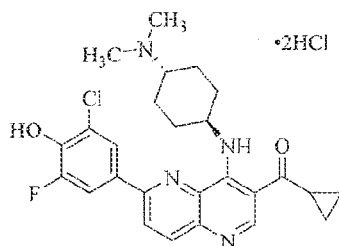
Cyclopropyl{6-(3,5-dichloro-4-hydroxyphenyl)-4-[*trans*-4-(dimethylamino)-cyclohexylamino]-1,5-naphthyridin-3-yl}methanone dihydrochloride



Following general procedure II, {6-chloro-4-[(*trans*-4-(dimethylamino)cyclohexylamino)-1,5-naphthyridin-3-yl]-(cyclopropyl)methanone (50 mg, 0.13 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (65 g, 0.23 mmol) followed by formation of the dihydrochloride salt to afford the desired product (65 g, 84%) as an off-white solid: ^1H NMR (500 MHz, CD_3OD) δ 9.43 (s, 1H), 8.46 (d, $J = 9.0$ Hz, 1H), 8.36 (d, $J = 9.0$ Hz, 1H), 8.11 (s, 2H), 5.64 – 5.54 (m, 1H), 3.51 – 3.44 (m, 1H), 2.91 (s, 6H), 2.93 – 2.89 (m, 1H), 2.63 – 2.56 (m, 2H), 2.32 – 2.24 (m, 2H), 1.87 – 1.68 (m, 4H), 1.33 – 1.18 (m, 4H).; ESI MS m/z 499 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 10.12$ min.

10 Example 81

1-[6-(3-Chloro-5-fluoro-4-methoxyphenyl)-4-{*trans*-4-[(dimethylamino)methyl]-cyclohexylamino}-1,5-naphthyridin-3-yl]ethanone dihydrochloride

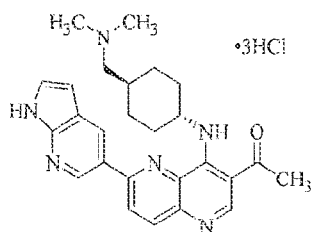


Following general procedure II, {6-chloro-4-[(*trans*-4-(dimethylamino)cyclohexylamino)-1,5-naphthyridin-3-yl]-(cyclopropyl)methanone (50 mg, 0.13 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (61 mg, 0.23 mmol) followed by formation of the dihydrochloride salt to afford the desired product (58 g, 78%) as an off-white solid: ^1H NMR (500 MHz, CD_3OD) δ 9.43 (s, 1H), 8.46 (d, $J = 8.9$ Hz, 1H), 8.36 (d, $J = 9.0$ Hz, 1H), 8.00 (t, $J = 1.9$ Hz, 1H), 7.91 (dd, $J = 11.6, 2.2$ Hz, 1H), 5.66 – 5.56 (m, 1H), 3.53 – 3.43 (m, 1H), 2.91 (s, 6H), 2.93 – 2.86 (m, 1H), 2.62 – 2.54

(m, 2H), 2.33 – 2.23 (m, 2H), 1.88 – 1.69 (m, 4H), 1.33 – 1.18 (m, 4H). ESI MS m/z 483 $[M + H]^+$; HPLC >99% (AUC), t_R = 9.84 min.

Example 82

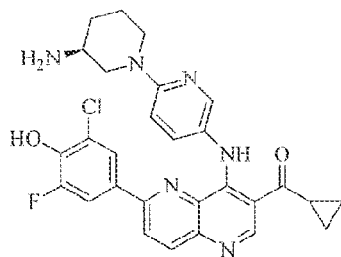
1-(4-{*trans*-4-[(Dimethylamino)methyl]cyclohexylamino}-6-(1H-pyrrolo[2,3-*b*]pyridin-5-yl)-1,5-naphthyridin-3-yl)ethanone trihydrochloride



Following general procedure II, 1-(6-chloro-4-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone (60 mg, 0.17 mmol) was reacted with 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-*b*]pyridine (60 mg, 0.25 mmol) followed by formation of the trihydrochloride salt to afford the desired product (7.5 mg, 9%) as an off-white solid: ^1H NMR (500 MHz, CD_3OD) δ 9.19 (s, 1H), 9.08 (s, 2H), 8.65 (d, J = 8.9 Hz, 1H), 8.44 (d, J = 8.9 Hz, 1H), 7.72 (d, J = 3.7 Hz, 1H), 6.91 (d, J = 3.6 Hz, 1H), 5.69 – 5.59 (m, 1H), 3.18 (d, J = 6.8 Hz, 2H), 2.94 (s, 6H), 2.77 (s, 3H), 2.55 – 2.45 (m, 2H), 2.08 – 1.98 (m, 3H), 1.76 – 1.64 (m, 2H), 1.48 – 1.36 (m, 2H). ESI MS m/z 443 $[M + H]^+$; HPLC >99% (AUC), t_R = 9.25 min.

Example 83

(*S*)-{4-[6-(3-Aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}(cyclopropyl)methanone

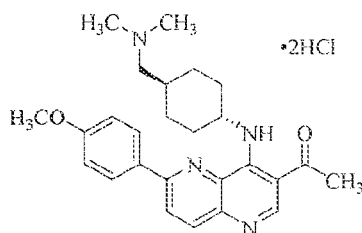


Following general procedure IV-2, (*S*)-*tert*-Butyl 1-{5-[6-(3-chloro-5-fluoro-4-

hydroxy-phenyl)-3-(cyclopropanecarbonyl)-1,5-naphthyridin-4-ylamino)pyridin-2-yl]piperidin-3-ylcarbamate (100 mg, 0.16 mmol) was reacted with TFA (3 mL) to afford the desired product (33 mg, 40%) as an orange-red solid: ^1H NMR (500 MHz, CD_3OD) δ 9.15 (s, 1H), 8.06 (d, $J = 9.0$ Hz, 1H), 8.01 (d, $J = 9.0$ Hz, 1H), 7.94 (d, $J = 2.7$ Hz, 1H), 7.40 (s, 1H), 7.33 (dd, $J = 9.0, 2.8$ Hz, 1H), 6.94 (dd, $J = 12.6, 2.3$ Hz, 1H), 6.69 (d, $J = 8.9$ Hz, 1H), 4.20–4.10 (m, 1H), 3.87–3.77 (m, 1H), 3.30–3.21 (m, 1H), 3.13–3.03 (m, 2H), 2.91–2.83 (m, 1H), 2.17–2.06 (m, 1H), 1.90–1.82 (m, 1H), 1.77–1.51 (m, 2H), 1.43–1.04 (m, 4H); ESI MS m/z 533 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 9.97$ min.

Example 84

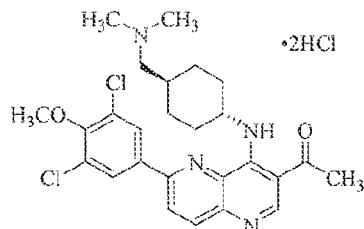
1-(4-{*trans*-4-[(Dimethylamino)methyl]cyclohexylamino}-6-(4-methoxyphenyl)-1,5-naphthyridin-3-yl)ethanone dihydrochloride



Following general procedure II, 1-(6-chloro-4-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone (72 g, 0.20 mmol) was reacted with (4-methoxyphenyl)boronic acid (45 g, 0.30 mmol) followed by formation of the dihydrochloride salt to afford the desired product (80 mg, 79%) as an orange solid: ^1H NMR (300 MHz, CD_3OD) δ 9.13 (s, 1H), 8.45 (d, $J = 9.0$ Hz, 1H), 8.31 (d, $J = 9.0$ Hz, 1H), 8.15–8.03 (m, 2H), 7.24–7.12 (m, 2H), 5.73–5.59 (m, 1H), 3.91 (s, 3H), 3.13 (d, $J = 6.7$ Hz, 2H), 2.94 (s, 6H), 2.75 (s, 3H), 2.50–2.42 (m, 2H), 2.09–1.96 (m, 3H), 1.77–1.60 (m, 2H), 1.45–1.25 (m, 2H); ESI MS m/z 433 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 9.83$ min.

Example 85

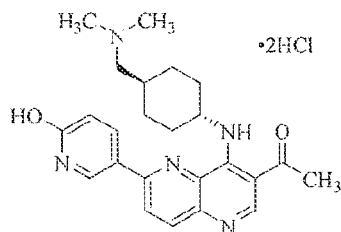
1-[6-(3,5-Dichloro-4-methoxyphenyl)-4-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl]ethanone dihydrochloride



Following general procedure II, 1-(6-chloro-4-{*trans*-4-[(dimethylamino)methyl]-cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone (77 g, 0.21 mmol) was reacted with (3,5-dichloro-4-methoxyphenyl)boronic acid (70 g, 0.32 mmol) followed by formation of the
 5 dihydrochloride salt to afford the desired product (80 g, 66%) as a brown solid: ^1H NMR (300 MHz, CD_3OD) δ 9.18 (s, 1H), 8.52 (d, $J = 9.0$ Hz, 1H), 8.39 (d, $J = 9.0$ Hz, 1H), 8.20 (s, 2H), 5.74 – 5.59 (m, 1H), 3.99 (s, 3H), 3.09 (d, $J = 6.6$ Hz, 2H), 2.94 (s, 6H), 2.76 (s, 3H), 2.48 – 2.40 (m, 2H), 2.10 – 2.00 (m, 3H), 1.79 – 1.61 (m, 2H), 1.50 – 1.31 (m, 2H); ESI MS m/z 501 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 10.49$ min.

10 Example 86

1-(4-{*trans*-4-[(Dimethylamino)methyl]cyclohexylamino}-6-(6-hydroxypyridin-3-yl)-1,5-naphthyridin-3-yl)ethanone dihydrochloride

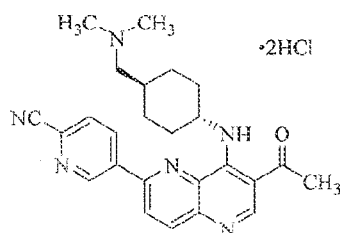


Following general procedure II, 1-(6-Chloro-4-{*trans*-4-[(dimethylamino)methyl]-cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone (74 g, 0.21 mmol) was reacted with (6-hydroxypyridin-3-yl)boronic acid (43 g, 0.31 mmol) followed by formation of the
 15 dihydrochloride salt to afford the desired product (49 g, 48%) as a yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 9.14 (s, 1H), 8.41 – 8.29 (m, 4H), 6.76 (d, $J = 9.5$ Hz, 1H), 5.58 – 5.50 (m, 1H), 3.13 (d, $J = 6.7$ Hz, 2H), 2.94 (s, 6H), 2.75 (s, 3H), 2.49 – 2.40 (m, 2H), 2.08
 20 – 2.00 (m, 3H), 1.73 – 1.61 (m, 2H), 1.39 – 1.27 (m, 2H); ESI MS m/z 420 $[\text{M} + \text{H}]^+$; HPLC

>99% (AUC), t_R = 8.43 min.

Example 87

5-(7-Acetyl-8-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-2-yl)picolinonitrile dihydrochloride

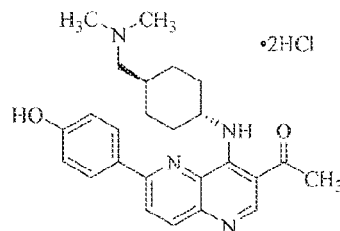


5

Following general procedure II, 1-(6-chloro-4-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone (77 g, 0.21 mmol) was reacted with 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinonitrile (72 g, 0.32 mmol) followed by formation of the dihydrochloride salt to afford the desired product (100 g, 95%) as a light brown solid: ^1H NMR (500 MHz, CD_3OD) δ 9.46 (d, J = 2.2 Hz, 1H), 9.21 (s, 1H), 8.70 (dd, J = 8.2, 2.2 Hz, 1H), 8.63 (d, J = 8.9 Hz, 1H), 8.47 (d, J = 8.9 Hz, 1H), 8.17 (d, J = 8.2 Hz, 1H), 5.58 – 5.50 (m, 1H), 3.14 (d, J = 6.8 Hz, 2H), 2.94 (s, 6H), 2.77 (s, 3H), 2.49 – 2.42 (m, 2H), 2.05 – 1.97 (m, 3H), 1.75 – 1.65 (m, 2H), 1.39 – 1.27 (m, 2H); ESI MS m/z 429 $[\text{M} + \text{H}]^+$; HPLC 96.2% (AUC), t_R = 8.88 min.

15 Example 88

1-(4-{*trans*-4-[(Dimethylamino)methyl]cyclohexylamino}-6-(4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone dihydrochloride

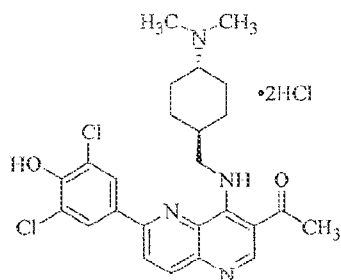


20 Following general procedure II, 1-(6-chloro-4-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone (76 g, 0.21 mmol) was reacted with (4-

hydroxyphenyl)boronic acid (43 g, 0.32 mmol) followed by formation of the dihydrochloride salt to afford the desired product (35 g, 34%) as a yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 9.11 (s, 1H), 8.41 (d, $J = 8.9$ Hz, 1H), 8.28 (d, $J = 8.9$ Hz, 1H), 8.03 – 7.97 (m, 2H), 7.04 – 6.98 (m, 2H), 5.73 – 5.62 (m, 1H), 3.11 (d, $J = 6.8$ Hz, 2H), 2.94 (s, 6H), 2.75 (s, 3H), 2.50 – 2.42 (m, 2H), 2.06 – 1.99 (m, 3H), 1.73 – 1.61 (m, 2H), 1.40 – 1.27 (m, 2H); ESI MS m/z 419 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 9.24$ min.

Example 89

1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4- $\{[trans\text{-}4\text{-(dimethylamino)cyclohexyl]methylamino}\}$ -1,5-naphthyridin-3-yl]ethanone dihydrochloride



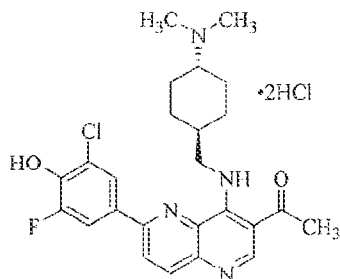
10

Following general procedure II, 1-(6-chloro-4- $\{[trans\text{-}4\text{-(dimethylamino)cyclohexyl]methylamino}\}$ -1,5-naphthyridin-3-yl)ethanone (100 mg, 0.27 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (86 g, 0.30 mmol) followed by formation of the dihydrochloride salt to afford the desired product (50 mg, 38%) as a pale yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 9.14 (s, 1H), 8.45 (dd, $J = 9.0, 1.5$ Hz, 1H), 8.37 (d, $J = 9.1$ Hz, 1H), 8.08 (d, $J = 2.1$ Hz, 2H), 4.51 (dd, $J = 7.2, 1.9$ Hz, 2H), 3.33 – 3.24 (m, 1H), 2.87 (s, 6H), 2.78 (s, 3H), 2.30 – 2.20 (m, 4H), 2.03 (dtd, $J = 18.7, 7.3, 6.9, 3.4$ Hz, 1H), 1.65 (qd, $J = 13.2, 12.3, 3.8$ Hz, 2H), 1.42 (qd, $J = 14.6, 13.8, 3.6$ Hz, 2H), 0.14 – 0.06 (m, 2H); ESI MS m/z 487 $[\text{M} + \text{H}]^+$; HPLC 95.0 % (AUC), $t_R = 9.74$ min.

20

Example 90

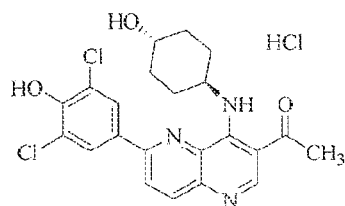
1-[6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4- $\{[trans\text{-}4\text{-(dimethylamino)cyclohexyl]methylamino}\}$ -1,5-naphthyridin-3-yl]ethanone dihydrochloride



Following general procedure II, 1-[6-chloro-4-{{*trans*-4-(dimethylamino)cyclohexyl}-methylamino}-1,5-naphthyridin-3-yl]ethanone (100 g, 0.27 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (85 g, 0.30 mmol) followed by formation of the dihydrochloride salt to afford the desired product (50 g, 38%) as a white solid: ^1H NMR (500 MHz, CD_3OD) δ 9.12 (s, 1H), 8.43 (d, $J = 9.0$ Hz, 1H), 8.36 (d, $J = 8.9$ Hz, 1H), 8.01 – 7.95 (m, 1H), 7.87 (dd, $J = 11.5, 2.2$ Hz, 1H), 4.51 (d, $J = 7.0$ Hz, 2H), 4.25 (d, $J = 6.7$ Hz, 1H), 3.27 (dt, $J = 12.2, 3.3$ Hz, 1H), 2.87 (s, 3H), 2.77 (d, $J = 16.7$ Hz, 6H), 2.28 – 2.19 (m, 1H), 2.09 – 1.95 (m, 1H), 1.84 (s, 1H), 1.64 (qd, $J = 12.8, 12.1, 3.7$ Hz, 1H), 1.41 (qd, $J = 14.0, 13.3, 3.4$ Hz, 1H), 1.27 (dd, $J = 23.6, 12.3$ Hz, 1H); ESI MS m/z 471 $[\text{M} + \text{H}]^+$; HPLC 98.9% (AUC), $t_R = 8.55$ min.

Example 91

1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4-(*trans*-4-hydroxycyclohexylamino)-1,5-naphthyridin-3-yl]-ethanone hydrochloride

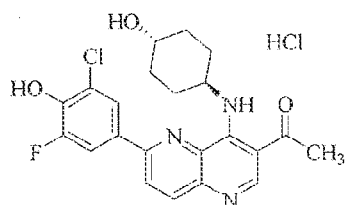


Following general procedure II, 1-[6-chloro-4-(*trans*-4-hydroxycyclohexylamino)-1,5-naphthyridin-3-yl]ethanone (160 mg, 0.50 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (165 mg, 0.60 mmol) followed by formation of the hydrochloride salt to afford the desired product (120 mg, 56%) as a pale

yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 9.11 (s, 1H), 8.44 (d, $J = 9.0$ Hz, 1H), 8.30 (d, $J = 9.0$ Hz, 1H), 8.00 (t, $J = 1.9$ Hz, 1H), 7.87 (dd, $J = 11.5, 2.3$ Hz, 1H), 5.60 (tt, $J = 10.5, 4.2$ Hz, 1H), 3.75 (tt, $J = 9.6, 4.2$ Hz, 1H), 2.75 (s, 3H), 2.42 – 2.35 (m, 2H), 2.14 – 2.06 (m, 2H), 1.74 – 1.54 (m, 4H); ESI MS m/z 430 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R =$
 5 10.9 min.

Example 92

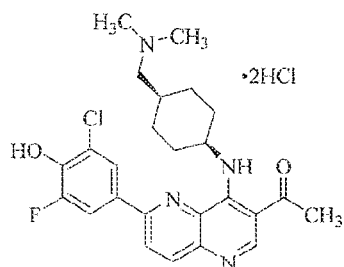
1-[6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-(*trans*-4-hydroxycyclohexylamino)-1,5-naphthyridin-3-yl]ethanone hydrochloride



10 Following general procedure II, 1-[6-chloro-4-(*trans*-4-hydroxycyclohexylamino)-1,5-naphthyridin-3-yl]ethanone (160 mg, 0.50 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (160 g, 0.60 mmol) followed by formation of the hydrochloride salt to afford the desired product (120 mg, 57%) as an off-white solid: ^1H NMR (500 MHz, CD_3OD) δ 9.11 (s, 1H), 8.45 (d, $J = 9.1$ Hz, 1H), 8.30
 15 (d, $J = 9.0$ Hz, 1H), 8.11 (s, 2H), 5.60 (dq, $J = 10.1, 4.5$ Hz, 1H), 4.94 – 4.83 (m, 1H), 3.75 (tt, $J = 7.6, 3.9$ Hz, 1H), 3.66 (s, 2H), 3.41 – 3.31 (m, 1H), 2.75 (s, 3H), 2.38 (dd, $J = 9.0, 5.3$ Hz, 2H), 2.14 – 2.07 (m, 2H), 2.03 (s, 1H), 1.74 – 1.57 (m, 4H); ESI MS m/z 446 $[\text{M} + \text{H}]^+$; HPLC 96.7% (AUC), $t_R = 11.1$ min.

Example 93

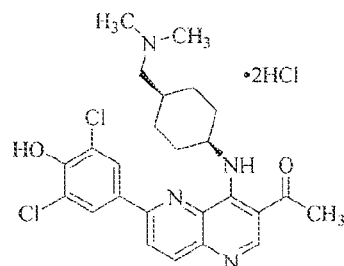
20 1-[6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-({*cis*-4-[(dimethylamino)methyl]cyclohexyl}-amino)-1,5-naphthyridin-3-yl]ethanone dihydrochloride



Following general procedure II, 1-(6-chloro-4-*cis*-4-[(dimethylamino)methyl]-cyclohexyl amino}-1,5-naphthyridin-3-yl)ethanone (120 mg, 0.30 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (100 mg, 0.30 mmol) followed by formation of the dihydrochloride salt to afford the desired product (150 mg, 81%) as an off-white solid: ^1H NMR (500 MHz, CD_3OD) δ 9.17 (s, 1H), 8.46 (d, J = 9.0 Hz, 1H), 8.45 – 8.30 (m, 1H), 7.99 (q, J = 2.7, 1.7 Hz, 1H), 7.90 – 7.82 (m, 1H), 5.93 (p, J = 4.2 Hz, 1H), 3.20 (d, J = 7.1 Hz, 2H), 2.95 (s, 6H), 2.78 (s, 3H), 2.15 (dddt, J = 44.4, 14.7, 11.4, 4.1 Hz, 3H), 2.01 – 1.86 (m, 2H), 1.61 (dtd, J = 14.3, 10.8, 3.6 Hz, 3H), 1.20 (s, 1H); ESI MS m/z 471 $[\text{M} + \text{H}]^+$; HPLC 95.7% (AUC), t_R = 9.9 min.

Example 94

1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-((*cis*-4-[(dimethylamino)methyl]-cyclohexyl)amino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride

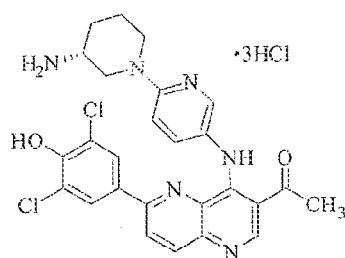


Following general procedure II, 1-(6-chloro-4-*cis*-4-[(dimethylamino)methyl]-cyclohexyl amino}-1,5-naphthyridin-3-yl)ethanone (120 mg, 0.30 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (100 mg, 0.30 mmol) followed by formation of the dihydrochloride salt to afford the desired product (150 mg, 81%) as an off-white solid: ^1H NMR (500 MHz, CD_3OD) δ 9.17 (s, 1H), 8.47 (d, J = 9.0 Hz, 1H), 8.34 (d, J = 8.9 Hz, 1H), 8.11 (s, 2H), 5.92 (p, J = 4.4 Hz, 1H), 3.21 (d, J = 7.2 Hz, 2H),

2.96 (s, 6H), 2.78 (s, 3H), 2.25 – 2.05 (m, 3H), 1.99 – 1.88 (m, 2H), 1.62 (dtd, $J = 14.1, 11.2, 10.8, 3.7$ Hz, 3H), 1.20 (s, 1H); ESI MS m/z 487 $[M + H]^+$; HPLC 96.5% (AUC), $t_R = 9.9$ min.

Example 95

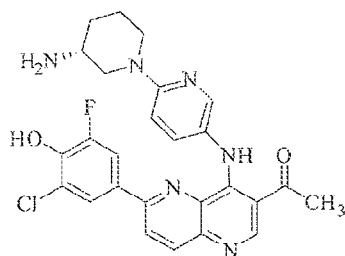
- 5 (R)-1-{4-[6-(3-Aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}ethanone trihydrochloride



- Following general procedure IV-2, (R)-*tert*-butyl 1-(5-(3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino)pyridin-2-yl)piperidin-3-ylcarbamate (60 mg, 0.10 mmol) was reacted with TFA (1.5 mL) to afford the desired product (37 mg, 74%) as a yellow-brown solid: ^1H NMR (500 MHz, CD_3OD) δ 9.28 (s, 1H), 8.49 – 8.31 (m, 2H), 8.16 (d, $J = 2.7$ Hz, 1H), 7.63 (dd, $J = 9.1, 2.8$ Hz, 1H), 7.51 (s, 2H), 6.98 (d, $J = 9.1$ Hz, 1H), 4.40 (dd, $J = 12.7, 3.6$ Hz, 1H), 3.93 (d, $J = 13.4$ Hz, 1H), 3.41 – 3.19 (m, 3H), 2.80 (s, 3H), 2.16 (m, 1H), 1.97 – 1.89 (m, 1H), 1.78 – 1.65 (m, 2H); ESI MS m/z 523 $[M + H]^+$; HPLC 98.1% (AUC), $t_R = 9.87$ min.

Example 96

(R)-1-{4-[6-(3-Aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}ethanone

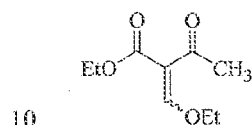


- 20 Following general procedure IV-2, (R)-*tert*-butyl 1-(5-(3-acetyl-6-(3-chloro-5-

fluoro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino)pyridin-2-yl)piperidin-3-ylcarbamate (100 mg, 0.16 mmol) was reacted with TFA (2.0 mL) to afford the desired product (56 mg, 67%) as a yellow-brown solid: ^1H NMR (500 MHz, CD_3OD) δ 9.27 (s, 1H), 8.40 (d, J = 9.0 Hz, 1H), 8.33 (d, J = 9.0 Hz, 1H), 8.16 (d, J = 2.7 Hz, 1H), 7.59 (dd, J = 9.1, 2.8 Hz, 1H), 7.44 (s, 1H), 7.20 (d, J = 11.7 Hz, 1H), 6.97 (d, J = 9.1 Hz, 1H), 4.39 (dd, J = 12.6, 3.4 Hz, 1H), 3.38-3.94 (m, 2H), 3.43-3.21 (m, 5H), 2.79 (s, 3H), 2.17 (m, 2H), 1.93 (m, 1H), 1.80-1.66 (m, 2H).; ESI MS m/z 507 $[\text{M} + \text{H}]^+$; HPLC 98.8% (AUC), t_R = 9.34 min.

Example 97

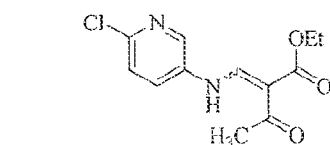
Ethyl 2-(ethoxymethylene)-3-oxobutanoate



A mixture of ethyl acetoacetate (100 g, 0.77 mol), triethyl orthoformate (130 g, 0.92 mol), and acetic anhydride (150 g, 1.5 mol) was heated at 135 °C for 6 – 18 h in a round bottomed flask that was equipped with a distillation apparatus to collect the ethanol generated during the reaction. The reaction was cooled, concentrated and the residue was distilled under high vacuum to obtain the desired product (100 g, 70%) as a pale yellow oil: ESI MS m/z 187 $[\text{M} + \text{H}]^+$.

Example 98

Ethyl 2-[(6-chloropyridin-3-ylamino)methylene]-3-oxobutanoate

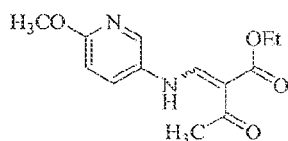


A mixture of ethyl 2-(ethoxymethylene)-3-oxobutanoate (48 g, 0.26 mol) and 2-chloro-5-aminopyridine (33 g, 0.26 mol) in chlorobenzene (150 mL) was heated at 135 °C for 4 h in a round bottomed flask that was equipped with a distillation apparatus to collect the ethanol generated during the reaction. The reaction mixture was cooled and concentrated and the residue was triturated in diethylether and filtered to obtain the desired

product (55 g, 79%) as an off-white solid: ^1H NMR (500 MHz, CDCl_3) δ 12.76 (d, 12.3 Hz, 1H), 8.42 (s, 1H), 8.38 (s, 1H), 8.31 (d, $J = 2.8$ Hz, 1H), 7.52 – 7.48 (m, 1H), 7.37 – 7.34 (m, 1H), 4.30 (q, $J = 7.1$ Hz, 2H), 2.56 (s, 1H), 1.35 (t, $J = 7.1$ Hz, 3H); ESI MS m/z 269 $[\text{M} + \text{H}]^+$.

5 Example 99

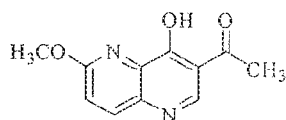
Ethyl 2-[(6-methoxypyridin-3-ylamino)methylene]-3-oxobutanoate



A mixture of ethyl 2-(ethoxymethylene)-3-oxobutanoate (100 g, 0.54 mol) and 2-methoxy-5-aminopyridine (67 g, 0.54 mol) in chlorobenzene (500 mL) was heated at 10 135 °C for 4 h in a round bottomed flask that was equipped with a distillation apparatus to collect the ethanol generated during the reaction. The reaction mixture was cooled and concentrated and the residue was triturated in diethylether and filtered to obtain the desired product (120 g, 84%) as an off-white solid: ^1H NMR (500 MHz, CDCl_3) δ 12.74 (d, 12.3 Hz, 1H), 8.35 (d, $J = 13.0$ Hz, 1H), 8.07 (d, $J = 2.8$ Hz, 1H), 7.55 (d, $J = 8.8, 2.9$ Hz, 1H), 6.79 (d, $J = 8.8$ Hz, 1H), 4.30 (q, $J = 7.1$ Hz, 2H), 2.55 (s, 3H), 1.33 (t, $J = 7.1$ Hz, 1H); ESI MS m/z 265 $[\text{M} + \text{H}]^+$. 15

Example 100

1-(4-Hydroxy-6-methoxy-1,5-naphthyridin-3-yl)ethanone

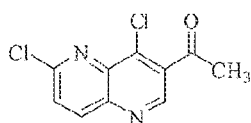


20 To a flask containing Dowtherm™ A (500 mL) at 250 °C was added ethyl 2-[(6-methoxypyridin-3-ylamino)methylene]-3-oxobutanoate (75 g, 0.28 mol) portion wise over 3 to 5 min and the reaction mixture was stirred for an additional 30 to 60 min. The reaction mixture was removed from the heat source, cooled to room temperature and diluted with hexanes to facilitate precipitation. The solids were filtered, washed with hexanes and

acetonitrile and dried under vacuum to afford the desired product (60 g, 46%) as an off-white solid: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 12.48 (bs, 1H), 8.45 (d, $J = 5.2$ Hz, 1H), 8.00 (d, $J = 8.9$ Hz, 1H), 7.40 – 7.37 (m, 1H), 7.21 (d, $J = 8.9$ Hz, 1H), 7.01 – 6.99 (m, 1H), 3.96 (s, 3H), 2.61 (s, 3H); ESI MS m/z 219 $[\text{M} + \text{H}]^+$.

5 Example 101

1-(4,6-Dichloro-1,5-naphthyridin-3-yl)ethanone



Preparation following the synthetic route outlined in Scheme 1:

To a flask containing DowthermTM A (500 mL) at 250 °C was added ethyl 2-[(6-chloropyridin-3-ylamino)methylene]-3-oxobutanoate (10 g, 27 mmol) portion wise over 3
 10 to 5 min and the reaction mixture was stirred for an additional 30 to 45 min. The reaction mixture was removed from the heat source, cooled to room temperature and diluted with hexanes to facilitate precipitation. The solids were filtered, washed with hexanes and dried under vacuum to afford the intermediate 1-(6-chloro-4-hydroxy-1,5-naphthyridin-3-yl)ethanone which was heated in neat phosphorus oxychloride with catalytic *N,N*-
 15 dimethylformamide for 4 h at 70 °C. The reaction was cooled and poured slowly into a vigorously stirring mixture of ice-cold satd. aq. sodium bicarbonate and ethyl acetate. The layers were separated and the organic layer was dried over sodium sulfate, filtered and the filtrate was concentrated. The residue was purified by column chromatography (silica,
 20 hexanes/ethyl acetate) to provide the desired product (3 g, 46% over two steps) as a brown solid: ESI MS m/z 241 $[\text{M} + \text{H}]^+$.

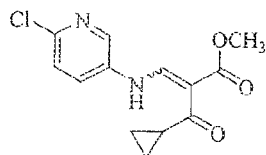
Preparation following the synthetic route outlined in Scheme 2:

To a suspension of ethyl 2-[(6-methoxypyridin-3-ylamino)methylene]-3-oxobutanoate (70 g, 0.32 mol) in acetonitrile (800 ml) was added trimethylsilylchloride
 25 (173 g, 1.6 mol) and sodium iodide (140 g, 0.96 mol) and the reaction mixture was heated at reflux for 2 h. The reaction mixture was cooled to room temperature and satd. aq. sodium

thiosulfate was added. The mixture was concentrated to remove acetonitrile, diluted with brine and the solids were filtered and dried to provide the intermediate 1-(4,6-dihydroxy-1,5-naphthyridin-3-yl)ethanone. This intermediate was suspended in dichloroethane (350 mL) followed by the addition of phosphorus oxychloride (200 mL) and catalytic *N,N*-dimethylformamide and the reaction mixture was stirred with heat at 80 °C for 3 h. The reaction mixture was cooled to room temperature and quenched by pouring slowly into ice-cold satd. aq. sodium bicarbonate or 3 N sodium hydroxide. The quenched reaction mixture was concentrated to remove the dichloroethane and the resulting solids were collected by filtration and purified by chromatography (silica, hexanes/ethyl acetate) to provide the desired product (50 g, 74% over 2 steps) as a brown solid: ¹H NMR (300 MHz, CDCl₃) δ 9.00 (s, 1H), 8.38 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.28 – 3.18 (m, 1H), 1.36 (t, J = 7.1 Hz, 3H). ESI MS *m/z* 241 [M + H]⁺.

Example 102

Methyl 3-(6-chloropyridin-3-ylamino)-2-(cyclopropanecarbonyl)acrylate

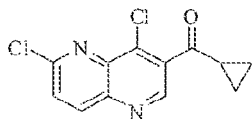


15

A mixture of methyl 3-cyclopropyl-3-oxopropanoate (7.2 g, 50 mmol), triethyl orthoformate (13 mL, 75 mmol) and 2-chloro-5-aminopyridine (6.4 g, 50 mmol) was heated at 145 °C for 3 h in a round bottomed flask that was equipped with a short path distillation apparatus to collect the ethanol generated during the reaction. The reaction was cooled, concentrated and the residue was purified by chromatography (silica, hexanes/ethyl acetate) to afford the desired product (4.2 g, 28%) as a pale yellow oil: ¹H NMR (300 MHz, CDCl₃) δ 12.78 (d, 12.5 Hz, 1H), 8.40 – 8.34 (m, 1H), 8.28 (d, J = 2.9 Hz, 1H), 7.51 – 7.44 (m, 1H), 7.35 (d, J = 8.6 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.28 – 3.18 (m, 1H), 1.36 (t, J = 7.1 Hz, 3H), 1.17 – 1.09 (m, 2H), 1.02 – 0.86 (m, 2H). ESI MS *m/z* 281 [M + H]⁺.

25 Example 103

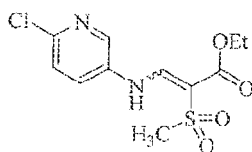
Cyclopropyl(4,6-dichloro-1,5-naphthyridin-3-yl)methanone



To a flask containing Dowtherm™ A (500 mL) at 250 °C was added methyl 3-(6-chloropyridin-3-ylamino)-2-(cyclopropanecarbonyl)acrylate (4.2 g, 15 mmol) portion wise over 3 to 5 min and the reaction mixture was stirred for an additional 30 to 45 min. The reaction mixture was removed from the heat source, cooled to room temperature and diluted with hexanes to facilitate precipitation. The solids were filtered, washed with hexanes and dried under vacuum to afford the intermediate (6-chloro-4-hydroxy-1,5-naphthyridin-3-yl)(cyclopropyl)methanone which was stirred with heat at 70 °C in neat phosphorus oxychloride (10 mL) with catalytic *N,N*-dimethylformamide for 4 h. The reaction was cooled and poured slowly into a vigorously stirring mixture of ice-cold satd. aq. sodium bicarbonate and ethyl acetate. The layers were separated and the organic layer was dried over sodium sulfate, filtered and concentrated. The residue was purified by chromatography (silica, methylene chloride/ethyl acetate) to provide the desired product (0.78 g, 20% over two steps) as a brown solid: ¹H NMR (500 MHz, CDCl₃) δ 8.93 (s, 1H), 8.39 (d, J = 8.7 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 2.65 (t, J = 7.7, 4.5 Hz, 1H), 1.52 – 1.42 (m, 2H), 1.32 – 1.22 (m, 2H); ESI MS *m/z* 268 [M + H]⁺.

Example 104

Ethyl 3-(6-chloropyridin-3-ylamino)-2-(methylsulfonyl)acrylate

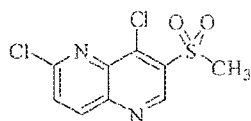


A mixture of ethyl 3-ethoxy-2-(methylsulfonyl)acrylate (7.0 g, 32 mmol) and 2-chloro-5-aminopyridine (4.1 g, 32 mmol) in chlorobenzene (16 mL) was stirred with heat at 135 °C for 3 h in a round bottomed flask that was equipped with a short path distillation apparatus to collect the ethanol generated during the reaction. The reaction was cooled, concentrated and the residue was purified by chromatography (silica, methylene

chloride/ethyl acetate) to afford the desired product (8.2 g, 84%) as a pale yellow oil: ^1H NMR (500 MHz, CDCl_3) δ 10.61 (d, 13.4 Hz, 1H), 8.34 (d, J = 13.4 Hz, 1H), 8.27 (d, J = 2.9 Hz, 1H), 7.50 (dd, J = 8.6, 3.0 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 4.41 (q, J = 7.2 Hz, 2H), 3.18 (s, 3H), 1.42 (t, J = 7.2 Hz, 3H); ESI MS m/z 305 $[\text{M} + \text{H}]^+$.

5 Example 105

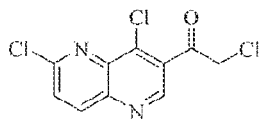
2,8-Dichloro-7-(methylsulfonyl)-1,5-naphthyridine



To a flask containing DowthermTM A (500 mL) at 250 °C was added ethyl 3-(6-chloropyridin-3-ylamino)-2-(methylsulfonyl)acrylate (8.2 g, 30 mmol) portion wise over 3
 10 to 5 min and the reaction mixture was stirred for an additional 30 to 45 min. The reaction mixture was removed from the heat source, cooled to room temperature and diluted with hexanes to facilitate precipitation. The solids were collected by filtration, filtered, washed with hexanes and dried under vacuum to afford the intermediate 6-chloro-3-(methylsulfonyl)-1,5-naphthyridin-4-ol which was stirred with heat at 70 °C in neat
 15 phosphorus oxychloride (31 mL) with catalytic *N,N*-dimethylformamide for 4 h. The reaction was cooled and poured slowly into a vigorously stirring mixture of ice-cold satd. aq. sodium bicarbonate and ethyl acetate. The layers were separated and the organic layer was dried over sodium sulfate, filtered and concentrated. The residue was purified by chromatography (silica, hexanes/ethyl acetate) to provide the desired product (2.7 g, 33%
 20 over two steps) as a brown solid: ^1H NMR (500 MHz, CDCl_3) δ 9.50 (s, 1H), 8.46 (d, J = 8.8 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 3.41 (s, 3H); ESI MS m/z 278 $[\text{M} + \text{H}]^+$.

Example 106

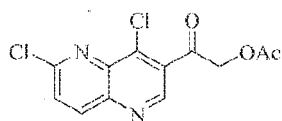
2-Chloro-1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone



To a solution of 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (3.0 g, 12 mmol) in THF (120 mL) was added benzyltrimethylammonium dichloroiodate (4.3 g, 12 mmol) and the reaction mixture was stirred at 70 °C for 5 h. The reaction mixture was cooled, diluted with satd. aq. sodium bicarbonate and extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated. The residue was purified by column chromatography (silica, dichloromethane/ethyl acetate) to afford the desired product (1.1 g, 32%) as an off-white solid. ESI MS m/z 275 $[M + H]^+$.

Example 107

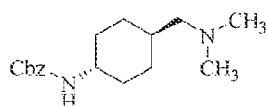
2-(4,6-Dichloro-1,5-naphthyridin-3-yl)-2-oxoethyl acetate



To a solution of acetic acid (0.32 mL, 5.5 mmol) and N,N-diisopropylethylamine (0.87 mL, 5.0 mmol) in acetone (20 mL) was added 2-chloro-1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (0.26 g, 0.96 mmol) and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with satd. aq. sodium bicarbonate and extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated. The residue was purified by column chromatography (silica, dichloromethane/ethyl acetate) to afford the desired product (0.12 g, 42%) as a white solid. ESI MS m/z 299 $[M + H]^+$.

Example 108

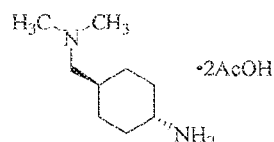
Benzyl 4-[(dimethylamino)methyl]cyclohexylcarbamate



To a suspension of commercially available benzyl 4-(aminomethyl)cyclohexylcarbamate (15 g, 57 mmol) in water (150 mL) was added formaldehyde (14 mL, 0.17 mol, 37% solution) and formic acid (6.5 mL, 0.17 mol). The mixture was heated to reflux for 2 h, cooled to rt, neutralized with 2 N NaOH, and extracted with CH₂Cl₂. The organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated to give desired product (16 g, 96%) as a tan, waxy solid.: APCI MS *m/z* 291 [C₁₇H₂₆N₂O₂ + H]⁺.

Example 109

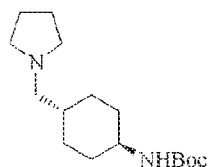
trans-4-[(Dimethylamino)methyl]cyclohexanamine diacetic salt



To a flask containing Pd/C (1.5 g, Degussa type E101) in methanol / acetic acid (100 mL, 3:1) was added benzyl 4-[(dimethylamino)methyl]cyclohexylcarbamate (16 g, 54 mmol) in methanol / acetic acid (300 mL, 3:1) and the reaction mixture was stirred under an atmosphere of H₂ (1 atm) at room temperature for 6 h. The reaction mixture was filtered through diatomaceous, the filtrate was concentrated, and azeotroped with toluene. The thick oil was dried under vacuum to give desired product (18 g, crude) as a waxy solid which was used without any purification: ¹H NMR (300 MHz, CD₃OD) δ 3.11 – 2.98 (m, 1H), 2.78 (d, *J* = 7.0 Hz, 2H), 2.69 (s, 6H), 2.07 (br d, *J* = 13.9 Hz, 4H), 2.02 – 1.86 (m, 2H), 1.92 (s, 6H), 1.79 – 1.67 (m, 1H), 1.53 – 1.35 (m, 2H), 1.20 – 1.05 (m, 2H).

Example 110

tert-Butyl [*trans*-4-(pyrrolidin-1-ylmethyl)cyclohexyl]carbamate

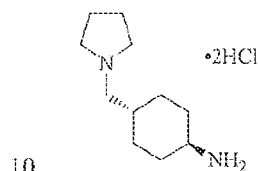


To a suspension of *trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexylmethyl methanesulfonate (1.8 g, 6.0 mmol), K₂CO₃ (1.7 g, 12 mmol) and KI (600 mg, 3.6 mmol) in

acetonitrile (30 mL) was added pyrrolidine (5.0 mL, 60 mmol) dropwise and the reaction mixture was heated at 85 °C for 16 h. The solution was cooled to room temperature, diluted with a saturated NaHCO₃ solution and extracted with a mixture of CHCl₃/isopropanol (3:1). The combined organic layers were dried over sodium sulfate, filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, methanol/dichloromethane) to afford the desired product (1.3 g, 76%) as a white solid. ESI MS *m/z* 283 [C₁₈H₃₀N₂O₂ + H]⁺

Example 111

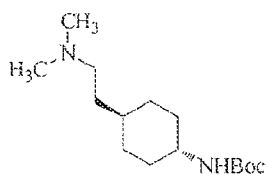
trans-4-(Pyrrolidin-1-ylmethyl)cyclohexanamine dihydrochloride



To a solution of *tert*-butyl (*trans*-4-(pyrrolidin-1-ylmethyl)cyclohexyl)carbamate (1.3 g, 4.5 mmol) in THF (15 mL) was added aqueous 6 N HCl (6 mL) and water (6 mL) and the reaction mixture was stirred with heat at 65 °C for 3 h. The reaction mixture was cooled to room temperature and concentrated to afford the desired product (1.2 g, >99%) as an off-white solid. ESI MS *m/z* 183 [C₁₁H₂₂N₂ + H]⁺

Example 112

tert-Butyl (*trans*-4-[2-(dimethylamino)ethyl]cyclohexyl)carbamate

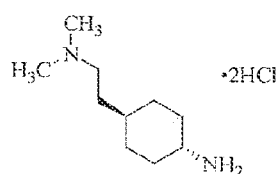


To a suspension of *tert*-butyl [*trans*-4-(2-aminoethyl)cyclohexyl]carbamate (970 mg, 4.0 mmol) and paraformaldehyde (360 mg, 12 mmol) in methanol (40 mL) was added sodium cyanoborohydride (750 mg, 12 mmol) and acetic acid (1 drop). The resultant suspension was stirred at room temperature for 16 h, diluted with a saturated NaHCO₃

solution and extracted with a mixture of CHCl_3 /isopropanol (3:1). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, methanol/dichloromethane) to afford the desired product (340 mg, 31%) as a white solid. ESI MS m/z 271 $[\text{C}_{15}\text{H}_{30}\text{N}_2\text{O}_2 + \text{H}]^+$

5 Example 113

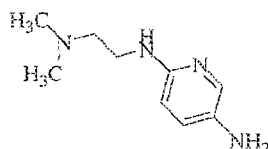
trans-4-[2-(Dimethylamino)ethyl]cyclohexanamine dihydrochloride



Following general procedure IV-1, *tert*-butyl {*trans*-4-[2-(dimethylamino)ethyl]-cyclohexyl} carbamate (330 mg, 1.2 mmol) was reacted with 6 N HCl (2 mL) to afford the
10 desired product as a viscous colorless oil that was used without purification..

Example 114

N^2 -[2-(Dimethylamino)ethyl]pyridine-2,5-diamine

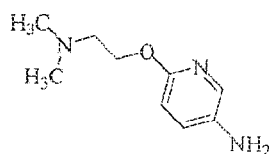


To a solution of 2-chloro-5-nitropyridine (500 mg, 3.1 mmol) in THF (30 mL) was
15 added N^1, N^1 -dimethylethane-1,2-diamine (310 mg, 3.5 mmol) and triethylamine (0.64 mL, 4.6 mmol) and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated, the residue was dissolved in dichloromethane and washed with 1 N HCl aq and water. The organic layer was dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated. The residue was dissolved in tetrahydrofuran (30 mL),
20 degassed with nitrogen, charged with catalytic 10wt. % Pd/C (0.3 g) and the reaction mixture was placed under an atmosphere of hydrogen (40 Psi) until the reduction was complete as indicated by LCMS analysis. The reaction mixture was filtered over diatomaceous earth and the filtrate was concentrated to provide the desired product (280 mg,

50%) as a purple solid: ESI MS m/z 181 $[\text{C}_9\text{H}_{16}\text{N}_4 + \text{H}]^+$.

Example 115

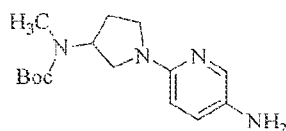
6-[2-(Dimethylamino)ethoxy]pyridin-3-amine



5 To a solution of 2-chloro-5-nitropyridine (500 mg, 3.1 mmol) in dioxane (30 mL) at room temperature was added 2-(dimethylamino)ethanol (309 mg, 3.5 mmol) and 60wt. % NaH (0.15 g, 3.7 mmol) and the reaction mixture was stirred at room temperature until the reaction was complete by LCMS analysis. The reaction mixture was poured onto ice-cold water and the product was extracted with dichloromethane. The organic layer was dried
10 over sodium sulfate, filtered and the filtrate was concentrated. The residue was dissolved in tetrahydrofuran (30 mL), degassed with nitrogen, charged with catalytic 10wt. % Pd/C (0.3 g) and the reaction mixture was placed under an atmosphere of hydrogen (40 Psi) until the reduction was complete by LCMS analysis. The reaction mixture was filtered over diatomaceous earth and the filtrate was concentrated to provide the desired product (340 mg,
15 61%) as a purple solid: ESI MS m/z 182 $[\text{C}_9\text{H}_{15}\text{N}_3\text{O} + \text{H}]^+$.

Example 116

tert-Butyl [1-(5-aminopyridin-2-yl)pyrrolidin-3-yl](methyl)carbamate

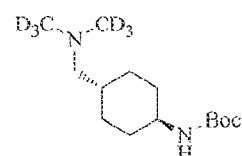


To a solution of commercially available *tert*-butyl methyl(pyrrolidin-3-yl)carbamate (1.0 g, 5.0 mmol) in THF (25 mL) was added triethylamine (0.70 mL, 5.0
20 mmol) and 2-chloro-5-nitropyridine (500 mg, 3.1 mmol) and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with a satd. aq. NaHCO_3 and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate was concentrated. The residue was purified by

chromatography (silica, ethyl acetate/hexanes) to afford the desired product (1.0 g, quant.) as a yellow solid. The solid was dissolved in tetrahydrofuran (50 mL), degassed with nitrogen, charged with catalytic 10wt. % Pd/C (0.5 g) and the reaction mixture was placed under an atmosphere of hydrogen (1 atm) until the reduction was complete by LCMS analysis. The reaction mixture was filtered over diatomaceous earth and the filtrate was concentrated to provide the desired product (940 mg, 100%) as a red oil. ESI MS m/z 293 $[C_{15}H_{24}N_4O_2 + H]^+$

Example 117

tert-Butyl {*trans*-4-[(dimethyl- d_6 -amino)methyl]cyclohexyl}carbamate



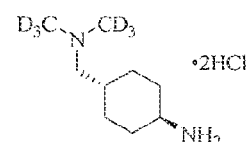
10

To a suspension of *trans*-4-[(*tert*-butoxycarbonyl)amino]cyclohexyl]methyl methanesulfonate (310 mg, 1.0 mmol), KI (330 mg, 2.0 mmol) and *N,N*-diisopropylethylamine (1.8 mL, 10 mmol) in acetonitrile (4 mL) was added dimethyl- d_6 -amine hydrochloride (350 mg, 4.0 mmol) and the reaction vessel was heated in a CEM[®] microwave at 100 °C for 1 h. The reaction mixture was cooled, diluted with a satd. aq. NaHCO₃ and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate was concentrated to afford the product (240 mg, 90%) as a light brown solid. ESI MS m/z 263 $[C_{14}H_{22}D_6N_2O_2 + H]^+$

15

Example 118

trans-4-[(Dimethylamino- d_6)methyl]cyclohexanamine dihydrochloride



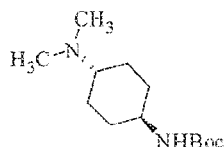
20

To a solution of *tert*-butyl {*trans*-4-[(dimethyl- d_6 -amino)methyl]cyclohexyl}carbamate (750 mg, 2.9 mmol) in THF (10 mL) was added water (5 mL) and HCl (6.0 M in H₂O, 5.0 mL, 30 mmol). The resultant solution was stirred with

heat at 65 °C for 2 h, concentrated and dried to obtain a white semisolid that was used without further purification or characterization.

Example 119

tert-Butyl *trans*-4-(dimethylamino)cyclohexylcarbamate



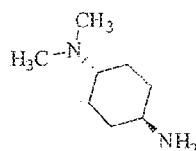
5

To a solution of *tert*-butyl *trans*-4-aminocyclohexylcarbamate (750 mg, 3.5 mmol), paraformaldehyde (320 mg, 10 mmol), and sodium cyanoborohydride (660 mg, 13 mmol) in methanol (30 mL) was added acetic acid (catalytic) and the reaction was stirred at room temperature for 18 h. The reaction mixture was diluted with water and methylene chloride the layers were separated. The aqueous layer was adjusted to pH 10 using 1 M sodium hydroxide followed by extraction with methylene chloride. The combined organic layers were dried over sodium sulfate, filtered and the filtrate was concentrated to afford the desired product (800 mg, 95%) as a white solid: ESI MS m/z 243 [$C_{13}H_{26}N_2O_2 + H$] $^+$.

10

Example 120

trans- N^1,N^1 -Dimethylcyclohexane-1,4-diamine



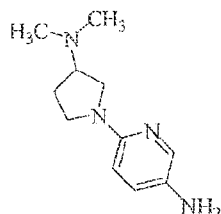
15

To a solution of *tert*-butyl *trans*-4-(dimethylamino)cyclohexylcarbamate (800 mg, 3.3 mmol) was added TFA (5 mL) and the reaction mixture was stirred with heat at 75 °C for 18 h. The reaction mixture was concentrated, the residue was loaded onto an SCX[®] ion-exchange column, flushed with methanol and then 7 N ammonia in methanol to obtain the desired product. The fractions containing the product were concentrated to dryness to obtain the desired product as the free base (400 mg, 85%) as an orange oil: ESI MS m/z 143 [$C_8H_{18}N_2 + H$] $^+$.

20

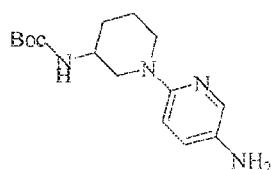
Example 121

6-[3-(Dimethylamino)pyrrolidin-1-yl]pyridin-3-amine



To a solution of 2-chloro-5-nitropyridine (500 mg, 3.1 mmol) in THF (30 mL) was added N,N-dimethylpyrrolidin-3-amine (400 mg, 3.5 mmol) and triethylamine (0.64 mL, 4.6 mmol) and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated to dryness, the residue was dissolved in dichloromethane and washed with 1 N HCl aq. and water. The organic layer was dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated to dryness. The residue was dissolved in tetrahydrofuran (30 mL), degassed with nitrogen, charged with catalytic 10wt. % Pd/C (0.3 g) and the reaction mixture was placed under an atmosphere of hydrogen (40 Psi) until the reduction was complete as indicated by LCMS analysis. The reaction mixture was filtered over diatomaceous earth and the filtrate was concentrated to provide the desired product (360 mg, 56%) as a purple solid: ESI MS m/z 207 $[C_{11}H_{18}N_4 + H]^+$.

Example 122

15 *tert*-Butyl 1-(5-aminopyridin-2-yl)piperidin-3-ylcarbamate

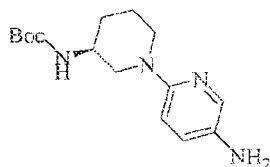
To a solution of 2-chloro-5-nitropyridine (500 mg, 3.1 mmol) in THF (30 mL) was added *tert*-butyl piperidin-3-ylcarbamate (700 mg, 3.5 mmol) and triethylamine (0.64 mL, 4.6 mmol) and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated to dryness, the residue was dissolved in dichloromethane and washed with 1 N HCl aq. and water. The organic layer was dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated to dryness. The residue was dissolved in

tetrahydrofuran (30 mL), degassed with nitrogen, charged with catalytic 10wt. % Pd/C (0.3 g) and the reaction mixture was placed under an atmosphere of hydrogen (40 Psi) until the reduction was complete as indicated by LCMS analysis. The reaction mixture was filtered over diatomaceous earth and the filtrate was concentrated to provide the desired product

5 (850 mg, 93%) as a purple solid: ESI MS m/z 293 [$C_{15}H_{24}N_4O_2 + H$] $^+$.

Example 123

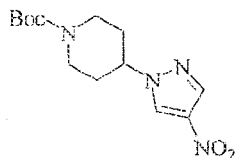
(*S*)-*tert*-Butyl 1-(5-aminopyridin-2-yl)piperidin-3-ylcarbamate



To a solution of 2-chloro-5-nitropyridine (500 mg, 3.1 mmol) in THF (30 mL) was
10 added (*S*)-*tert*-butyl piperidin-4-ylcarbamate (700 mg, 3.5 mmol) and triethylamine (0.64 mL, 4.6 mmol) and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated to dryness, the residue was dissolved in dichloromethane and washed with 1 N HCl aq. and water. The organic layer was dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated to dryness. The residue was
15 dissolved in tetrahydrofuran (30 mL), degassed with nitrogen, charged with catalytic 10wt. % Pd/C (0.3 g) and the reaction mixture was placed under an atmosphere of hydrogen (40 Psi) until the reduction was complete as indicated by LCMS analysis. The reaction mixture was filtered over diatomaceous earth and the filtrate was concentrated to provide the desired product (945 mg, quant.) as a purple solid: ESI MS m/z 293 [$C_{15}H_{24}N_4O_2 + H$] $^+$.

20 Example 124

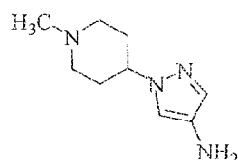
tert-Butyl 4-(4-nitro-1H-pyrazol-1-yl)piperidine-1-carboxylate



To a solution of nitropyrazole (3.0 g, 25 mmol), *tert*-butyl 4-hydroxypiperidine-1-carboxylate (6.0 g, 30 mmol) and triphenylphosphine (7.9 g, 30 mmol) in THF (200 mL) at room temperature was added diisopropyl azodicarboxylate (6.0 g, 30 mmol) and the reaction mixture was stirred for 16 h. The reaction mixture was concentrated and the residue was purified by chromatography (silica, hexanes/ethyl acetate) to provide the desired product (4.2 g, 57%) as a white solid:

Example 125

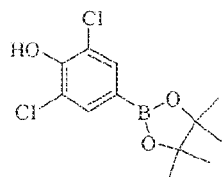
1-(1-Methylpiperidin-4-yl)-1H-pyrazol-4-amine



To a suspension of lithium aluminum hydride (0.32 g, 8.4 mmol) in THF (15 mL) was added a solution of *tert*-butyl 4-(4-nitro-1H-pyrazol-1-yl)piperidine-1-carboxylate (500 mg, 1.7 mmol) in THF (10 mL) and the reaction mixture was stirred with heat at 60 °C for 16 h. The reaction mixture was cooled to 0 °C and quenched by the slow addition of ethanol (0.3 mL) then water (0.3 mL) and finally 3 N NaOH aq. (0.3 mL). The resulting mixture was stirred for 30 min, filtered and the filtrate was concentrated and dried to obtain the desired product (280 mg) which was used without any purification: ESI MS m/z 181 [M + H]⁺.

Example 126

2,6-Dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol

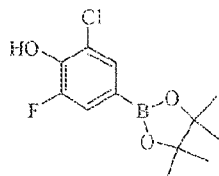


A flask was charged with 4-bromo-2,6-dichlorophenol (45 g, 0.20 mol), KOAc (39 g, 0.40 mol), bis(pinacolato)diboron (61 g, 0.22 mol) and Pd(dppf)Cl₂ (8.1 g, 0.010 mol)

followed by the addition of 1,4-dioxane (1200 mL). The reaction mixture was degassed with nitrogen and stirred with heat at 90 °C for 16 h. The reaction mixture was cooled, diluted with methylene chloride, filtered and the filtrate was concentrated to dryness. The residue was purified by chromatography (silica, hexanes/ethyl acetate) to obtain a yellow oil which was treated with hexanes and the resulting solids were filtered to obtain the desired product (24 g, 44%) as a white solid: ^1H NMR (500 MHz, CDCl_3) δ 7.57 (t, J = 1.3 Hz, 1H), 7.42 (dd, J = 10.2, 1.3 Hz, 1H), 1.33 (s, 12H).

Example 127

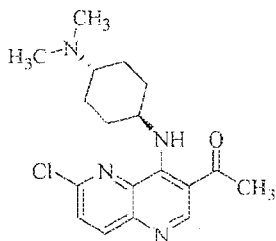
2-Chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol



Following the procedure outlined in Example 106, 4-bromo-2-chloro-6-fluorophenol (270 mg, 1.2 mmol) was reacted with bis(pinacolato)diboron (305 mg, 1.2 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (98 mg, 0.12 mmol) to afford the desired product (340 mg, quant.) as a colorless oil: ^1H NMR (500 MHz, CDCl_3) δ 7.57 (t, J = 1.3 Hz, 1H), 7.42 (dd, J = 10.2, 1.3 Hz, 1H), 1.33 (s, 12H).

Example 128

1-{6-Chloro-4-[*trans*-4-(dimethylamino)cyclohexylamino]-1,5-naphthyridin-3-yl}ethanone



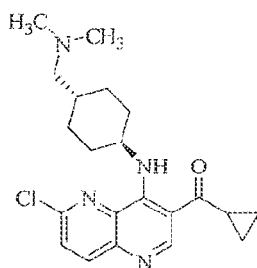
Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (250 mg, 1.0 mmol) was reacted with *trans*- N^1, N^1 -dimethylcyclohexane-1,4-diamine

dihydrochloride (336 mg, 1.6 mmol) to afford the desired product (156 mg, 38%) as a light brown solid: ^1H NMR (500 MHz, CDCl_3) δ 10.88 (br s, 1H), 8.94 (s, 1H), 8.08 (d, $J = 8.7$ Hz, 1H), 7.53 (d, $J = 8.8$ Hz, 1H), 5.07 – 4.92 (m, 1H), 2.67 (s, 3H), 2.34 (s, 6H), 2.39 – 2.32 (m, 2H), 2.31 – 2.22 (m, 1H), 2.07 – 1.99 (m, 2H), 1.56 – 1.35 (m, 4H); ESI MS

5 m/z 347 $[\text{M} + \text{H}]^+$

Example 129

(6-Chloro-4-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)(cyclopropyl)methanone

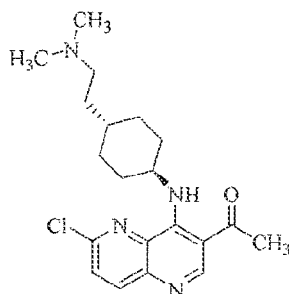


10 Following general procedure I, cyclopropyl(4,6-dichloro-1,5-naphthyridin-3-yl)-methanone (267 mg, 1.0 mmol) was reacted with *trans*-4-[(dimethylamino)methyl]cyclohexylamine diacetic acid salt (270 mg, 1.0 mmol) to afford the desired product (150 mg, 39%) as an off-white solid: ^1H NMR (500 MHz, CDCl_3) δ 10.85 (br s, 1H), 9.19 (s, 1H), 8.08 (d, $J = 8.7$ Hz, 1H), 7.51 (d, $J = 8.7$ Hz, 1H), 4.97 (br s, 1H), 2.72 – 2.62 (m, 1H),
 15 2.31 – 2.24 (m, 2H), 2.22 (s, 6H), 2.13 (d, $J = 7.2$ Hz, 2H), 1.96 – 1.89 (m, 2H), 1.55 – 1.46 (m, 1H), 1.36 (qd, $J = 12.4, 3.3$ Hz, 2H), 1.28 – 1.22 (m, 2H), 1.21 – 1.09 (m, 2H), 1.08 – 1.02 (m, 2H); ESI MS m/z 387 $[\text{M} + \text{H}]^+$

Example 130

1-(6-Chloro-4-{*trans*-4-[2-(dimethylamino)ethyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone

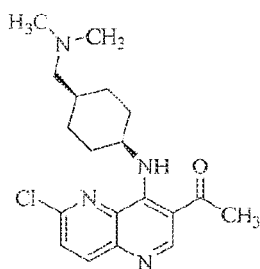
20



Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (250 mg, 1.0 mmol) was reacted with *trans*-4-[2-(dimethylamino)ethyl]cyclohexanamine dihydrochloride (300 mg, 1.2 mmol) to afford the desired product (140 mg, 36%) as an off-white solid: ^1H NMR (500 MHz, CDCl_3) δ 10.88 (br s, 1H), 8.93 (s, 1H), 8.07 (d, $J = 8.7$ Hz, 1H), 7.52 (d, $J = 8.8$ Hz, 1H), 5.04 – 4.96 (m, 1H), 2.67 (s, 3H), 2.36 – 2.22 (m, 4H), 2.24 (s, 6H), 1.93 – 1.83 (dd, $J = 13.9, 3.5$ Hz, 2H), 1.49 – 1.31 (m, 5H), 1.27 – 1.15 (m, 2H); ESI MS m/z 375 $[\text{M} + \text{H}]^+$

Example 131

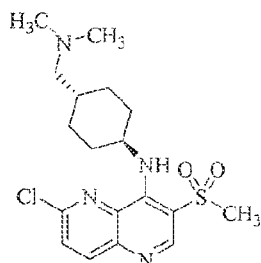
1-(6-Chloro-4-{*cis*-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone



Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (500 mg, 2.1 mmol) was reacted with *cis*-4-[(dimethylamino)methyl]cyclohexanamine (300 mg, 2.0 mmol) to afford the desired product (400 mg, 55%) as a yellow solid: ESI MS m/z 361 $[\text{M} + \text{H}]^+$;

Example 132

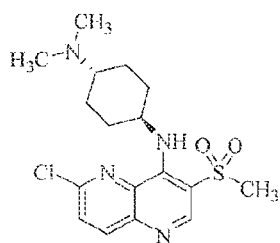
6-Chloro-N-{*trans*-4-[(dimethylamino)methyl]cyclohexyl}-3-(methylsulfonyl)-1,5-naphthyridin-4-amine



Following general procedure I, 2,8-dichloro-7-(methylsulfonyl)-1,5-naphthyridine (150 mg, 0.54 mmol) was reacted with *trans*-4-[(dimethylamino)methyl]cyclohexanamine diacetic acid salt (190 mg, 0.68 mmol) to afford the desired product (150 mg, 68%) as a light yellow solid: ^1H NMR (500 MHz, CDCl_3) δ 8.84 (s, 1H), 8.14 (d, $J = 8.8$ Hz, 1H), 7.70 – 7.60 (m, 1H), 7.57 (d, $J = 8.8$ Hz, 1H), 5.05 – 4.95 (m, 1H), 3.09 (s, 3H), 2.34 – 2.24 (m, 8H), 2.18 (d, $J = 7.0$ Hz, 2H), 2.00 – 1.92 (m, 2H), 1.57 – 1.50 (m, 1H), 1.42 – 1.30 (m, 2H), 1.24 – 1.12 (m, 2H); ESI MS m/z 397 $[\text{M} + \text{H}]^+$

Example 133

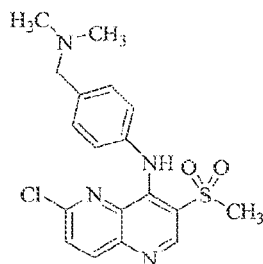
trans-N¹-[6-Chloro-3-(methylsulfonyl)-1,5-naphthyridin-4-yl]-N⁴,N⁴-dimethylcyclohexane-1,4-diamine



Following general procedure I, 2,8-dichloro-7-(methylsulfonyl)-1,5-naphthyridine (140 mg, 0.52 mmol) was reacted with *trans*-N¹,N¹-dimethylcyclohexane-1,4-diamine dihydrochloride (140 mg, 0.65 mmol) to afford the desired product (68 mg, 34%) as an off-white solid: ^1H NMR (500 MHz, CDCl_3) δ 8.85 (s, 1H), 8.15 (d, $J = 8.8$ Hz, 1H), 7.66 (d, $J = 7.7$ Hz, 1H), 7.58 (d, $J = 8.8$ Hz, 1H), 5.06 – 4.96 (m, 1H), 3.09 (s, 3H), 2.33 (s, 6H), 2.33 – 2.28 (m, 2H), 2.27 – 2.17 (m, 1H), 2.06 – 1.99 (m, 2H), 1.56 – 1.32 (m, 4H); ESI MS m/z 383 $[\text{M} + \text{H}]^+$

Example 134

6-Chloro-N-{4-[(dimethylamino)methyl]phenyl}-3-(methylsulfonyl)-
1,5-naphthyridin-4-amine

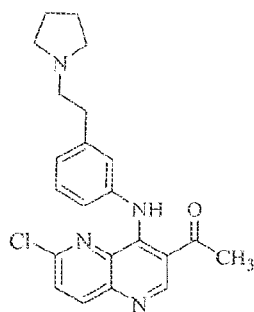


Following general procedure I, 2,8-dichloro-7-(methylsulfonyl)-1,5-naphthyridine

(150 mg, 0.53 mmol) was acted with 4-[(dimethylamino)methyl]aniline (120 mg, 0.80
mmol) to afford the desired product (150 mg, 80%) as a yellow solid: ^1H NMR (500 MHz,
 CDCl_3) δ 9.05 (s, 1H), 8.95 (s, 1H), 8.18 (d, $J = 8.8$ Hz, 1H), 7.52 (d, $J = 8.7$ Hz, 1H), 7.34
– 7.27 (m, 2H), 7.12 – 7.04 (m, 2H), 3.49 (s, 2H), 3.17 (s, 3H), 2.30 (s, 6H); ESI MS m/z
391 $[\text{M} + \text{H}]^+$

10 Example 135

1-(6-Chloro-4-{3-[2-(pyrrolidin-1-yl)ethyl]phenylamino}-1,5-naphthyridin-3-yl)ethanone

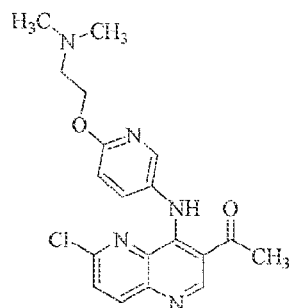


Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone

(250 mg, 1.0 mmol) was reacted with 3-[2-(pyrrolidin-1-yl)ethyl]aniline (240 mg, 1.3
mmol) to afford the desired product (230 mg, 57%) as a yellow solid: ^1H NMR (500 MHz,
 CDCl_3) δ 10.79 (br s, 1H), 8.99 (s, 1H), 8.16 (d, $J = 8.7$ Hz, 1H), 7.52 (d, $J = 8.8$ Hz, 1H),
7.29 – 7.20 (m, 1H), 7.07 (d, $J = 7.7$ Hz, 1H), 7.03 – 6.96 (m, 2H), 2.85 – 2.77 (m, 2H),
2.72 – 2.66 (m, 2H), 2.59 – 2.49 (m, 4H), 2.53 (s, 3 H), 1.84 – 1.74 (m, 4H); ESI MS m/z
395 $[\text{M} + \text{H}]^+$

Example 136

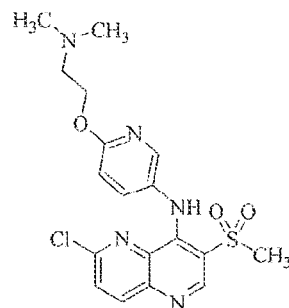
1-(6-Chloro-4-{6-[2-(dimethylamino)ethoxy]pyridin-3-ylamino}-
1,5-naphthyridin-3-yl)ethanone



5 Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone
(170 mg, 0.71 mmol) was reacted with 6-[2-(dimethylamino)ethoxy]pyridin-3-amine (160
mg, 0.90 mmol) to afford the desired product (120 mg, 44%) as a light brown solid: ^1H
NMR (500 MHz, CDCl_3) δ 11.63 (br s, 1H), 9.08 (s, 1H), 8.11 (d, $J = 8.8$ Hz, 1H), 7.99 (d,
 $J = 2.7$ Hz, 1H), 7.47 (d, $J = 8.7$ Hz, 1H), 7.41 (dd, $J = 8.8, 2.8$ Hz, 1H), 6.80 (d, $J = 8.7$ Hz,
10 1H), 4.46 (t, $J = 5.6$ Hz, 2H), 2.76 (t, $J = 5.6$ Hz, 2H), 2.74 (s, 3H), 2.36 (s, 6H); ESI MS
 m/z 386 $[\text{M} + \text{H}]^+$

Example 137

6-Chloro-N-(6-(2-(dimethylamino)ethoxy)pyridin-3-yl)-3-(
(methylsulfonyl)-1,5-naphthyridin-4-amine



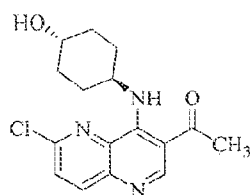
15

Following general procedure I, 2,8-dichloro-7-(methylsulfonyl)-1,5-naphthyridine
(150 mg, 0.54 mmol) was reacted with 6-[2-(dimethylamino)ethoxy]pyridin-3-amine (120
mg, 0.65 mmol) to afford the desired product (160 mg, 70%) as a light yellow solid; ^1H

NMR (500 MHz, CDCl_3) δ 9.03 (s, 1H), 8.98 (s, 1H), 8.17 (d, $J = 8.8$ Hz, 1H), 7.98 (d, $J = 2.8$ Hz, 1H), 7.52 (d, $J = 8.8$ Hz, 1H), 7.42 (dd, $J = 8.8, 2.8$ Hz, 1H), 6.82 (d, $J = 8.8$ Hz, 1H), 4.46 (t, $J = 5.5$ Hz, 2H), 3.20 (s, 3H), 2.76 (t, $J = 5.6$ Hz, 2H), 2.37 (s, 6H); ESI MS m/z 422 $[\text{M} + \text{H}]^+$

5 Example 138

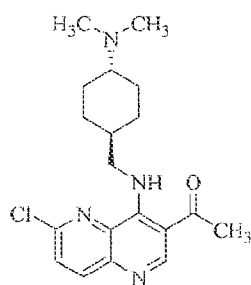
1-[6-Chloro-4-(*trans*-4-hydroxycyclohexylamino)-1,5-naphthyridin-3-yl]ethanone



Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (480 mg, 2.0 mmol) was reacted with *trans*-4-aminocyclohexanol (287 mg, 2.5 mmol) to afford the desired product (500 mg, 78%) as an orange-red solid: ^1H NMR (500 MHz, CDCl_3) δ 10.90 (s, 1H), 8.95 (s, 1H), 8.09 (d, $J = 8.7$ Hz, 1H), 7.53 (d, $J = 8.7$ Hz, 1H), 5.10 (tdt, $J = 11.2, 8.0, 3.9$ Hz, 1H), 3.76 (tt, $J = 10.0, 4.3$ Hz, 1H), 2.68 (s, 3H), 2.33 – 2.24 (m, 2H), 2.13 – 2.04 (m, 2H), 1.63 – 1.41 (m, 8H); ESI MS m/z 320 $[\text{M} + \text{H}]^+$

Example 139

15 1-(6-Chloro-4-([*trans*-4-(dimethylamino)cyclohexyl]methylamino)-1,5-naphthyridin-3-yl)ethanone

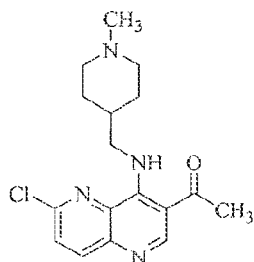


Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (300 mg, 1.2 mmol) was reacted with *trans*-4-(aminomethyl)-N,N-dimethylcyclohexanamine (350 mg, 1.5 mmol) to afford the desired product (400 mg, 86%)

as an orange-red solid: ^1H NMR (300 MHz, CD_3OD) δ 8.95 (s, 1H), 8.11 (d, $J = 8.8$ Hz, 1H), 7.69 (d, $J = 8.8$ Hz, 1H), 4.07 (d, $J = 6.5$ Hz, 2H), 2.69 (s, 3H), 2.32 (s, 6H), 2.13 – 1.95 (m, 4H), 1.43 – 1.08 (m, 4H); ESI MS m/z 361 $[\text{M} + \text{H}]^+$

Example 140

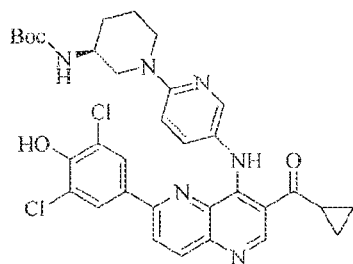
- 5 1-{6-Chloro-4-[(1-methylpiperidin-4-yl)methylamino]-1,5-naphthyridin-3-yl}ethanone



- Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (250 mg, 1.0 mmol) was reacted with (1-methylpiperidin-4-yl)methanamine (160 mg, 1.3 mmol) to afford the desired product (170 mg, 49%) as a light yellow-brown solid: ^1H NMR (500 MHz, CDCl_3) δ 11.06 (br s, 1H), 8.95 (s, 1H), 8.10 (d, $J = 8.8$ Hz, 1H), 7.53 (d, $J = 8.7$ Hz, 1H), 4.13 (t, $J = 6.4$ Hz, 2H), 2.99 – 2.92 (m, 2H), 2.69 (s, 3H), 2.32 (s, 3H), 2.07 – 1.98 (m, 2H), 1.97 – 1.89 (m, 2H), 1.85 – 1.75 (m, 1H), 1.57 – 1.47 (m, 2H); ESI MS m/z 333 $[\text{M} + \text{H}]^+$
- 10

Example 141

- 15 (*S*)-*tert*-Butyl 1-{5-[3-(cyclopropanecarbonyl)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino]pyridin-2-yl}piperidin-3-ylcarbamate

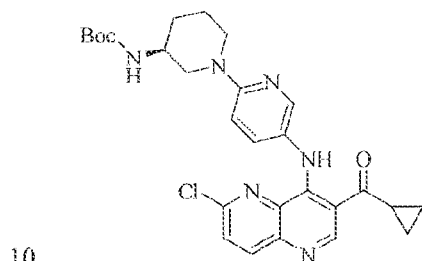


- Following general procedure II, (*S*)-*tert*-butyl 1-{5-[6-chloro-3-(cyclopropanecarbonyl)-1,5-naphthyridin-4-ylamino]pyridin-2-yl}piperidin-3-ylcarbamate (98 mg, 0.19 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-
- 20

dioxaborolan-2-yl)phenol (87 mg, 0.30 mmol) to afford the desired product (73 mg, 60%) as a red-brown solid: ^1H NMR (500 MHz, CDCl_3) δ 11.55 (br s, 1H), 9.29 (s, 1H), 8.25 (d, $J = 8.8$ Hz, 1H), 8.03 (d, $J = 2.7$ Hz, 1H), 7.92 (d, $J = 8.8$ Hz, 1H), 7.46 (s, 2H), 7.32 (dd, $J = 9.0, 2.8$ Hz, 1H), 6.67 (d, $J = 9.0$ Hz, 1H), 4.78 – 4.72 (m, 1H), 3.87 – 3.69 (m, 3H),
 5 3.29 – 3.07 (m, 2H), 2.79 – 2.71 (m, 1H), 1.98 – 1.69 (m, 2H), 1.45 (s, 9H), 1.31 – 1.22 (m, 2H), 1.16 – 1.06 (m, 2H); ESI MS m/z 649 $[\text{M} + \text{H}]^+$

Example 142

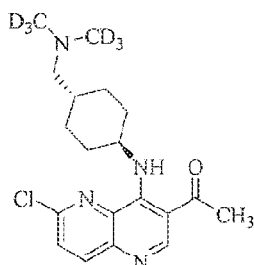
(*S*)-*tert*-Butyl 1-{5-[6-chloro-3-(cyclopropanecarbonyl)-1,5-naphthyridin-4-ylamino]-pyridin-2-yl}piperidin-3-ylcarbamate



Following general procedure I, cyclopropyl(4,6-dichloro-1,5-naphthyridin-3-yl)-methanone (267 mg, 1.0 mmol) was reacted with (*S*)-*tert*-butyl 1-(5-aminopyridin-2-yl)-piperidin-3-ylcarbamate (340 mg, 1.2 mmol) to afford the desired product (329 mg, 63%) as a brown solid: ^1H NMR (500 MHz, CDCl_3) δ 10.19 (br s, 1H), 9.03 (s, 1H), 8.17 (d, $J =$
 15 8.8 Hz, 1H), 8.04 (d, $J = 2.8$ Hz, 1H), 7.53 (d, $J = 8.8$ Hz, 1H), 7.31 – 7.25 (m, 1H), 6.70 (d, $J = 9.1$ Hz, 1H), 4.78 (br s, 1H), 3.83 – 3.62 (m, 3H), 3.47 – 3.25 (m, 2H), 2.55 – 2.47 (m, 1H), 1.97 – 1.83 (m, 2H), 1.73 – 1.58 (m, 1H), 1.45 (s, 9H), 1.12 – 1.04 (m, 2H), 1.00 – 0.90 (m, 2H); ESI MS m/z 523 $[\text{M} + \text{H}]^+$

Example 143

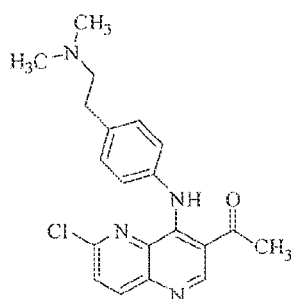
20 1-(6-Chloro-4-(*trans*-4-((dimethylamino- d_6)methyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone



Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (100 mg, 0.42 mmol) was reacted with *trans*-4-[(dimethylamino-*d*₆)methyl]cyclohexanamine (87 mg, 0.37 mmol) to afford the desired product (85 mg, 63%) as a light brown solid: ¹H NMR (500 MHz, CD₃OD) δ 8.96 (s, 1H), 8.11 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 8.7 Hz, 1H), 5.08 – 4.98 (m, 1H), 2.68 (s, 3H), 2.34 – 2.24 (m, 4H), 2.00 – 1.91 (m, 2H), 1.68 – 1.53 (m, 1H), 1.46 – 1.36 (m, 2H), 1.25 – 1.15 (m, 2H); ESI MS *m/z* 367 [M + H]⁺

Example 144

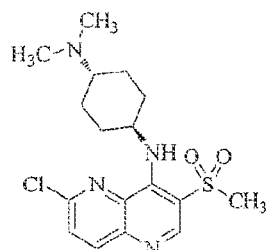
10 1-(6-Chloro-4-{4-[2-(dimethylamino)ethyl]phenylamino}-1,5-naphthyridin-3-yl)ethanone



Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (150 mg, 0.64 mmol) was reacted with 4-[2-(dimethylamino)ethyl]aniline (110 mg, 0.64 mmol) to afford the desired product (143 mg, 60%) as a yellow solid: ¹H NMR (500 MHz, CDCl₃) δ 10.86 (br s, 1H), 8.99 (s, 1H), 8.14 (d, J = 8.8 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.22 – 7.15 (m, 2H), 7.11 – 7.04 (m, 2H), 2.87 (t, J = 8.1 Hz, 2H), 2.70 – 2.60 (m, 2H), 2.55 (s, 3H), 2.39 (s, 6 H); ESI MS *m/z* 369 [M + H]⁺

Example 145

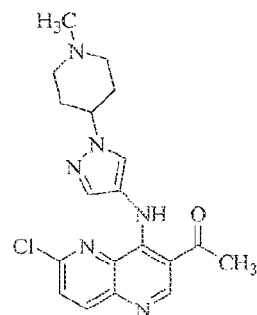
trans-N¹-[6-Chloro-3-(methylsulfonyl)-1,5-naphthyridin-4-yl]-N⁴,N⁴-dimethylcyclohexane-1,4-diamine



Following general procedure I, 2,8-dichloro-7-(methylsulfonyl)-1,5-naphthyridine (140 mg, 0.52 mmol) was reacted with *trans*-N¹,N¹-dimethylcyclohexane-1,4-diamine dihydrochloride (140 mg, 0.65 mmol) to afford the desired product (68 mg, 34%) as an off-white solid: ESI MS *m/z* 383 [M + H]⁺

Example 146

1-{6-Chloro-4-[1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-ylamino]-1,5-naphthyridin-3-yl}ethanone

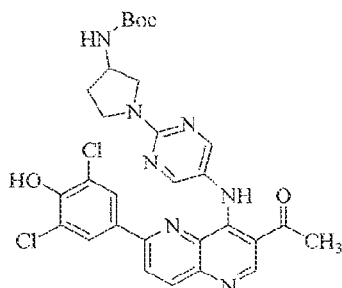


Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (250 mg, 1.0 mmol) was reacted with 1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-amine (216 mg, 1.2 mmol) to afford the desired product (304 mg, 76%) as a light orange solid: ¹H NMR (500 MHz, CDCl₃) δ 8.99 (s, 1H), 8.12 (d, *J* = 8.7 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.42 (d, *J* = 0.6 Hz, 1H), 4.18 – 4.11 (m, 1H), 3.00 (d, *J* = 11.4 Hz, 2H), 2.67 (s, 3H), 2.34 (s, 3H), 2.26 – 2.02 (m, 6H); ESI MS *m/z* 385 [M + H]⁺

Example 147

tert-Butyl 1-{5-[3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-

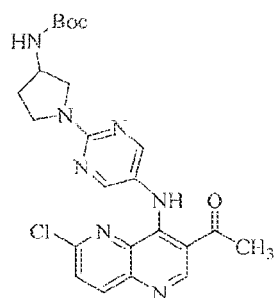
ylamino]pyrimidin-2-yl}pyrrolidin-3-ylcarbamate



Following general procedure II, *tert*-butyl 1-[5-(3-acetyl-6-chloro-1,5-naphthyridin-4-ylamino)pyrimidin-2-yl]pyrrolidin-3-ylcarbamate (120 mg, 0.25 mmol) was
 5 reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (110 mg, 0.38 mmol) to afford the product (120 mg, 80%) as an orange solid: ^1H NMR (500 MHz, CDCl_3) δ 12.02 (s, 1H), 9.12 (s, 1H), 8.28 – 8.20 (m, 3H), 7.93 (d, J = 8.8 Hz, 1H), 7.39 (s, 2H), 4.72 (br s, 1H), 4.36 (br s, 1H), 3.86 (br s, 1H), 3.65 (br s, 2H), 3.40 (br s, 1H), 2.80 (s, 3H), 2.28 (br s, 1H), 2.03 – 1.93 (m, 1H), 1.48 (s, 9H); ESI MS m/z 610 $[\text{M} + \text{H}]^+$

10 Example 148

tert-Butyl 1-[5-(3-acetyl-6-chloro-1,5-naphthyridin-4-ylamino)pyrimidin-2-yl]pyrrolidin-3-ylcarbamate

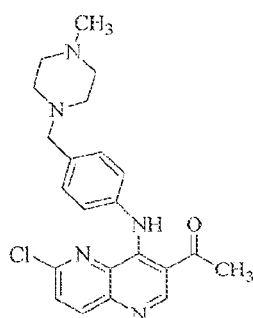


Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone
 15 (300 mg, 1.2 mmol) was reacted with *tert*-butyl 1-(5-aminopyrimidin-2-yl)pyrrolidin-3-ylcarbamate (380 mg, 1.4 mmol) to afford the desired product (468 mg, 78%) as a yellow-orange solid: ^1H NMR (500 MHz, CDCl_3) δ 11.72 (s, 2H), 9.09 (s, 2H), 8.21 (s, 3H), 8.11 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 8.8 Hz, 2H), 7.26 (s, 2H), 4.70 (s, 2H), 4.38 (s, 2H), 3.90

(dd, $J = 11.6, 6.1$ Hz, 2H), 3.78 – 3.66 (m, 4H), 3.52 (dd, $J = 11.6, 4.3$ Hz, 2H), 2.77 (s, 5H), 2.31 (dq, $J = 13.4, 7.2$ Hz, 2H), 1.57 (s, 2H), 1.47 (s, 17H), 1.19 (s, 1H); ESI MS m/z 484 $[M + H]^+$

Example 149

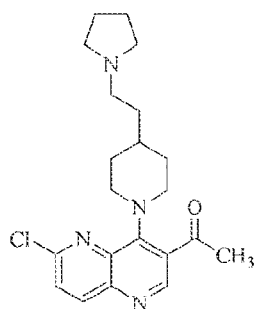
- 5 1-(6-Chloro-4-{4-[(4-methylpiperazin-1-yl)methyl]phenylamino}-1,5-naphthyridin-3-yl)ethanone



- Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (250 mg, 1.0 mmol) was reacted with 4-[(4-methylpiperazin-1-yl)methyl]aniline (260 mg, 1.3 mmol) to afford the desired product (250 mg, 58%) as a yellow solid: ^1H NMR (500 MHz, CDCl_3) δ 11.04 (br s, 1H), 9.01 (s, 1H), 8.14 (d, $J = 8.7$ Hz, 1H), 7.49 (d, $J = 8.7$ Hz, 1H), 7.30 (d, $J = 8.0$ Hz, 2H), 7.10 (d, $J = 8.0$ Hz, 2H), 3.52 (s, 2H), 2.58 (s, 3H), 2.48 (br s, 8H), 2.30 (s, 3H); ESI MS m/z 410 $[M + H]^+$

Example 150

- 15 1-(6-Chloro-4-{4-[2-(pyrrolidin-1-yl)ethyl]piperidin-1-yl}-1,5-naphthyridin-3-yl)ethanone

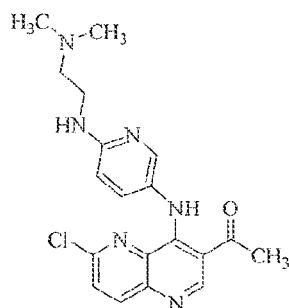


Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (250 mg, 1.0 mmol) was reacted with 4-[2-(pyrrolidin-1-yl)ethyl]piperidine (230 mg, 1.3

mmol) to afford the desired product (190 mg, 47%) as a yellow solid: ^1H NMR (500 MHz, CDCl_3) δ 8.74 (s, 1 H), 8.18 (d, $J = 8.8$ Hz, 1H), 7.53 (d, $J = 8.7$ Hz, 1H), 3.98 – 3.90 (m, 2H), 3.32 – 3.23 (m, 2H), 2.58 – 2.50 (m, 6H), 2.55 (s, 3H), 1.86 – 1.53 (m, 11H); ESI MS m/z 387 $[\text{M} + \text{H}]^+$

5 Example 151

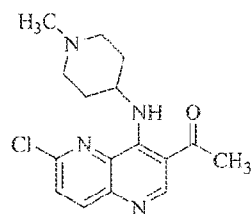
1-(6-Chloro-4-{6-[2-(dimethylamino)ethylamino]pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone



Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (300 mg, 1.2 mmol) was reacted with N^2 -[2-(dimethylamino)ethyl]pyridine-2,5-diamine (320 mg, 1.5 mmol) to afford the desired product (210 mg, 37%) as an orange solid: ^1H NMR (500 MHz, CDCl_3) δ 11.41 (br s, 1H), 9.02 (s, 1H), 8.13 – 8.07 (m, 1H), 7.95 (d, $J = 2.5$ Hz, 1H), 7.47 (dd, $J = 8.7, 1.1$ Hz, 1H), 7.29 – 7.23 (m, 1H), 6.44 (d, $J = 8.8$ Hz, 1H), 5.12 (t, $J = 5.1$ Hz, 1H), 3.41 (q, $J = 5.7$ Hz, 2H), 2.69 (s, 3H), 2.60 (t, $J = 6.0$ Hz, 2H), 2.30 (s, 6H); ESI MS m/z 385 $[\text{M} + \text{H}]^+$

Example 152

1-[6-Chloro-4-(1-methylpiperidin-4-ylamino)-1,5-naphthyridin-3-yl]ethanone

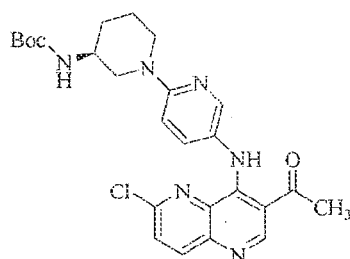


Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (220 mg, 0.91 mmol) was reacted with 1-methylpiperidin-4-amine (160 mg, 1.4 mmol) to

afford the desired product (200 mg, 69%) as a light brown solid: ^1H NMR (500 MHz, CDCl_3) δ 10.98 (s, 1H), 8.96 (s, 1H), 8.10 (d, $J = 8.7$ Hz, 1H), 7.53 (d, $J = 8.7$ Hz, 1H), 5.11 (br s, 1H), 2.98 – 2.870 (m, 2H), 2.69 (s, 3H), 2.41 – 2.28 (m, 5H), 2.28 – 2.20 (m, 2H), 1.85 – 1.73 (m, 2H); ESI MS m/z 319 $[\text{M} + \text{H}]^+$; ESI MS m/z 319 $[\text{M} + \text{H}]^+$

5 Example 153

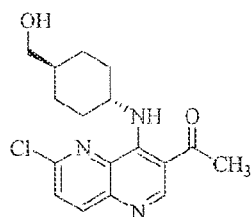
(*S*)-*tert*-Butyl 1-[5-(3-acetyl-6-chloro-1,5-naphthyridin-4-ylamino)pyridin-2-yl]piperidin-3-ylcarbamate



Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (260 mg, 1.1 mmol) was reacted with (*S*)-*tert*-butyl 1-(5-aminopyridin-2-yl)piperidin-3-ylcarbamate (470 mg, 1.6 mmol) to afford the desired product (350 mg, 65%) as an orange-red solid: ^1H NMR (300 MHz, CDCl_3) δ 11.48 (s, 1H), 9.04 (s, 1H), 8.10 (d, $J = 8.7$ Hz, 1H), 8.01 (d, $J = 2.8$ Hz, 1H), 7.46 (d, $J = 8.7$ Hz, 1H), 7.31 (dd, $J = 9.0, 2.8$ Hz, 1H), 6.73 (d, $J = 9.0$ Hz, 1H), 4.80 (br s, 1H), 3.85 – 3.62 (m, 3H), 3.55 – 3.25 (m, 3H), 2.71 (s, 3H), 1.96 – 1.84 (m, 1H), 1.82 – 1.70 (m, 1H), 1.72 – 1.55 (m, 1H), 1.45 (s, 9H); ESI MS m/z 497 $[\text{M} + \text{H}]^+$

Example 154

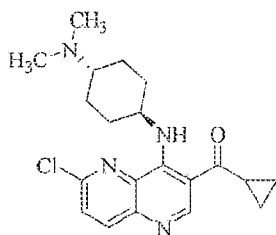
1-[6-Chloro-4-[(*trans*-4-(hydroxymethyl)cyclohexylamino)-1,5-naphthyridin-3-yl]ethanone



Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (200 mg, 0.83 mmol) was reacted with (*trans*-4-aminocyclohexyl)methanol (130 mg, 1.0 mmol) to afford the desired product (180 mg, 65%) as an orange-yellow solid: ^1H NMR (500 MHz, CDCl_3) δ 10.90 (s, 1H), 8.94 (s, 1H), 8.08 (d, $J = 8.7$ Hz, 1H), 7.52 (d, $J = 8.7$ Hz, 1H), 5.10 – 4.92 (m, 1H), 3.58 – 3.47 (m, 2H), 2.68 (s, 3H), 2.37 – 2.23 (m, 2H), 2.01 – 1.89 (m, 2H), 1.65 – 1.51 (m, 1H), 1.42 – 1.30 (m, 2H), 1.29 – 1.18 (m, 2H); ESI MS m/z 334 $[\text{M} + \text{H}]^+$

Example 155

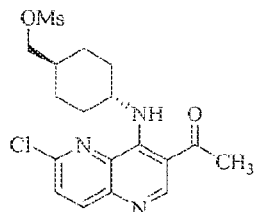
{6-Chloro-4-[(*trans*-4-(dimethylamino)cyclohexylamino)-1,5-naphthyridin-3-yl]}(cyclopropyl)methanone



Following general procedure I, cyclopropyl(4,6-dichloro-1,5-naphthyridin-3-yl)methanone (243 mg, 0.91 mmol) was reacted with *trans*-N¹,N¹-dimethylcyclohexane-1,4-diamine (168 mg, 1.2 mmol) to afford the desired product (150 mg, 44%) as a light yellow solid. ^1H NMR (500 MHz, Chloroform- d) δ 10.83 (br s, 1H), 9.20 (s, 1H), 8.09 (d, $J = 8.7$ Hz, 1H), 7.52 (d, $J = 8.8$ Hz, 1H), 4.98 (br s, 1H), 2.71 – 2.63 (m, 1H), 2.33 (s, 6H), 2.34 – 2.29 (m, 2H), 2.28 – 2.19 (m, 1H), 2.06 – 1.97 (m, 2H), 1.54 – 1.33 (m, 4H), 1.31 – 1.22 (m, 2H), 1.11 – 1.01 (m, 2H). ESI MS m/z 373 $[\text{M} + \text{H}]^+$.

Example 156

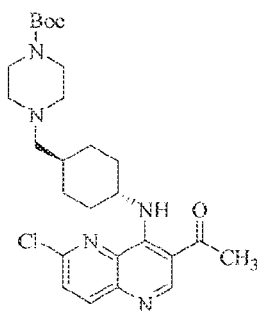
{*trans*-4-[(3-Acetyl-6-chloro-1,5-naphthyridin-4-yl)amino]cyclohexyl}methyl methanesulfonate



To a solution of 1-(6-chloro-4-[(*trans*-4-(hydroxymethyl)cyclohexylamino]-1,5-naphthyridin-3-yl)ethanone (140 mg, 0.42 mmol) in methylene chloride (10 mL) was added triethylamine (0.12 mL, 0.84 mmol) and methanesulfonyl chloride (65 μ L, 0.84 mmol) and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with satd. aq. sodium bicarbonate, the layers were separated and the organic layer was concentrated to afford the crude product (180 mg) as a yellow solid which was used without further purification: ^1H NMR (500 MHz, CDCl_3) δ 10.90 (br s, 1H), 8.95 (s, 1H), 8.09 (d, $J = 8.7$ Hz, 1H), 7.53 (d, $J = 8.7$ Hz, 1H), 5.10 – 4.95 (m, 1H), 4.11 (d, $J = 6.5$ Hz, 2H), 3.03 (s, 3H), 2.68 (s, 3H), 2.39 – 2.26 (m, 2H), 2.01 – 1.92 (m, 2H), 1.90 – 1.78 (m, 1H), 1.47 – 1.24 (m, 4H); ESI MS m/z 412 $[\text{M} + \text{H}]^+$

Example 157

tert-Butyl 4-[(*trans*-4-(3-acetyl-6-chloro-1,5-naphthyridin-4-ylamino)cyclohexyl)methyl]piperazine-1-carboxylate



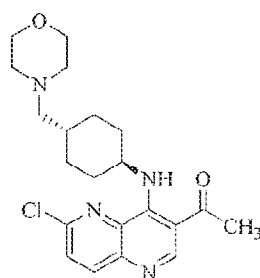
15

Following general procedure V, {4-[(3-acetyl-6-chloro-1,5-naphthyridin-4-yl)amino]-cyclohexyl}methyl methanesulfonate (170 mg, 0.42 mmol) was reacted with *tert*-butyl 4-[(*trans*-4-aminocyclohexyl)methyl]piperazine-1-carboxylate (93 mg, 0.50 mmol) to afford the desired product (150 mg, 73%) as a yellow solid. ESI MS m/z 502 $[\text{M} +$

HJ⁺

Example 158

1-[6-Chloro-4-[(*trans*-4-(morpholinomethyl)cyclohexylamino)]-
1,5-naphthyridin-3-yl]ethanone



5

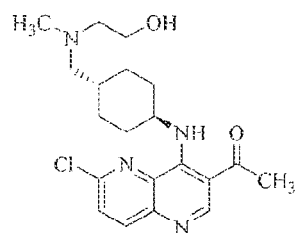
Following general procedure V, {*trans*-4-[(3-acetyl-6-chloro-1,5-naphthyridin-4-yl)-amino]cyclohexyl}methyl methanesulfonate (230 mg, 0.56 mmol) was reacted with morpholine (72 mg, 0.84 mmol) to afford the desired product (85 mg, 38%) as a yellow solid: ¹H NMR (300 MHz, CDCl₃) δ 10.90 (br s, 1H), 8.94 (s, 1H), 8.08 (d, *J* = 8.7 Hz, 1H), 7.52 (d, *J* = 8.7 Hz, 1H), 5.11 – 4.88 (m, 1H), 3.77 – 3.65 (m, 4H), 2.68 (s, 3H), 2.46 – 2.38 (m, 4H), 2.36 – 2.21 (m, 2H), 2.21 – 2.15 (m, 2H), 2.01 – 1.89 (m, 2H), 1.64 – 1.50 (m, 1H), 1.46 – 1.07 (m, 4H); ESI MS *m/z* 403 [M + H]⁺

10

Example 159

1-[6-Chloro-4-[(*trans*-4-[(2-hydroxyethyl)(methyl)amino]methyl]cyclohexylamino)]-
1,5-naphthyridin-3-yl]ethanone

15

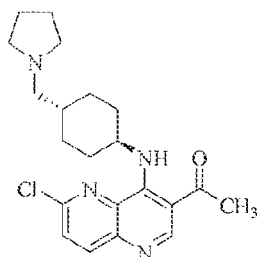


Following general procedure V, {*trans*-4-[(3-acetyl-6-chloro-1,5-naphthyridin-4-yl)-amino]cyclohexyl}methyl methanesulfonate (240 mg, 0.58 mmol) was reacted with 2-methylamino ethanol (88 mg, 1.2 mmol) to afford the desired product (110 mg, 47%) as a

yellow solid: ^1H NMR (300 MHz, CDCl_3) δ 10.89 (s, 1H), 8.94 (s, 1H), 8.08 (d, $J = 8.8$ Hz, 1H), 7.52 (d, $J = 8.8$ Hz, 1H), 5.09 – 4.88 (m, 1H), 3.63 (t, $J = 5.3$ Hz, 2H), 2.68 (s, 3H), 2.59 (br s, 2H), 2.31 (br s, 7H), 2.04 – 1.91 (m, 2H), 1.68 – 1.50 (m, 1H), 1.48 – 1.07 (m, 4H); ESI MS m/z 391 $[\text{M} + \text{H}]^+$

5 Example 160

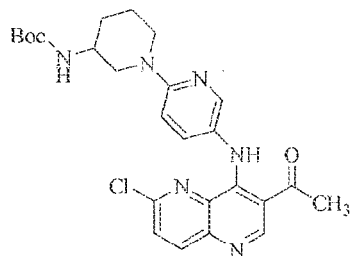
1-{6-Chloro-4-[*trans*-4-(pyrrolidin-1-ylmethyl)cyclohexylamino]-1,5-naphthyridin-3-yl}ethanone



Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (220 mg, 0.92 mmol) was reacted with 4-(pyrrolidin-1-ylmethyl)cyclohexylamine (200 mg, 1.1 mmol) to afford the desired product (67 mg, 19%) as a brown solid: ^1H NMR (300 MHz, CDCl_3) δ 10.88 (br s, 1H), 8.93 (s, 1H), 8.07 (d, $J = 8.7$ Hz, 1H), 7.51 (d, $J = 8.7$ Hz, 1H), 5.09 – 4.88 (m, 1H), 2.66 (br s, 7H), 2.46 (d, $J = 7.1$ Hz, 2H), 2.37 – 2.25 (m, 2H), 2.08 – 1.76 (m, 6H), 1.72–1.55 (m, 1H), 1.51 – 1.12 (m, 4H); ESI MS m/z 387 $[\text{M} + \text{H}]^+$

15 Example 161

tert-Butyl 1-[5-(3-acetyl-6-chloro-1,5-naphthyridin-4-ylamino)pyridin-2-yl]-piperidin-3-ylcarbamate

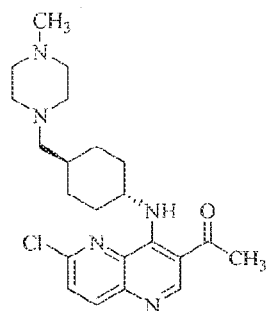


Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (610 mg, 2.5 mmol) was reacted with *tert*-butyl 1-(5-aminopyridin-2-yl)piperidin-3-

ylcarbamate (590 mg, 3.0 mmol) to afford the desired product (420 mg, 35%) as an orange-red solid: ^1H NMR (500 MHz, CDCl_3) δ 11.47 (s, 1H), 9.01 (s, 1H), 8.09 (d, $J = 8.7$ Hz, 1H), 8.01 (d, $J = 2.6$ Hz, 1H), 7.45 (d, $J = 8.7$ Hz, 1H), 7.34 – 7.28 (m, 1H), 6.72 (d, $J = 9.1$ Hz, 1H), 4.95 – 4.90 (m, 1H), 3.85 – 3.67 (m, 3H), 3.47 – 3.27 (m, 2H), 2.69 (s, 3H), 1.97 – 1.88 (m, 1H), 1.86 – 1.75 (m, 1H), 1.73 – 1.59 (m, 2H), 1.45 (s, 9H); ESI MS m/z 497 $[\text{M} + \text{H}]^+$

Example 162

1-(6-Chloro-4-{*trans*-4-[(4-methylpiperazin-1-yl)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone



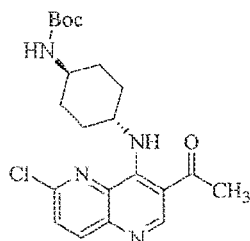
10

Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (250 mg, 1.0 mmol) was reacted with *trans*-4-[(4-methylpiperazin-1-yl)methyl]cyclohexanamine (330 mg, 1.6 mmol) to afford the desired product (32 mg, 7%) as a yellow solid: ^1H NMR (300 MHz, CDCl_3) δ 10.93 – 10.89 (m, 1H), 8.95 (s, 1H), 8.11 (d, $J = 8.7$ Hz, 1H), 7.53 (d, $J = 8.7$ Hz, 1H), 5.09–4.90 (m, 1H), 3.31 (br s, 4H), 2.90 (br s, 4H), 2.75 (s, 3H), 2.68 (s, 3H), 2.43 – 2.24 (m, 4H), 1.99 – 1.87 (m, 2H), 1.62 – 1.46 (m, 1H), 1.47 – 1.07 (m, 4H); ESI MS m/z 416 $[\text{M} + \text{H}]^+$

15

Example 163

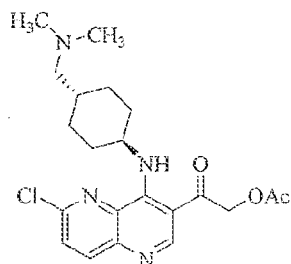
tert-Butyl {*trans*-4-[(3-acetyl-6-chloro-1,5-naphthyridin-4-yl)amino]cyclohexyl} carbamate



Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (480 mg, 2.0 mmol) was reacted with *tert*-butyl (*trans*-4-aminocyclohexyl)carbamate (430 mg, 2.0 mmol) to afford the desired product (600 mg, 71%) as a light orange solid: ^1H NMR (500 MHz, CDCl_3) δ 10.91 (br s, 1H), 8.96 (s, 1H), 8.10 (d, $J = 8.8$ Hz, 1H), 7.54 (d, $J = 8.8$ Hz, 1H), 5.10 – 4.99 (m, 1H), 4.48 (br s, 1H), 3.55 (br s, 1H), 2.69 (s, 3H), 2.34 – 2.25 (m, 2H), 2.19 – 2.10 (m, 2H), 1.56 – 1.45 (m, 2H), 1.47 (s, 9H), 1.44 – 1.33 (m, 2H); ESI MS m/z 419 $[\text{M} + \text{H}]^+$

Example 164

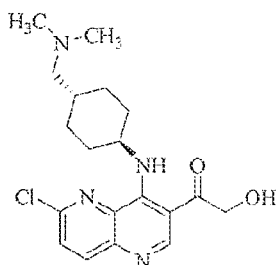
2-(6-Chloro-4-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)-2-oxoethyl acetate



Following general procedure I, 2-(4,6-dichloro-1,5-naphthyridin-3-yl)-2-oxoethyl acetate (101 mg, 0.33 mmol) was reacted with *trans*-4-[(dimethylamino)methyl]cyclohexanamine (67 mg, 0.43 mmol) to afford the desired product (90 mg, 65%) as an off-white solid. ESI MS m/z 419 $[\text{M} + \text{H}]^+$.

Example 165

1-(6-Chloro-4-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)-2-hydroxyethanone

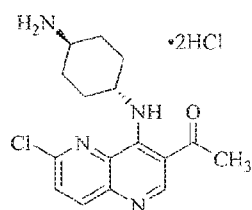


To a solution of 2-(6-chloro-4-{*trans*-4-
 [(dimethylamino)methyl]cyclohexylamino}-

- 5 1,5-naphthyridin-3-yl)-2-oxoethyl acetate (90 mg, 0.22 mmol) in methanol was added
 freshly ground potassium carbonate (90 mg, 0.65 mmol) and the reaction mixture was
 stirred at room temperature for 30 minutes. The reaction mixture was diluted with satd. aq.
 sodium bicarbonate and extracted with ethyl acetate. The combined organic layers were
 dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated. The
 10 residue was purified by column chromatography (silica, dichloromethane/methanol) to
 afford the desired product (18 mg, 22%) as a yellow solid. ESI MS m/z 377 $[M + H]^+$.

Example 166

1-{4-[(4-Aminocyclohexyl)amino]-6-chloro-1,5-naphthyridin-3-yl}ethanone
 dihydrochloride

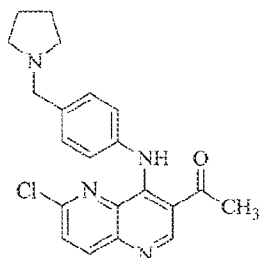


15

Following general procedure IV-1, *tert*-butyl {*trans*-4-[(3-acetyl-6-chloro-1,5-
 naphthyridin-4-yl)amino]cyclohexyl}carbamate (360 mg, 0.86 mmol) was reacted with HCl
 (5 mL, 2 M in ether) to afford the desired product (190 mg, 56%) as a white solid. ESI MS
 m/z 318 $[M + H]^+$

20 Example 167

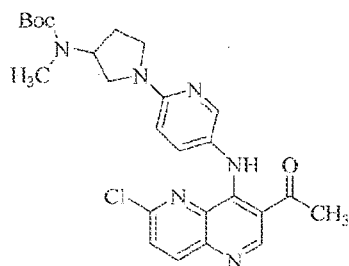
1-{6-Chloro-4-[4-(pyrrolidin-1-ylmethyl)phenylamino]-1,5-naphthyridin-3-yl}ethanone



Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (200 mg, 0.83 mmol) was reacted with 4-(pyrrolidin-1-ylmethyl)aniline (310 mg, 1.24 mmol) to afford the desired product (78 mg, 25%) as a brown-orange solid: ^1H NMR (300 MHz, CDCl_3) δ 11.06 (s, 1H), 9.03 (s, 1H), 8.15 (d, $J = 8.7$ Hz, 1H), 7.50 (d, $J = 8.7$ Hz, 1H), 7.41 (d, $J = 8.3$ Hz, 2H), 7.13 (d, $J = 8.3$ Hz, 2H), 3.85 (br s, 2H), 2.80 (br s, 4H), 2.60 (s, 3H), 1.92 (br s, 4H); ESI MS m/z 381 $[\text{M} + \text{H}]^+$

Example 168

tert-Butyl 1-[5-(3-acetyl-6-chloro-1,5-naphthyridin-4-ylamino)pyridin-2-yl]-pyrrolidin-3-yl(methyl)carbamate

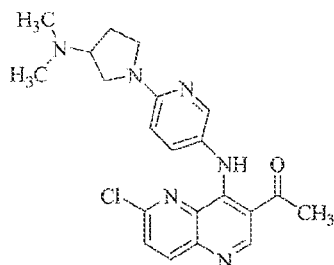


Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (200 mg, 0.83 mmol) was reacted with *tert*-butyl 1-(5-aminopyridin-2-yl)pyrrolidin-3-yl(methyl) carbamate (360 mg, 1.2 mmol) to afford the desired product (360 mg, 85%) as a dark red solid: ^1H NMR (500 MHz, CDCl_3) δ 11.39 (s, 1H), 9.02 (s, 1H), 8.10 (d, $J = 8.7$ Hz, 1H), 8.02 (d, $J = 2.6$ Hz, 1H), 7.47 (d, $J = 8.7$ Hz, 1H), 7.32 (dd, $J = 8.8, 2.6$ Hz, 1H), 6.37 (d, $J = 8.8$ Hz, 1H), 4.91 (br s, 1H), 3.73 – 3.62 (m, 2H), 3.51 – 3.38 (m, 2H), 2.83 (s, 3H), 2.68 (s, 3H), 2.28 – 2.06 (m, 2H), 1.49 (s, 9H); ESI MS m/z 497 $[\text{M} + \text{H}]^+$

Example 169

1-(6-Chloro-4-{6-[3-(dimethylamino)pyrrolidin-1-yl]pyridin-3-ylamino}-

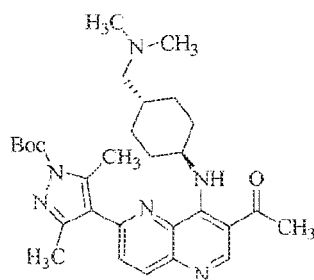
1,5-naphthyridin-3-yl)ethanone



Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (250 mg, 1.0 mmol) was reacted with N,N-dimethylpyrrolidin-3-amine (260 mg, 1.2 mmol) to afford the desired product (380 mg, 89%) as an orange solid: ^1H NMR (300 MHz, CDCl_3) δ 11.35 (s, 1H), 9.00 (s, 1H), 8.10 (d, $J = 8.7$ Hz, 1H), 8.02 (dd, $J = 2.7, 0.7$ Hz, 1H), 7.47 (d, $J = 8.7$ Hz, 1H), 7.30 (dd, $J = 8.9, 2.7$ Hz, 1H), 6.35 (d, $J = 8.9$ Hz, 1H), 3.88 – 3.77 (m, 1H), 3.62 – 3.72 (m, 1H), 3.49 – 3.37 (m, 1H), 3.33 – 3.22 (m, 1H), 2.94 – 2.76 (m, 1H), 2.68 (s, 3H), 2.34 (s, 6H), 2.34 – 2.18 (m, 1H), 2.06 – 1.89 (m, 1H); ESI MS m/z 411 $[\text{M} + \text{H}]^+$

Example 170

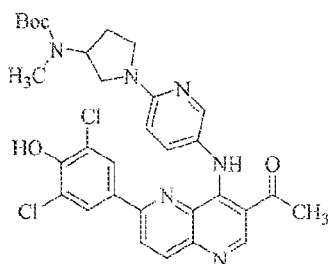
tert-Butyl 4-[7-acetyl-8-({*trans*-4-[(dimethylamino)methyl]cyclohexyl}amino)-1,5-naphthyridin-2-yl]-3,5-dimethyl-1H-pyrazole-1-carboxylate



Following general procedure II, 1-(6-chloro-4-({*trans*-4-[(dimethylamino)methyl]cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone (92 mg, 0.25 mmol) was reacted with *tert*-butyl 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (120 mg, 0.37 mmol) to afford crude product (100 mg) as a brown solid which was carried forward without any purification: ESI MS m/z 521 $[\text{M} + \text{H}]^+$

Example 171

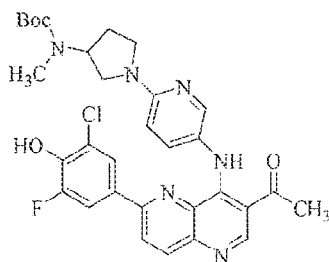
tert-Butyl 1-(5-(3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino)-pyridin-2-yl)pyrrolidin-3-yl(methyl)carbamate



- 5 Following general procedure II, *tert*-butyl 1-(5-(3-acetyl-6-chloro-1,5-naphthyridin-4-ylamino)-pyridin-2-yl)pyrrolidin-3-yl (methyl) carbamate (91 mg, 0.183 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (79 mg, 0.273 mmol) to afford crude product (72 mg) as an orange solid which was carried forward without any purification: ESI MS m/z 623 $[M + H]^+$

10 Example 172

tert-Butyl 1-(5-(3-acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino)pyridin-2-yl)pyrrolidin-3-yl(methyl)carbamate

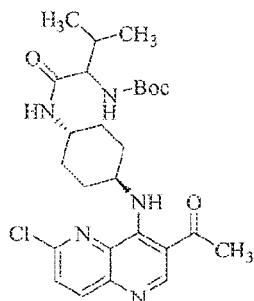


- 15 Following general procedure II, *tert*-butyl 1-[5-(3-acetyl-6-chloro-1,5-naphthyridin-4-ylamino)-pyridin-2-yl]pyrrolidin-3-yl(methyl)carbamate (91 mg, 0.19 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (77 mg, 0.28 mmol) to afford crude product (79 mg) as an orange solid which was carried forward without any purification: ESI MS m/z 607 $[M + H]^+$

Example 173

- 20 *tert*-Butyl (1-{*trans*-4-[(3-acetyl-6-chloro-1,5-naphthyridin-4-yl)amino]cyclohexyl-

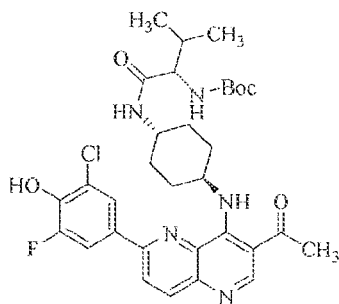
amino}-3-methyl-1-oxobutan-2-yl)carbamate



Following general procedure VI, 1-{4-[(4-aminocyclohexyl)amino]-6-chloro- 1,5-naphthyridin-3-yl} ethanone dihydrochloride (300 mg, 0.94 mmol) was reacted with 2-[(*tert*-butoxycarbonyl) amino]-3-methylbutanoic acid (310 mg, 1.4 mmol) to afford the desired product (320 mg, 65%) as a white solid. ESI MS m/z 518 $[M + H]^+$

Example 174

tert-Butyl 1-{*trans*-4-[3-acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)- 1,5-naphthyridin-4-ylamino]cyclohexylamino}-3-methyl-1-oxobutan-2-ylcarbamate



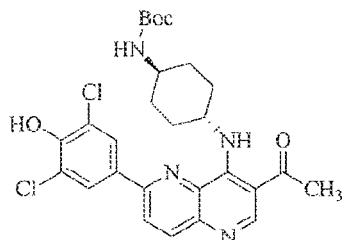
10

Following general procedure II, *tert*-Butyl 1-{*trans*-4-[(3-acetyl-6-chloro-1,5-naphthyridin-4-yl)amino]cyclohexylamino}-3-methyl-1-oxobutan-2-yl)carbamates (100 mg, 0.19 mmol) was reacted with 2-chloro-6-fluoro- 4-(1,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (50 mg, 0.23 mmol) to afford the crude product (115 mg) as an off-white solid: ESI MS m/z 628 $[M + H]^+$.

15

Example 175

tert-Butyl *trans*-4-[[3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)- 1,5-naphthyridin-4-yl]aminocyclohexyl]carbamate

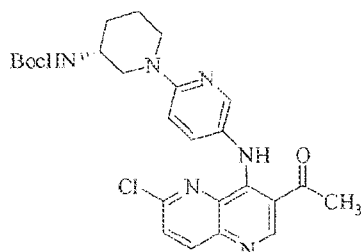


Following general procedure II, *tert*-butyl *trans*-4-[(3-acetyl-6-chloro-1,5-naphthyridin-4-yl)-aminocyclohexyl]carbamate (100 mg, 0.23 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (81 mg, 0.28 mmol) to afford crude product which was carried forward without any purification: ESI MS m/z 545 $[M + H]^+$.

Example 176

(*R*)-*tert*-Butyl 1-(5-(3-acetyl-6-chloro-1,5-naphthyridin-4-ylamino)pyridin-2-yl)piperidin-3-ylcarbamate

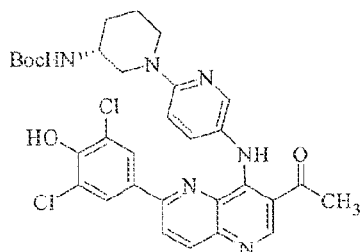
10



Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (340 mg, 1.4 mmol) was reacted with (*R*)-*tert*-butyl 1-(5-aminopyridin-2-yl)piperidin-3-ylcarbamate (500 mg, 1.7 mmol) to afford the desired product (410 mg, 58%) as a brown-orange solid. ESI MS m/z 497 $[M + H]^+$

Example 177

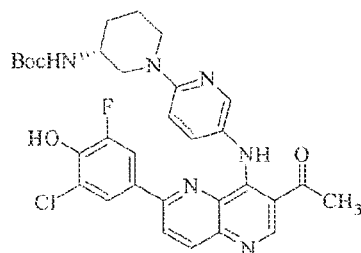
(*R*)-*tert*-Butyl 1-(5-(3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino)pyridin-2-yl)piperidin-3-ylcarbamate



Following general procedure II, (*R*)-*tert*-butyl 1-(5-(3-acetyl-6-chloro-1,5-naphthyridin-4-ylamino)pyridin-2-yl)piperidin-3-ylcarbamate (200 mg, 0.40 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (170 mg, 0.60 mmol) to afford the desired product (210 mg, 85%) as a orange solid. ESI MS m/z 623 $[M + H]^+$

Example 178

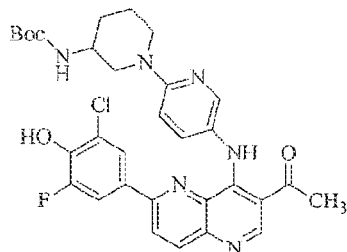
(*R*)-*tert*-Butyl 1-(5-(3-acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino)pyridin-2-yl)piperidin-3-ylcarbamate



Following general procedure II, (*R*)-*tert*-butyl 1-(5-(3-acetyl-6-chloro-1,5-naphthyridin-4-ylamino)pyridin-2-yl)piperidin-3-ylcarbamate (200 mg, 0.40 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (165 mg, 0.60 mmol) to afford the desired product (125 g, 51%) as a yellow-orange solid. ESI MS m/z 607 $[M + H]^+$

Example 179

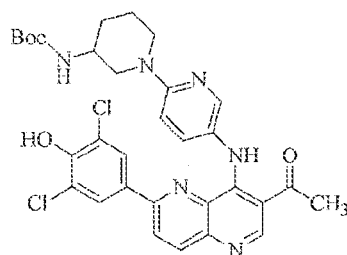
tert-Butyl [1-(5-{[3-acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl]amino}pyridin-2-yl)piperidin-3-yl]carbamate



Following general procedure II, *tert*-butyl (1-(5-[(3-acetyl-6-chloro-1,5-naphthyridin-4-yl)amino]pyridin-2-yl)piperidin-3-yl)carbamate (100 mg, 0.20 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (65
5 mg, 0.24 mmol) to afford crude product which was carried forward without any purification: ESI MS m/z 607 $[M + H]^+$.

Example 180

tert-Butyl [1-(5-{[3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl]amino}pyridin-2-yl)piperidin-3-yl]carbamate

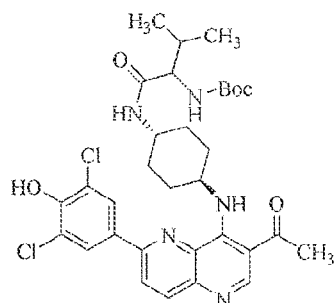


10

Following general procedure II, *tert*-butyl (1-(5-[(3-acetyl-6-chloro-1,5-naphthyridin-4-yl)amino]pyridin-2-yl)piperidin-3-yl)carbamate (100 mg, 0.20 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (68 mg, 0.24 mmol) to afford crude product (45 mg) which was carried forward without any purification: ESI MS
15 m/z 623 $[M + H]^+$.

Example 181

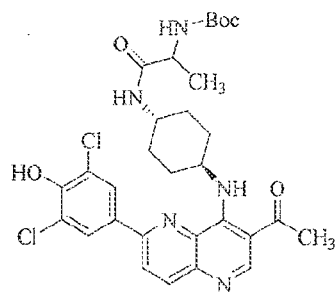
tert-Butyl 1-{4-[3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-*trans*-4-ylamino]cyclohexylamino}-3-methyl-1-oxobutan-2-ylcarbamate



Following general procedure II, *tert*-butyl 1-({4-[(3-acetyl-6-chloro-1,5-naphthyridin-*trans*-4-yl)amino]cyclohexyl}amino)-3-methyl-1-oxobutan-2-yl]carbamate (100 mg, 0.19 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (65 mg, 0.23 mmol) to afford crude product (80 mg) as a brown solid which was carried forward without any purification: ESI MS m/z 644 $[M + H]^+$

Example 182

tert-Butyl 1-({*trans*-4-[3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino]cyclohexylamino}-1-oxopropan-2-yl)carbamate



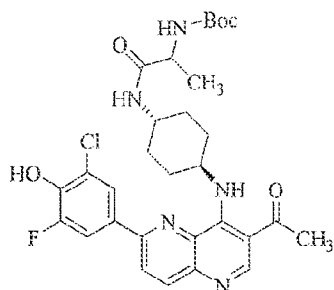
10

Following general procedure II, *tert*-butyl 1-[{*trans*-4-(3-acetyl-6-chloro-1,5-naphthyridin-*trans*-4-ylamino)cyclohexylamino}-1-oxopropan-2-yl]carbamate (65 mg, 0.13 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (45 mg, 0.16 mmol) to afford crude product that was carried forward without any purification.

15

Example 183

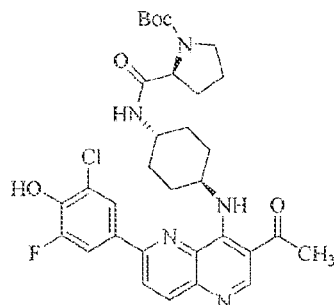
tert-Butyl 1-({4-[3-acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-*trans*-4-ylamino]cyclohexylamino}-1-oxopropan-2-yl)carbamate



Following general procedure II, *tert*-butyl 1-[4-(3-acetyl-6-chloro-1,5-naphthyridin-*trans*-4-ylamino)cyclohexylamino]-1-oxopropan-2-ylcarbamate (68 mg, 0.13 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (43 mg, 0.16 mmol) to afford crude product that was carried forward without any purification.

Example 184

(*S*)-*tert*-Butyl 2-[4-[3-acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-*trans*-4-ylamino]cyclohexylcarbamoyl]pyrrolidine-1-carboxylate



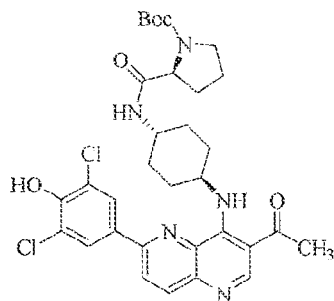
10

Following general procedure II, (*S*)-*tert*-butyl 2-[4-(3-acetyl-6-chloro-1,5-naphthyridin-*trans*-4-ylamino)cyclohexylcarbamoyl]pyrrolidine-1-carboxylate (100 mg, 0.19 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (63 mg, 0.23 mmol) to afford crude product (75 mg) as a brown solid that was carried forward without any purification: ESI MS m/z 626 $[M + H]^+$

15

Example 185

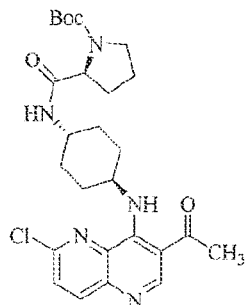
(*S*)-*tert*-butyl 2-[4-[3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-*trans*-4-ylamino]-cyclohexylcarbamoyl]pyrrolidine-1-carboxylate



Following general procedure II, (*S*)-*tert*-butyl 2-[4-(3-acetyl-6-chloro-1,5-naphthyridin-*trans*-4-ylamino)cyclohexylcarbamoyl]pyrrolidine-1-carboxylate (100 mg, 0.195 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (66 mg, 0.234 mmol) to afford crude product (113 mg) as a yellow solid product that was carried forward without any purification.

Example 186

(*S*)-*tert*-butyl 2-[4-(3-acetyl-6-chloro-1,5-naphthyridin-*trans*-4-ylamino)-cyclohexylcarbamoyl]pyrrolidine-1-carboxylate

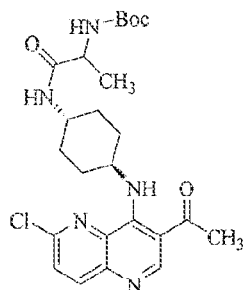


10

Following general procedure V, 1-[4-(*trans*-4-aminocyclohexyl)amino]-6-chloro-1,5-naphthyridin-3-yl]ethanone dihydrochloride (220 mg, 0.564 mmol) was reacted with (*S*)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid (145 mg, 0.676 mmol) to afford the desired product (290 mg, 99%) as an off-white solid. ESI MS m/z 518 $[M + H]^+$

Example 187

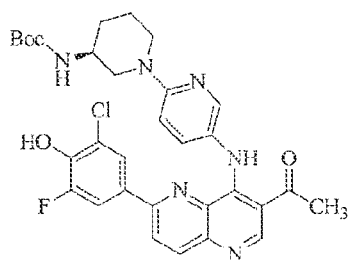
tert-Butyl 1-[4-(3-acetyl-6-chloro-1,5-naphthyridin-4-ylamino)cyclohexylamino]-1-oxopropan-2-ylcarbamate



Following general procedure V, (1-[4-(*trans*-4-aminocyclohexyl)amino]-6-chloro-1,5-naphthyridin-3-yl) ethanone dihydrochloride (130 mg, 0.35 mmol) was reacted with 2-(*tert*-butoxycarbonylamino)propanoic acid (78 mg, 0.42 mmol) to afford the desired product
 5 (130 mg, 79%) as a yellow solid. ESI MS m/z 490 $[M + H]^+$

Example 188

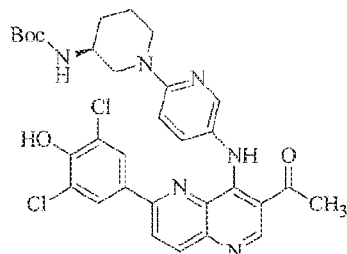
(*S*)-*tert*-Butyl [1-(5-{[3-acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl]amino}pyridin-2-yl)piperidin-3-yl]carbamate



10 Following general procedure II, (*S*)-*tert*-butyl (1-{5-[(3-acetyl-6-chloro-1,5-naphthyridin-4-yl)amino]pyridin-2-yl}piperidin-3-yl)carbamate (100 mg, 0.20 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (82 mg, 0.30 mmol) to afford the crude product (72 mg) which was carried forward without any purification: ESI MS m/z 607 $[M + H]^+$.

15 Example 189

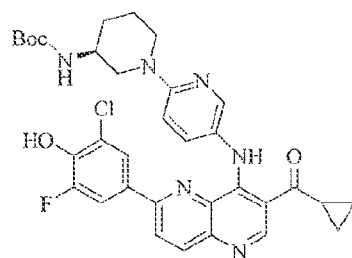
(*S*)-*tert*-Butyl [1-(5-{[3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl]amino}pyridin-2-yl)piperidin-3-yl]carbamate



Following general procedure II, (*S*)-*tert*-butyl 1-({5-[(3-acetyl-6-chloro-1,5-naphthyridin-4-yl)-amino]pyridin-2-yl}piperidin-3-yl)carbamate (98 mg, 0.20 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (85 mg, 0.30 mmol) to
 5 afford the product (56 mg) which was carried forward without any purification: ESI MS m/z 625 $[M + H]^+$.

Example 190

(*S*)-*tert*-Butyl [1-(5-{[3-(cyclopropylcarbonyl)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl]amino}pyridin-2-yl)piperidin-3-yl]carbamate

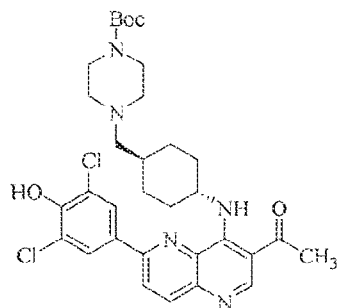


10

Following general procedure II, (*S*)-*tert*-Butyl 1-({5-[6-chloro-3-(cyclopropanecarbonyl)-1,5-naphthyridin-4-ylamino]pyridin-2-yl}piperidin-3-yl)carbamate (131 mg, 0.25 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (102 mg, 0.38 mmol) to afford the desired product (100 mg, 63%)
 15 as an orange red solid. ESI MS m/z 633 $[M + H]^+$.

Example 191

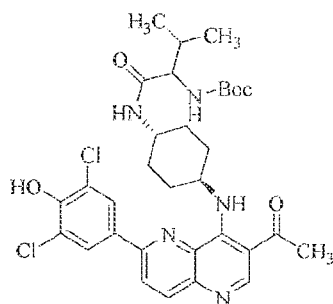
tert-Butyl 4-({*trans*-4-[3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino]cyclohexyl}methyl)piperazine-1-carboxylate



Following general procedure II, *tert*-butyl 4-({[*trans*-4-(3-acetyl-6-chloro-1,5-naphthyridin-4-ylamino) cyclohexyl]methyl} piperazine-1-carboxylate (150 mg, 0.30 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (130 mg, 0.45 mmol) to afford the product (170 mg) which was carried forward without any purification: ESI MS m/z 628 $[M + H]^+$.

Example 192

tert-Butyl 1-{4-[3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-*trans*-4-ylamino]cyclohexylamino}-3-methyl-1-oxobutan-2-ylcarbamate



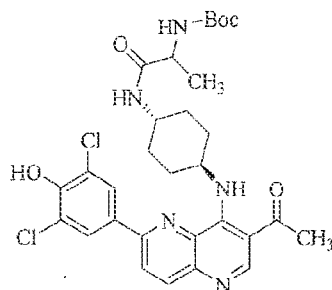
10

Following general procedure B, *tert*-butyl (1-{4-[(3-acetyl-6-chloro-1,5-naphthyridin-*trans*-4-yl)aminocyclohexyl]amino}-3-methyl-1-oxobutan-2-yl)carbamate (100 mg, 0.19 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (65 mg, 0.23 mmol) to afford crude product (80 mg) as a brown solid. ESI MS m/z 644 $[M + H]^+$

15

Example 193

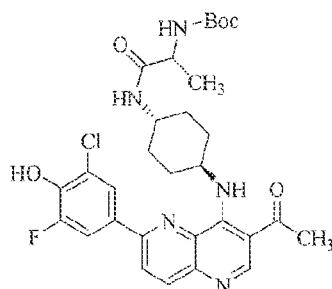
tert-Butyl 1-{*trans*-4-[3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino]cyclohexylamino}-1-oxopropan-2-ylcarbamate



Following general procedure B, *tert*-butyl 1-[(*trans*-4-(3-acetyl-6-chloro-1,5-naphthyridin-*trans*-4-ylamino)cyclohexylamino]-1-oxopropan-2-ylcarbamate (65 mg, 0.13 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (45 mg, 0.16 mmol) to afford crude product.

Example 194

tert-Butyl 1-{4-[3-acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-*trans*-4-ylamino]cyclohexylamino}-1-oxopropan-2-ylcarbamate

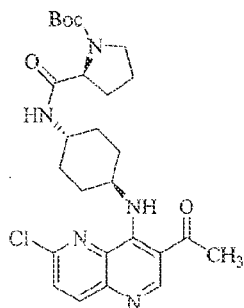


10

Following general procedure B, *tert*-butyl 1-[4-(3-acetyl-6-chloro-1,5-naphthyridin-*trans*-4-ylamino)cyclohexylamino]-1-oxopropan-2-ylcarbamate (68 mg, 0.13 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (43 mg, 0.16 mmol) to afford crude product which was carried forward without further purification or characterization.

Example 195

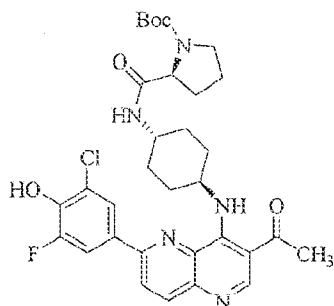
(*S*)-*tert*-Butyl 2-[4-(3-acetyl-6-chloro-1,5-naphthyridin-*trans*-4-ylamino)-cyclohexylcarbamoyl]pyrrolidine-1-carboxylate



Following general procedure D, 1-[4-(*trans*-4-aminocyclohexyl)amino]-6-chloro-1,5-naphthyridin-3-yl ethanone dihydrochloride (220 mg, 0.564 mmol) was reacted with (S)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid (145 mg, 0.676 mmol) to afford the desired product (290 mg, 99%) as an off-white solid. ESI MS m/z 518 $[M + H]^+$

Example 196

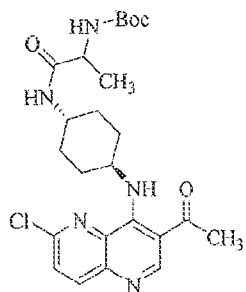
(S)-*tert*-Butyl 2-[4-[3-acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-*trans*-4-ylamino]cyclohexylcarbamoyl]pyrrolidine-1-carboxylate



Following general procedure B, (S)-*tert*-butyl 2-[4-(3-acetyl-6-chloro-1,5-naphthyridin-*trans*-4-ylamino)cyclohexylcarbamoyl]pyrrolidine-1-carboxylate (100 mg, 0.19 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (63 mg, 0.23 mmol) to afford crude product (75 mg) as a brown solid which was carried forward without further purification or characterization: ESI MS m/z 626 $[M + H]^+$

Example 197

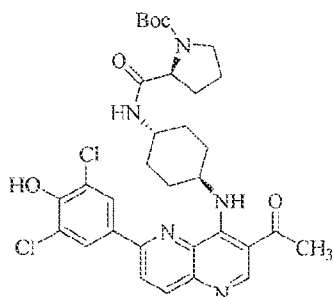
tert-Butyl 1-[4-(3-acetyl-6-chloro-1,5-naphthyridin-4-ylamino)cyclohexylamino]-1-oxopropan-2-ylcarbamate



Following general procedure C, 1-[4-(*trans*-4-aminocyclohexyl)amino]-6-chloro-1,5-naphthyridin-3-yl)ethanone dihydrochloride (130 mg, 0.35 mmol) was reacted with 2-(*tert*-butoxycarbonylamino)propanoic acid (78 mg, 0.42 mmol) to afford the desired product (130 mg, 79%) as a yellow solid . ESI MS m/z 490 $[M + H]^+$

Example 198

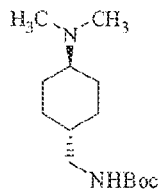
(*S*)-*tert*-Butyl 2-(4-(3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-*trans*-4-ylamino)cyclohexylcarbamoyl)pyrrolidine-1-carboxylate



Following general procedure B, (*S*)-*tert*-butyl 2-[4-(3-acetyl-6-chloro-1,5-naphthyridin-*trans*-4-ylamino)cyclohexylcarbamoyl]pyrrolidine-1-carboxylate (100 mg, 0.19 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (66 mg, 0.23 mmol) to afford crude product (113 mg) as a yellow solid which was carried forward without further purification or characterization.

Example 199

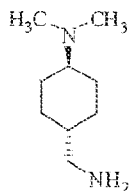
tert-Butyl [4-(dimethylamino)cyclohexyl]methylcarbamate



To a solution of *tert*-butyl [*trans*-4-aminocyclohexyl]methylcarbamate (1.15 g, 5.00 mmol), paraformaldehyde (454 mg, 15.0 mmol), and sodium cyanoborohydride (940 mg, 15.0 mmol) in methanol (40 mL) was added acetic acid (catalytic) and the reaction mixture
 5 stirred at room temperature for 18 h. The reaction mixture was quenched with water and concentrated to remove methanol. The pH of the aqueous layer was adjusted to 10 with 1 M aqueous sodium hydroxide followed by extraction with methylene chloride. The organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated to afford the desired product (1.2 g, 96%) as a thick oil: ESI MS *m/z* 257 [$C_{14}H_{28}N_2O_2 + H$]⁺.

10 Example 200

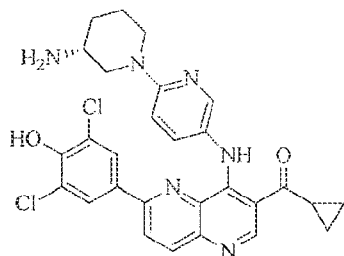
trans-4-(Aminomethyl)-*N,N*-dimethylcyclohexanamine



Following general procedure IV-1, *tert*-butyl [*trans*-4-(dimethylamino)cyclohexyl]methyl carbamate (1.2 g, 4.8 mmol) was reacted with 3 M hydrochloric acid (10 mL) to afford the
 15 dihydrochloride salt as the desired product (1.2 g, >99%) as white solid: ESI MS *m/z* 230 [$C_9H_{20}N_2 + H$]⁺.

Example 201

(*R*)-(4-{{6-(3-aminopiperidin-1-yl)pyridin-3-yl}amino}-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)(cyclopropyl)methanone



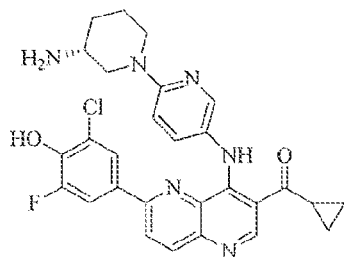
Following general procedure IV-2, (R)-tert-butyl [1-(5-({3-(cyclopropanecarbonyl)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl}amino)pyridin-2-yl)piperidin-3-yl]carbamate (0.12 g, 0.18 mmol) was reacted with TFA (2 mL). The resulting

5 trifluoroacetate salt of the product was converted to the free base to afford the desired product (67 mg, 67%) as an orange solid: ^1H NMR (500 MHz, CD_3OD) δ 9.17 (s, 1H), 8.09 (d, $J = 9.0$ Hz, 1H), 8.03 (d, $J = 9.0$ Hz, 1H), 7.92 (d, $J = 2.5$ Hz, 1H), 7.44 (s, 2H), 7.37 (dd, $J = 9.0, 2.5$ Hz, 1H), 6.70 (d, $J = 9.0$ Hz, 1H), 4.16 – 4.13 (m, 1H), 3.87 – 3.84 (m, 1H), 3.27 – 3.21 (m, 1H), 3.09 – 3.05 (m, 2H), 2.89 – 2.86 (m, 1H), 2.18 – 2.08 (m, 1H), 1.90 –

10 1.81 (m, 1H), 1.73 – 1.58 (m, 2H), 1.21 – 1.08 (m, 4H); ESI MS m/z 549 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 10.15$ min.

Example 202

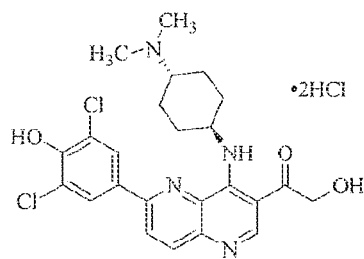
(R)-(4-([6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)(cyclopropyl)methanone



5 Following general procedure IV-2, (R)-tert-butyl [1-(5-([3-(cyclopropanecarbonyl)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl]amino)pyridin-2-yl)piperidin-3-yl]carbamate (0.98 g, 0.16 mmol) was reacted with TFA (2 mL). The resulting trifluoroacetate salt of the product was converted to the free base to afford the desired product (58 mg, 71%) as an orange solid: ^1H NMR (500 MHz, CD_3OD) δ 9.18 (s, 1H), 8.09 (d, $J = 9.0$ Hz, 1H), 8.04 (d, $J = 9.0$ Hz, 1H), 7.97 (d, $J = 2.0$ Hz, 1H), 7.37 (dd, $J = 9.0, 2.0$ Hz, 1H), 6.97 (d, $J = 13.0$ Hz, 1H), 6.75 (d, $J = 9.0$ Hz, 1H), 4.18 – 4.15 (m, 1H), 3.83 – 3.81 (m, 1H), 3.31 – 3.22 (m, 1H), 3.15 – 3.05 (m, 2H), 2.91 – 2.85 (m, 1H), 2.12 – 2.08 (m, 1H), 1.91 – 1.83 (m, 1H), 1.71 – 1.58 (m, 2H), 1.25 – 1.08 (m, 4H); ESI MS m/z 533 $[\text{M} + \text{H}]^+$; HPLC 99.0% (AUC), $t_R = 9.18$ min.

15 Example 203

1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-([trans-4-(dimethylamino)cyclohexyl]amino)-1,5-naphthyridin-3-yl]-2-hydroxyethanone dihydrochloride

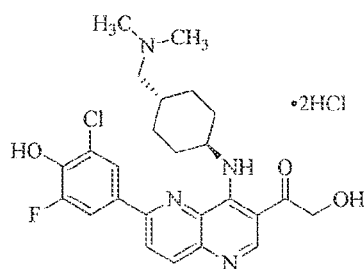


20 Following general procedure II, 2-[(tert-butyl(dimethylsilyl)oxy)]-1-[6-chloro-4-[(trans-4-(dimethylamino)cyclohexyl]amino)-1,5-naphthyridin-3-yl]ethanone (44 mg,

0.093 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (43 mg, 0.15 mmol) followed by formation of the dihydrochloride salt to afford the product (10 mg, 20%) as a yellow solid: solid: ^1H NMR (500 MHz, CD_3OD) δ 9.15 (s, 1H), 8.47 (d, $J=9.0$ Hz, 1H), 8.35 (d, $J=9.0$ Hz, 1H), 8.11 (s, 2H), 5.68 – 5.60 (m, 1H),
 5 4.92 (s, 2H), 3.51 – 3.42 (m, 1H), 2.92 (s, 6H), 2.63 – 2.59 (m, 2H), 2.33 – 2.28 (m, 2H), 1.88 – 1.73 (m, 4H); ESI MS m/z 489 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 9.16$ min.

Example 204

1-[6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-({*trans*-4-
 [(dimethylamino)methyl]cyclohexyl} amino)-1,5-naphthyridin-3-yl)]-2-hydroxyethanone
 10 dihydrochloride

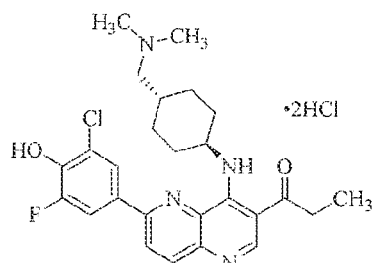


Following general procedure II, 1-(6-chloro-4-({*trans*-4-[(dimethylamino)methyl]cyclohexylamino})-1,5-naphthyridin-3-yl)-2-hydroxyethanone (49 mg, 0.13 mmol) was
 15 reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (53 mg, 0.12 mmol) followed by formation of the dihydrochloride salt to afford the product (31 mg, 42%) as an off-white solid: ^1H NMR (500 MHz, CD_3OD) δ 9.12 (s, 1H), 8.45 (d, $J=9.0$ Hz, 1H), 8.32 (d, $J=9.0$ Hz, 1H), 8.03 (s, 1H), 7.89 (d, $J=11.0$ Hz, 1H), 5.80 – 5.65 (m, 1H), 4.91 (s, 2H), 3.13 – 3.05 (m, 2H), 2.94 (s, 6H), 2.50 – 2.43 (m, 2H), 2.12 – 1.98
 20 (m, 2H), 1.78 – 1.65 (m, 2H), 1.48 – 1.35 (m, 2H); ESI MS m/z 487 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 9.26$ min.

Example 205

1-[6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-({*trans*-4-
 [(dimethylamino)methyl]cyclohexyl} amino)-1,5-naphthyridin-3-yl)]propan-1-one

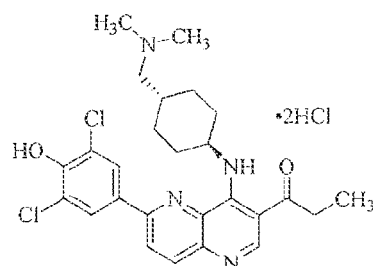
dihydrochloride



Following general procedure II, 1-(6-chloro-4-((*trans*-4-((dimethylamino)methyl)cyclohexylamino)-1,5-naphthyridin-3-yl)-2-hydroxyethanone (170 mg, 0.50 mmol) was
 5 reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (170 mg, 0.60 mmol). After work up and purification the dihydrochloride salt was obtained (31 mg, 42%) as an off-white solid: ^1H NMR (500 MHz, CD_3OD) δ 9.17 (s, 1H), 8.44 (d, J = 9.0 Hz, 1H), 8.33 (d, J = 9.0 Hz, 1H), 8.02 (d, J = 2.0 Hz, 1H), 7.88 (dd, J = 11.5, 2.0 Hz, 1H), 5.72 – 5.53 (m, 1H), 3.20 (q, J = 7.0 Hz, 2H), 3.13 – 3.08 (m, 2H), 2.94 (s, 6H), 2.50 –
 10 2.43 (m, 2H), 2.12 – 2.00 (m, 3H), 1.78 – 1.65 (m, 2H), 1.48 – 1.35 (m, 2H), 1.25 (t, J = 7.0 Hz, 3H); ESI MS m/z 485 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), t_R = 9.96 min.

Example 206

1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-((*trans*-4-
 [(dimethylamino)methyl]cyclohexylamino)-1,5-naphthyridin-3-yl)]propan-1-one
 15 dihydrochloride



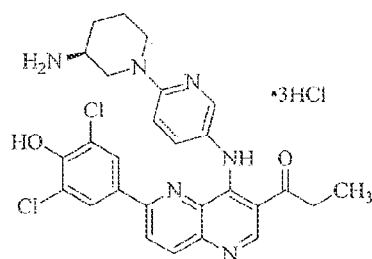
Following general procedure II, 1-(6-chloro-4-((*trans*-4-
 [(dimethylamino)methyl]cyclohexylamino)-1,5-naphthyridin-3-yl)-2-hydroxyethanone
 (170 mg, 0.50 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-
 20 dioxaborolan-2-yl)phenol (170 mg, 0.60 mmol). After work up and purification the

dihydrochloride salt was obtained (45 mg, 14%) as a white solid: ^1H NMR (500 MHz, CD_3OD) δ 9.17 (s, 1H), 8.45 (d, $J=9.0$ Hz, 1H), 8.34 (d, $J=9.0$ Hz, 1H), 8.11 (s, 2H), 5.75 – 5.66 (m, 1H), 3.20 (q, $J=7.0$ Hz, 2H), 3.13 – 3.08 (m, 2H), 2.94 (s, 6H), 2.50 – 2.41 (m, 2H), 2.10 – 2.00 (m, 3H), 1.74 – 1.62 (m, 2H), 1.48 – 1.36 (m, 2H), 1.25 (t, $J=7.0$ Hz, 3H);

5 ESI MS m/z 501 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 10.17$ min.

Example 207

(S)-1-(4-{{[6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino}-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}propan-1-one trihydrochloride

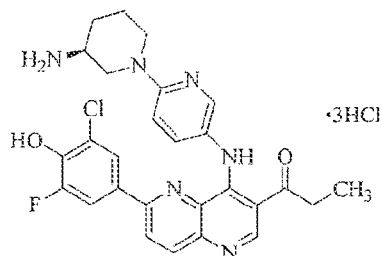


10 Following general procedure IV-2, (S)-tert-butyl (1-(5-((6-(3,5-dichloro-4-hydroxyphenyl)-3-propionyl-1,5-naphthyridin-4-yl)amino)pyridin-2-yl)piperidin-3-yl)carbamate (0.195 mmol) was reacted with TFA (2 mL) followed by formation of the trihydrochloride salt to afford the desired product (78 mg, 62% over two steps) as an orange-brown solid: ^1H NMR (500 MHz, CD_3OD) δ 9.32 (s, 1H), 8.47 (d, $J=9.0$ Hz, 1H), 8.37 (d, $J=9.0$ Hz, 1H), 8.20 (d, $J=2.5$ Hz, 1H), 7.76 (dd, $J=9.0, 2.5$ Hz, 1H), 7.61 (s, 2H), 7.11 (d, $J=9.0$ Hz, 1H), 4.41 – 4.38 (m, 1H), 3.97 – 3.95 (m, 1H), 3.48 – 3.16 (m, 5H), 2.24 – 2.15 (m, 1H), 2.03 – 1.91 (m, 1H), 1.82 – 1.74 (m, 2H), 1.32 – 1.19 (m, 3H);

15 ESI MS m/z 537 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 9.92$ min.

Example 208

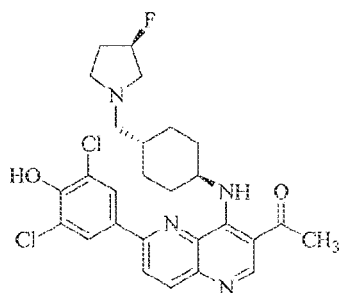
20 (S)-1-(4-{{[6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino}-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}propan-1-one trihydrochloride



Following general procedure IV-2, (S)-tert-butyl [1-(5-([6-(3-chloro-5-fluoro-4-hydroxyphenyl)-3-propionyl-1,5-naphthyridin-4-yl]amino)pyridin-2-yl)piperidin-3-yl]carbamate (0.21 mmol) was reacted with TFA (2 mL) followed by formation of the trihydrochloride salt to afford the desired product (67 mg, 52%) as a green-brown solid: ^1H NMR (500 MHz, CD_3OD) δ 9.32 (s, 1H), 8.46 (d, $J = 9.0$ Hz, 1H), 8.37 (d, $J = 9.0$ Hz, 1H), 8.21 (d, $J = 2.5$ Hz, 1H), 7.75 (dd, $J = 9.3, 2.5$ Hz, 1H), 7.63 – 7.26 (m, 2H), 7.12 (d, $J = 9.3$ Hz, 1H), 4.39 (d, $J = 10.5$ Hz, 1H), 4.01 – 3.96 (m, 1H), 3.48 – 3.16 (m, 5H), 2.25 – 2.15 (m, 1H), 2.04 – 1.93 (m, 1H), 1.82 – 1.71 (m, 2H), 1.32 – 1.19 (m, 3H); ESI MS m/z 521 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 9.75$ min.

Example 209

1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-({4-[(*R*)-3-fluoropyrrolidin-1-yl]methyl}cyclohexyl)amino)-1,5-naphthyridin-3-yl]ethanone

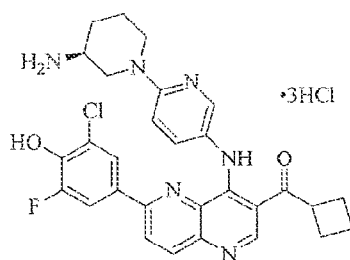


Following general procedure II, 1-(6-chloro-4-((4-((*R*)-3-fluoropyrrolidin-1-yl)methyl) cyclohexyl)amino)-1,5-naphthyridin-3-yl]ethanone (58 mg, 0.143 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (62 mg, 0.21 mmol) to afford the desired product (52 mg, 60%) as an orange solid: ^1H NMR (500 MHz, CD_3OD) δ 9.15 (s, 1H), 8.46 (d, $J = 9.0$ Hz, 1H), 8.33 (d, $J = 9.0$ Hz, 1H), 8.12 (s,

2H), 5.74 – 5.69 (m, 1H), 5.53 – 5.43 (m, 1H), 4.12 – 3.84 (m, 2H), 3.31 – 3.17 (m, 2H), 2.76 (s, 3H), 2.50 – 2.43 (m, 2H), 2.18 – 1.96 (m, 3H), 1.74 – 1.62 (m, 2H), 1.50 – 1.38 (m, 2H); ESI MS m/z 531 $[M + H]^+$; HPLC 96.7% (AUC), t_R = 10.05 min.

Example 210

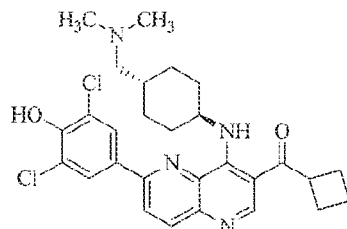
- 5 (S)-(4-([6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)(cyclobutyl)methanone trihydrochloride



- Following general procedure IV-2, (S)-tert-butyl [1-(5-{[6-(3-chloro-5-fluoro-4-hydroxyphenyl)-3-(cyclobutanecarbonyl)-1,5-naphthyridin-4-yl]amino}pyridin-2-yl)piperidin-3-yl]carbamate (0.20 mmol) was reacted with TFA (2 mL) followed by formation of the trihydrochloride salt to afford the desired product (94 mg, 72% over two steps) as a orange-brown solid: ^1H NMR (500 MHz, CD_3OD) δ 9.10 (s, 1H), 8.45 (d, J = 9.0 Hz, 1H), 8.36 (d, J = 9.0 Hz, 1H), 8.22 (d, J = 3.0 Hz, 1H), 7.74 (dd, J = 9.3, 3.0 Hz, 1H), 7.63 – 7.23 (m, 2H), 7.10 (d, J = 9.3 Hz, 1H), 4.40 (d, J = 10.5 Hz, 1H), 4.38 – 4.23 (m, 1H), 4.03 – 3.92 (m, 1H), 3.45 – 3.36 (m, 2H), 2.60 – 2.36 (m, 4H), 2.26 – 2.13 (m, 2H), 2.03 – 1.90 (m, 2H), 1.81 – 1.70 (m, 2H); ESI MS m/z 547 $[M + H]^+$; HPLC 98.2% (AUC), t_R = 10.33 min.

Example 211

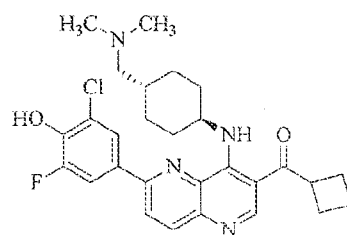
- (6-(3,5-dichloro-4-hydroxyphenyl)-4-((4-[(dimethylamino)methyl(cyclohexyl)amino)-1,5-naphthyridin-3-yl](cyclobutyl)methanone



Following general procedure II, (6-chloro-4-((4-
 ((dimethylamino)methyl)cyclohexyl) amino)-1,5-naphthyridin-3-yl)(cyclobutyl)methanone
 (40 mg, 0.10 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-
 5 dioxaborolan-2-yl)phenol (43 mg, 0.15 mmol) to afford the desired product (53 mg, 68%)
 as light yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 8.93 (s, 1H), 8.45 (d, $J = 9.0$ Hz, 1H),
 8.33 (d, $J = 9.0$ Hz, 1H), 8.12 (s, 2H), 5.76 – 5.65 (m, 1H), 4.30 – 4.20 (m, 1H), 3.12 – 3.07
 (m, 2H), 2.95 (s, 6H), 2.52 – 2.41 (m, 4H), 2.39 – 2.34 (m, 2H), 2.22 – 2.12 (m, 1H), 2.09 –
 2.00 (m, 2H), 1.98 – 1.90 (m, 1H), 1.76 – 1.64 (m, 2H), 1.49 – 1.36 (m, 2H); ESI MS m/z
 10 527 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 10.72$ min.

Example 212

(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-((4-((dimethylamino)methyl)cyclohexyl)amino)-
 1,5-naphthyridin-3-yl)(cyclobutyl)methanone

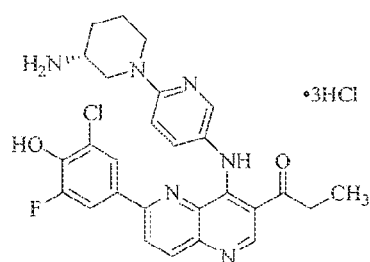


Following general procedure II, (6-chloro-4-((4-
 ((dimethylamino)methyl)cyclohexyl) amino)-1,5-naphthyridin-3-yl)(cyclobutyl)methanone
 (65 mg, 0.16 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-
 dioxaborolan-2-yl)phenol (65 mg, 0.24 mmol) to afford the desired product (72 mg, 77%)
 as light yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 8.93 (s, 1H), 8.44 (d, $J = 9.0$ Hz, 1H),
 8.33 (d, $J = 9.0$ Hz, 1H), 8.02 (s, 1H), 7.88 (dd, $J = 11.5, 2.0$ Hz, 1H), 5.74 – 5.64 (m, 1H),
 20 5.54 – 5.44 (m, 1H), 4.30 – 4.20 (m, 1H), 3.12 – 3.07 (m, 2H), 2.95 (s, 6H), 2.52 – 2.41 (m, 4H), 2.39 – 2.34 (m, 2H), 2.22 – 2.12 (m, 1H), 2.09 – 2.00 (m, 2H), 1.98 – 1.90 (m, 1H), 1.76 – 1.64 (m, 2H), 1.49 – 1.36 (m, 2H); ESI MS m/z 527 $[\text{M} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 10.72$ min.

4.29 – 4.19 (m, 1H), 3.12 – 3.07 (m, 2H), 2.95 (s, 6H), 2.52 – 2.41 (m, 4H), 2.39 – 2.34 (m, 2H), 2.24 – 2.12 (m, 1H), 2.09 – 1.98 (m, 2H), 1.98 – 1.89 (m, 1H), 1.78 – 1.66 (m, 2H), 1.49 – 1.35 (m, 2H); ESI MS m/z 511 $[M + H]^+$; HPLC >99% (AUC), t_R = 10.52 min.

Example 213

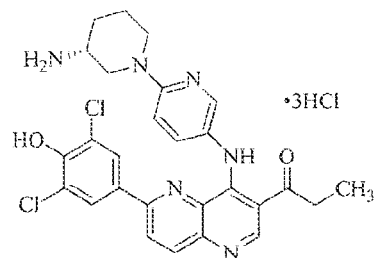
- 5 (R)-1-(4-((6-(3-aminopiperidin-1-yl)pyridin-3-yl)amino)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)propan-1-one trichloride



- Following general procedure IV-2, (R)-tert-butyl (1-(5-((6-(3-chloro-5-fluoro-4-hydroxyphenyl)-3-propionyl-1,5-naphthyridin-4-yl)amino)pyridin-2-yl)piperidin-3-yl)carbamate (120 mg, 0.19 mmol) was reacted with TFA (2 mL) followed by formation of the trihydrochloride salt to afford the desired product (78 mg, 65%) as a orange-brown solid: ^1H NMR (500 MHz, CD_3OD) δ 9.38 (s, 1H), 8.48 (d, J = 9.0 Hz, 1H), 8.41 (d, J = 9.0 Hz, 1H), 8.25 (d, J = 2.5 Hz, 1H), 7.90 (dd, J = 9.5, 2.5 Hz, 1H), 7.56 – 7.30 (m, 2H), 7.27 (d, J = 9.5 Hz, 1H), 4.43 – 4.32 (m, 1H), 4.08 – 3.96 (m, 1H), 3.53 – 3.38 (m, 3H), 3.29 – 3.20 (m, 2H), 2.29 – 2.20 (m, 1H), 2.09 – 1.98 (m, 1H), 1.88 – 1.74 (m, 2H), 1.38 – 1.21 (m, 3H); ESI MS m/z 521 $[M + H]^+$; HPLC 97.6% (AUC), t_R = 9.86 min.

Example 214

- (R)-1-(4-((6-(3-aminopiperidin-1-yl)pyridin-3-yl)amino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)propan-1-one trihydrochloride

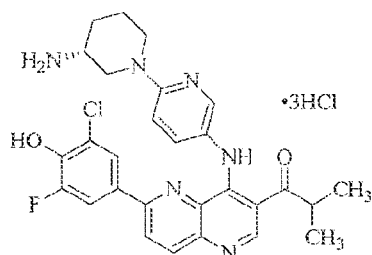


20

Following general procedure IV-2, (R)-tert-butyl [1-(5-{{3-(cyclopropanecarbonyl)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl}amino}pyridin-2-yl)piperidin-3-yl]carbamate (80 mg, 0.12 mmol) was reacted with TFA (2 mL) followed by formation of the trihydrochloride salt to afford the desired product (48 mg, 62%) as an orange solid: ¹H NMR (500 MHz, CD₃OD) δ 9.39 (s, 1H), 8.49 (d, *J* = 9.5 Hz, 1H), 8.42 (d, *J* = 9.0 Hz, 1H), 8.26 (d, *J* = 2.0 Hz, 1H), 7.92 (dd, *J* = 9.5, 2.0 Hz, 1H), 7.58 (s, 2H), 7.28 (d, *J* = 9.5 Hz, 1H), 4.42 – 4.32 (m, 1H), 4.16 – 3.96 (m, 1H), 3.52 – 3.22 (m, 5H), 2.29 – 2.18 (m, 1H), 2.08 – 1.98 (m, 1H), 1.88 – 1.75 (m, 2H), 1.37 – 1.20 (m, 3H); ESI MS *m/z* 537 [M + H]⁺; HPLC 98.0% (AUC), *t_R* = 9.92 min

10 Example 215

(R)-1-(4-((6-(3-aminopiperidin-1-yl)pyridin-3-yl)amino)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)-2-methylpropan-1-one trihydrochloride

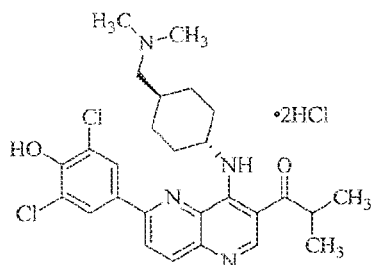


Following general procedure IV-2, (R)-tert-butyl (1-(5-((6-(3-chloro-5-fluoro-4-hydroxyphenyl)-3-isobutyryl-1,5-naphthyridin-4-yl)amino)pyridin-2-yl)piperidin-3-yl)carbamate (168 mg, 0.26 mmol) was reacted with TFA (2 mL) followed by formation of the trihydrochloride salt to afford the desired product (110 mg, 78%) as an orange solid: ¹H NMR (500 MHz, CD₃OD) δ 9.31 (s, 1H), 8.35 (s, 2H), 8.18 (d, *J* = 2.5 Hz, 1H), 7.64 (d, *J* = 9.0, 2.5 Hz, 1H), 7.38 (bs, 1H), 7.22 – 7.12 (m, 1H), 7.02 (d, *J* = 9.0 Hz, 1H), 4.44 – 4.32 (m, 1H), 3.98 – 3.90 (m, 1H), 3.82 – 3.70 (m, 1H), 3.46 – 3.22 (m, 3H), 2.22 – 2.12 (m, 1H), 2.01 – 1.88 (m, 1H), 1.80 – 1.68 (m, 2H), 1.36 – 1.20 (m, 6H); ESI MS *m/z* 535 [M + H]⁺; HPLC >99% (AUC), *t_R* = 10.07 min.

Example 216

1-[6-(3,5-dichloro-5-4-hydroxyphenyl)-4-({*trans*-4-[(dimethylamino)methyl]cyclohexyl}

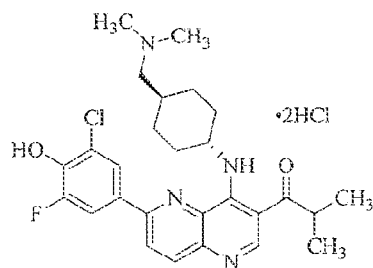
amino)-1,5-naphthyridin-3-yl]-2-methylpropan-1-one dihydrochloride



Following general procedure II, 1-[6-chloro-4-({*trans*-4-
 5 [(dimethylamino)methyl]cyclohexyl}amino)-1,5-naphthyridin-3-yl]-2-methylpropan-1-one
 (0.25 g, 0.64 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-
 dioxaborolan-2-yl)phenol (0.28 g, 0.96 mmol). After work up and purification the
 dihydrochloride salt was formed to afford the desired product (150 mg, 41%) as a yellow
 solid: ^1H NMR (500 MHz, CD_3OD) δ 9.23 (s, 1H), 8.45 (d, $J = 9.0$ Hz, 1H), 8.35 (d, $J = 9.0$
 Hz, 1H), 8.10 (s, 2H), 5.77 – 5.63 (m, 1H), 3.83 – 3.71 (m, 1H), 3.11 – 3.04 (m, 2H), 2.94
 10 (s, 6H), 2.47 – 2.42 (m, 1H), 2.08 – 2.00 (m, 3H), 1.73 – 1.65 (m, 2H), 1.50 – 1.37 (m, 2H),
 1.36 – 1.24 (m, 6H); ESI MS m/z 515 $[\text{M} + \text{H}]^+$; HPLC 98.7% (AUC), $t_R = 10.57$ min.

Example 217

1-[6-chloro-4-({*trans*-4-[(dimethylamino)methyl]cyclohexyl}amino)-1,5-naphthyridin-3-
 yl]-2-methylpropan-1-one



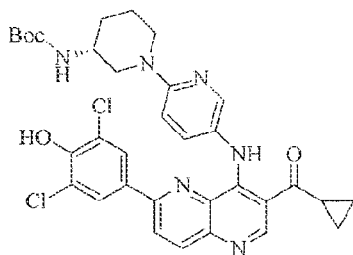
15

Following general procedure II, 1-[6-chloro-4-({*trans*-4-
 [(dimethylamino)methyl]cyclohexyl}amino)-1,5-naphthyridin-3-yl]-2-methylpropan-1-one
 (0.25 g, 0.64 mmol) was reacted with 3,5-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-
 dioxaborolan-2-yl)phenol (0.26 g, 0.96 mmol). After work up and purification the
 20 dihydrochloride salt was formed to afford the desired product (175 mg, 46%) as a light

brown solid: ^1H NMR (500 MHz, CD_3OD) δ 9.22 (s, 1H), 8.45 (d, $J = 9.0$ Hz, 1H), 8.34 (d, $J = 9.0$ Hz, 1H), 8.03 (d, $J = 2.0$, 2H), 7.88 (dd, $J = 11.5$, 2.0 Hz, 1H), 5.75 – 5.68 (m, 1H), 3.83 – 3.74 (m, 1H), 3.13 – 3.08 (m, 2H), 2.94 (s, 6H), 2.50 – 2.38 (m, 2H), 2.12 – 1.99 (m, 3H), 1.78 – 1.65 (m, 2H), 1.49 – 1.37 (m, 2H), 1.33 – 1.25 (m, 6H); ESI MS m/z 499 $[\text{M} + \text{H}]^+$; HPLC 97.5% (AUC), $t_R = 10.24$ min.

Example 218

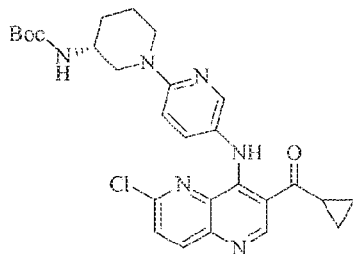
(R)-tert-butyl [1-(5-{[3-(cyclopropanecarbonyl)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl]amino}pyridin-2-yl)piperidin-3-yl]carbamate



Following general procedure II, (R)-tert-butyl [1-(5-{[6-chloro-3-(cyclopropanecarbonyl)-1,5-naphthyridin-4-yl]amino}pyridin-2-yl)piperidin-3-yl]carbamate (150 mg, 0.29 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (120 mg, 0.43 mmol) to afford the product (119 mg, 64%) as an orange solid: ESI MS m/z 649 $[\text{M} + \text{H}]^+$.

Example 219

(R)-tert butyl [1-(5-{[6-chloro-3-(cyclopropanecarbonyl)-1,5-naphthyridin-4-yl]amino}pyridin-2-yl)piperidin-3-yl]carbamate



Following general procedure I, 4,6-dichloro-1,5-naphthyridin-3-yl(cyclopropyl) methanone (400 mg, 1.5 mmol) was reacted with (R)-tert-butyl [1-(5-aminopyridin-2-yl) piperidine-3-

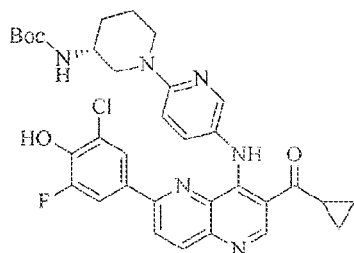
yl]carbamate (550 mg, 1.9 mmol) to afford the product (600 mg, 76%) as an orange foam:

ESI MS m/z 523 $[M + H]^+$.

Example 220

(R)-tert-butyl [1-(5-{[3-(cyclopropanecarbonyl)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-

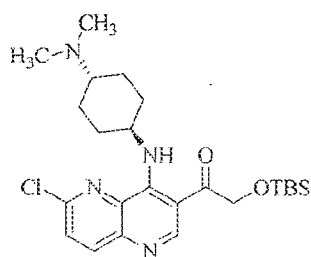
1,5-naphthyridin-4-yl]amino}pyridin-2-yl)piperidin-3-yl]carbamate



Following general procedure II, (R)-tert-butyl [1-(5-{[6-chloro-3-(cyclopropanecarbonyl)-1,5-naphthyridin-4-yl]amino}pyridin-2-yl)piperidin-3-yl]carbamate (150 mg, 0.29 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (120 mg, 0.43 mmol) to afford the product (100 mg, 54%) as an orange-red solid: ESI MS m/z 633 $[M + H]^+$.

Example 221

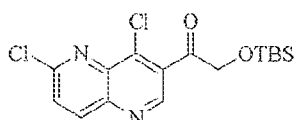
2-((tert-butyldimethylsilyl)oxy)-1-(6-chloro-4-((trans-4-(dimethylamino)cyclohexyl)amino)-1,5-naphthyridin-3-yl)ethanone



Following general procedure I, 2-((tert-butyldimethylsilyl)oxy)-1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (87 mg, 0.23 mmol) was reacted with trans-dimethylcyclohexane-1,4-diamine (50 mg, 0.35 mmol) to afford the product (44 mg, 40%) as a light yellow oil: ESI MS m/z 477 $[M + H]^+$.

Example 222

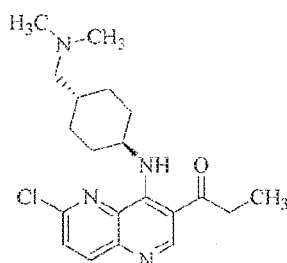
2-((tert-butyl(dimethylsilyl)oxy)-1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone



To a solution of 1-(4,6-dichloro-1,5-naphthyridin-3-yl)-2-hydroxyethanone (128 mg, 0.5
 5 mmol) in DMF (5 mL) was added imidazole (68 mg, 1.0 mmol) and *tert*-
 butyldimethylsilyl chloride (90 mg, 0.6 mmol) at 0 °C. The mixture was stirred for 3 h,
 poured into NaHCO₃ (saturated), and extracted with ethyl acetate. The organic layer was
 dried over Na₂SO₄, concentrated, and purified by chromatography to afford product (87 mg,
 47%) as a light yellow oil: ESI MS *m/z* 371 [M + H]⁺.

10 Example 223

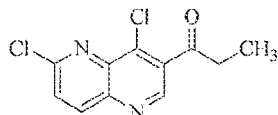
1-(6-chloro-4-(((4-((dimethylamino)methyl)cyclohexyl)amino)-1,5-naphthyridin-3-yl)propan-1-one



Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)propan-1-one
 15 (255 mg, 1.0 mmol) was reacted with *trans*-4-((dimethylamino)methyl)cyclohexanamine
 (310 mg, 2.0 mmol) to afford the product (350 mg, 93%) as a white solid: ESI MS *m/z* 375
 [M + H]⁺.

Example 224

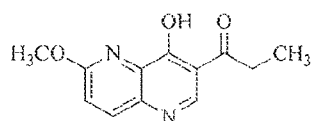
1-(4,6-dichloro-1,5-naphthyridin-3-yl)propan-1-one



To a suspension of 1-(4-hydroxy-6-methoxy-1,5-naphthyridin-3-yl)propan-1-one (5.2 g, 22.4 mmol) in acetonitrile (100 ml) was added trimethylsilylchloride (12 g, 112 mmol) and sodium iodide (10 g, 67 mmol) and the reaction mixture was heated at reflux for 5 16 h. The reaction mixture was cooled to room temperature and satd. aq. sodium thiosulfate was added. The mixture was concentrated to remove acetonitrile, diluted with brine and the solids were filtered and dried to provide the intermediate 1-(4,6-dihydroxy-1,5-naphthyridin-3-yl)propan-1-one. This intermediate was suspended in dichloroethane (10 mL) followed by the addition of phosphorus oxychloride (10 mL) and catalytic *N,N*-10 dimethylformamide and the reaction mixture was stirred with heat at 80 °C for 2 h. The reaction mixture was cooled to room temperature and quenched by pouring slowly into ice-cold satd. aq. sodium bicarbonate or 3 N sodium hydroxide. The quenched reaction mixture was concentrated to remove the dichloroethane and the resulting solids were collected by filtration and purified by chromatography (silica, hexanes/ethyl acetate) to 15 provide the desired product (3.2 g, 56% over 2 steps) as a brown solid: ESI MS *m/z* 255 [M + H]⁺.

Example 225

1-(4-hydroxy-6-methoxy-1,5-naphthyridin-3-yl)propan-1-one

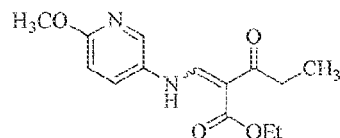


20 To a flask containing DowthermTM A (200 mL) at 250 °C was added ethyl 2-[(6-chloropyridin-3-ylamino)methylene]-3-oxobutanoate (10 g, 36 mmol) portion wise over 3 to 5 min and the reaction mixture was stirred for an additional 30 to 45 min. The reaction mixture was removed from the heat source, cooled to room temperature and diluted with hexanes to facilitate precipitation. The solids were filtered, washed with hexanes and

dried under vacuum to afford the desired product (5.0 g, crude) as a brown solid: ESI MS m/z 241 $[M + H]^+$.

Example 226

ethyl 2-(((6-methoxypyridin-3-yl)amino)methylene)-3-oxopentanoate

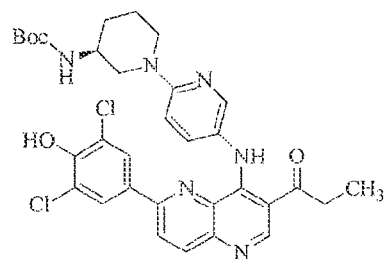


5

Ethyl 2-(((6-methoxypyridin-3-yl)amino)methylene)-3-oxopentanoate was prepared with conditions described in Example 99 using 2-methoxy-5-aminopyridine and ethyl 2-(ethoxymethylene)-3-oxopentanoate.

Example 227

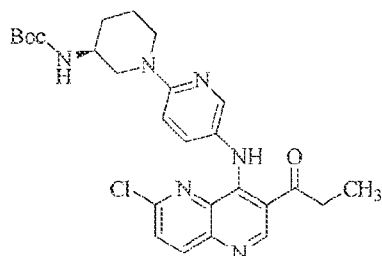
10 (S)-tert-butyl (1-(5-((6-(3,5-dichloro-4-hydroxyphenyl)-3-propionyl-1,5-naphthyridin-4-yl)amino)pyridin-2-yl)piperidin-3-yl)carbamate



Following general procedure II, (S)-tert-butyl (1-(5-((6-chloro-3-propionyl-1,5-naphthyridin-4-yl)amino)pyridin-2-yl)piperidin-3-yl)carbamate (100 mg, 0.20 mmol) was
 15 reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (85 mg, 0.30 mmol) to afford the product (100 mg) which was carried forward without any purification: ESI MS m/z 637 $[M + H]^+$.

Example 228

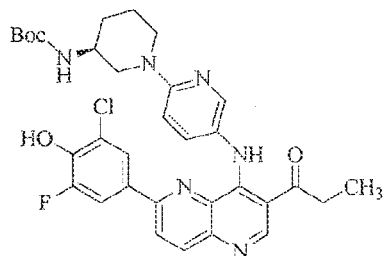
(S)-tert-butyl (1-(5-((6-chloro-3-propionyl-1,5-naphthyridin-4-yl)amino)pyridin-2-yl)piperidin-3-yl)carbamate
 20



Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)propan-1-one (250 mg, 0.98 mmol) was reacted with (S)-tert-butyl 1-(5-aminopyridin-2-yl)piperidin-3-ylcarbamate (430 mg, 1.5 mmol) to afford the desired product (550 mg, crude) as an dark brown solid: ^1H NMR (500 MHz, CDCl_3) δ 11.29 (s, 1H), 9.03 (s, 1H), 8.11 (d, $J = 9.0$ Hz, 1H), 8.01 (d, $J = 3.0$ Hz, 1H), 7.47 (d, $J = 9.0$ Hz, 1H), 7.31–7.29 (m, 1H), 6.72 (d, $J = 9.0$ Hz, 1H), 4.79 (br s, 1H), 3.90–3.61 (m, 4H), 3.51–3.25 (m, 2H), 3.07 (q, $J = 7.0$ Hz, 2H), 1.96–1.84 (m, 1H), 1.82–1.70 (m, 1H), 1.72–1.55 (m, 1H), 1.45 (s, 9H), 1.26 (t, $J = 7.0$ Hz, 3H); ESI MS m/z 511 $[\text{M} + \text{H}]^+$

10 Example 229

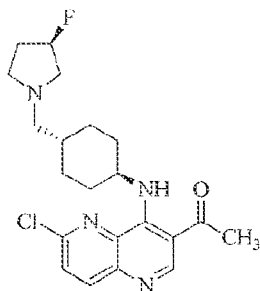
(S)-tert-butyl (1-(5-((6-(3-chloro-5-fluoro-4-hydroxyphenyl)-3-propionyl-1,5-naphthyridin-4-yl)amino)pyridin-2-yl)piperidin-3-yl)carbamate



Following general procedure II, (S)-tert-butyl (1-(5-((6-chloro-3-propionyl-1,5-naphthyridin-4-yl)amino)pyridin-2-yl)piperidin-3-yl)carbamate (100 mg, 0.20 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (83 mg, 0.31 mmol) to afford the product (102 mg) which was carried forward without any purification: ESI MS m/z 621 $[\text{M} + \text{H}]^+$.

Example 230

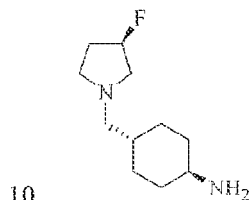
1-(6-chloro-4-((4-(((R)-3-fluoropyrrolidin-1-yl)methyl)cyclohexyl)amino)-1,5-naphthyridin-3-yl)ethanone



Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)ethanone (240 mg, 1.0 mmol) was reacted with 4-(((R)-3-fluoropyrrolidin-1-yl)methyl)cyclohexanamine (100 mg, 0.5 mmol) to afford the product (61 mg, 15%) as a brown solid: ESI MS m/z 405 $[M + H]^+$.

Example 231

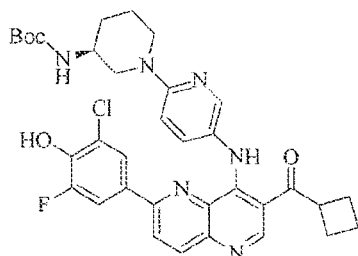
4-(((R)-3-fluoropyrrolidin-1-yl)methyl)cyclohexanamine



4-(((R)-3-fluoropyrrolidin-1-yl)methyl)cyclohexanamine was prepared with conditions described in Example 117 and 118 using trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl] methyl methanesulfonate and (R)-3-fluoropyrrolidine.

Example 232

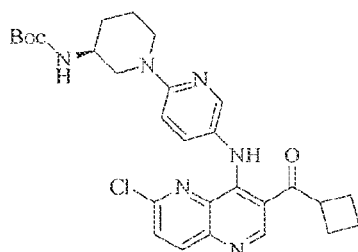
(S)-tert-butyl (1-(5-((6-(3-chloro-5-fluoro-4-hydroxyphenyl)-3-(cyclobutanecarbonyl)-1,5-naphthyridin-4-yl)amino)pyridin-2-yl)piperidin-3-yl)carbamate



Following general procedure II, (S)-tert-butyl 1-(5-((6-chloro-3-(cyclobutanecarbonyl)-1,5-naphthyridin-4-yl)amino)pyridin-2-yl)piperidin-3-ylcarbamate (110 mg, 0.20 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (82 mg, 0.30 mmol) to afford the product (134 mg) which was carried forward without any purification: ESI MS m/z 647 $[M + H]^+$.

Example 233

(S)-tert-butyl 1-(5-((6-chloro-3-(cyclobutanecarbonyl)-1,5-naphthyridin-4-yl)amino)pyridin-2-yl)piperidin-3-ylcarbamate



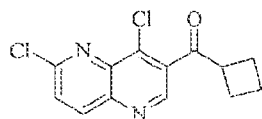
10

Following general procedure I, cyclobutyl(4,6-dichloro-1,5-naphthyridin-3-yl)methanone (200 mg, 0.71 mmol) was reacted with (S)-tert-butyl 1-(5-aminopyridin-2-yl)piperidin-3-ylcarbamate (311 mg, 1.1 mmol) to afford the desired product (350 mg, 78%) as an orange solid: ^1H NMR (300 MHz, CDCl_3) δ 11.52 (s, 1H), 8.88 (s, 1H), 8.08 (d, $J = 8.7$ Hz, 1H), 8.02 (d, $J = 2.7$ Hz, 1H), 7.45 (d, $J = 8.7$ Hz, 1H), 7.31 (dd, $J = 9.0, 2.7$ Hz, 1H), 6.72 (d, $J = 9.0$ Hz, 1H), 4.81 (br s, 1H), 4.15 – 3.97 (m, 1H), 3.91 – 3.60 (m, 3H), 3.58 – 3.31 (m, 2H), 2.54 – 2.21 (m, 4H), 2.20 – 2.00 (m, 1H), 2.00 – 1.85 (m, 2H), 1.82 – 1.63 (m, 2H), 1.51 (s, 9H); ESI MS m/z 537 $[M + H]^+$.

15

Example 234

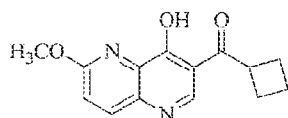
cyclobutyl(4,6-dichloro-1,5-naphthyridin-3-yl)methanone



Cyclobutyl(4,6-dichloro-1,5-naphthyridin-3-yl)methanone was prepared with conditions described in Example 101 (Scheme 2) using cyclobutyl(4-hydroxy-6-methoxy-1,5-naphthyridin-3-yl)methanone.

Example 235

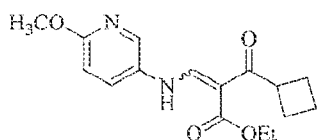
cyclobutyl(4-hydroxy-6-methoxy-1,5-naphthyridin-3-yl)methanone



Cyclobutyl(4-hydroxy-6-methoxy-1,5-naphthyridin-3-yl)methanone was prepared with conditions described in Example 100 using ethyl 2-(cyclobutanecarbonyl)-3-((6-methoxypyridin-3-yl)amino)acrylate.

Example 236

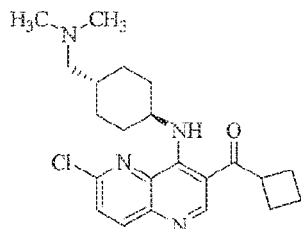
ethyl 2-(cyclobutanecarbonyl)-3-((6-methoxypyridin-3-yl)amino)acrylate



Ethyl 2-(cyclobutanecarbonyl)-3-((6-methoxypyridin-3-yl)amino)acrylate was prepared with conditions described in Example 99 using 2-methoxy-5-aminopyridine and ethyl 2-(cyclobutanecarbonyl)-3-ethoxyacrylate.

Example 237

(6-chloro-4-((4-((dimethylamino)methyl)cyclohexyl)amino)-1,5-naphthyridin-3-yl)(cyclobutyl)methanone

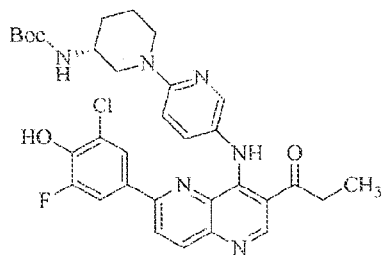


(6-Chloro-4-((4-((dimethylamino)methyl)cyclohexyl)amino)-1,5-naphthyridin-3-yl)(cyclobutyl)methanone was prepared with conditions described in **Example 131** using cyclobutyl(4,6-dichloro-1,5-naphthyridin-3-yl)methanone and trans-4-

5 ((dimethylamino)methyl)cyclohexanamine.

Example 238

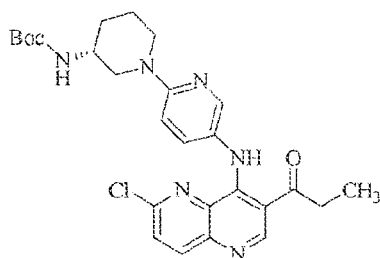
(R)-tert-butyl (1-(5-((6-(3-chloro-5-fluoro-4-hydroxyphenyl)-3-propionyl-1,5-naphthyridin-4-yl)amino)pyridin-2-yl)piperidin-3-yl)carbamate



10 Following general procedure II, (R)-tert-butyl (1-(5-((6-chloro-3-propionyl-1,5-naphthyridin-4-yl)amino)pyridin-2-yl)piperidin-3-yl)carbamate (175 mg, 0.34 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (140 mg, 0.51 mmol) to afford the desired product (120 mg, 57%) as a solid: ESI MS m/z 621 $[M + H]^+$.

15 Example 239

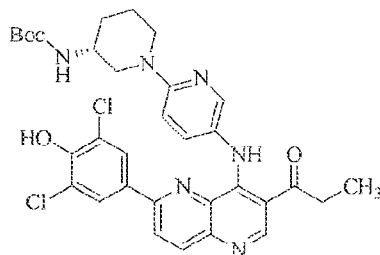
(R)-tert-butyl (1-(5-((6-chloro-3-propionyl-1,5-naphthyridin-4-yl)amino)pyridin-2-yl)piperidin-3-yl)carbamate



Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)propan-1-one (500 mg, 1.96 mmol) was reacted with (R)-tert-butyl (1-(5-aminopyridin-2-yl)piperidin-3-yl)carbamate (860 mg, 2.94 mmol) to afford the desired product (850 mg, 84%) as a light brown solid: ESI MS m/z 511 $[M + H]^+$.

Example 240

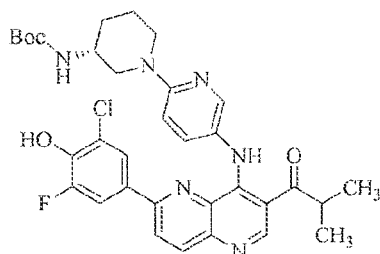
(R)-tert-butyl (1-(5-((6-(3,5-dichloro-4-hydroxyphenyl)-3-propionyl-1,5-naphthyridin-4-yl)amino)pyridin-2-yl)piperidin-3-yl)carbamate



Following general procedure II, (R)-tert-butyl (1-(5-((6-chloro-3-propionyl-1,5-naphthyridin-4-yl)amino)pyridin-2-yl)piperidin-3-yl)carbamate (175 mg, 0.34 mmol) was reacted with 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (149 mg, 0.51 mmol) to afford the desired product (100 mg, 46%) as a solid: ESI MS m/z 637 $[M + H]^+$.

Example 241

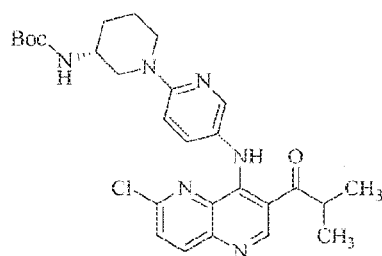
(R)-tert-butyl (1-(5-((6-(3-chloro-5-fluoro-4-hydroxyphenyl)-3-isobutyryl-1,5-naphthyridin-4-yl)amino)pyridin-2-yl)piperidin-3-yl)carbamate



Following general procedure II, (R)-tert-butyl (1-(5-((6-chloro-3-isobutyryl-1,5-naphthyridin-4-yl)amino)pyridin-2-yl)piperidin-3-yl)carbamate (225 mg, 0.63 mmol) was reacted with 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (175 mg, 0.66 mmol) to afford the desired product (168 mg, 62%) solid: ESI MS m/z 635 $[M + H]^+$.

Example 242

(R)-tert-butyl (1-(5-((6-chloro-3-isobutyryl-1,5-naphthyridin-4-yl)amino)pyridin-2-yl)piperidin-3-yl)carbamate

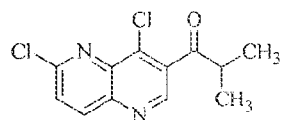


10

Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)-2-methylpropan-1-one (500 mg, 1.85 mmol) was reacted with (R)-tert-butyl (1-(5-aminopyridin-2-yl)piperidin-3-yl)carbamate (815 mg, 2.78 mmol) to afford the desired product (830 mg, 88%) as a red solid: ESI MS m/z 525 $[M + H]^+$.

Example 243

1-(4,6-dichloro-1,5-naphthyridin-3-yl)-2-methylpropan-1-one

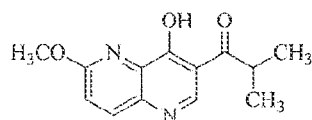


To a suspension of 1-(4,6-dihydroxy-1,5-naphthyridin-3-yl)-2-methylpropan-1-one

(15.5 g, 63.0 mmol) in acetonitrile (250 ml) was added trimethylsilylchloride (20.5 g, 189 mmol) and sodium iodide (28.3 g, 189 mmol) and the reaction mixture was heated at reflux for 3 h. The reaction mixture was cooled to room temperature and satd. aq. sodium thiosulfate was added. The mixture was concentrated to remove acetonitrile, diluted with
 5 brine and the solids were filtered and dried to provide the intermediate 1-(4-hydroxy-6-methoxy-1,5-naphthyridin-3-yl)-2-methylpropan-1-one. This intermediate was suspended in phosphorus oxychloride (60 mL) and catalytic *N,N*-dimethylformamide and the reaction mixture was stirred with heat at 70 °C for 30 min. The reaction mixture was cooled to room temperature and quenched by pouring slowly into ice-cold satd. aq. sodium
 10 bicarbonate or 3 N sodium hydroxide. The quenched reaction mixture was concentrated to remove the dichloroethane and the resulting solids were collected by filtration and purified by chromatography (silica, hexanes/ethyl acetate) to provide the desired product (12.0 g, 75% over 2 steps) as a yellow solid: ESI MS *m/z* 255 [M + H]⁺.

Example 244

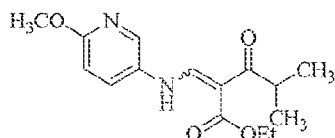
15 1-(4-hydroxy-6-methoxy-1,5-naphthyridin-3-yl)-2-methylpropan-1-one



To a flask containing DowthermTM A (400 mL) at 250 °C was added ethyl 2-(((6-methoxypyridin-3-yl)amino)methylene)-4-methyl-3-oxopentanoate (11.5 g, 39.3 mmol) portion wise over 3 to 5 min and the reaction mixture was stirred for an additional 30 to 45
 20 min. The reaction mixture was removed from the heat source, cooled to room temperature and diluted with hexanes to facilitate precipitation. The solids were filtered, washed with hexanes and dried under vacuum to afford the desired product (13.7 g, crude) as a yellow-brown solid: ESI MS *m/z* 247 [M + H]⁺.

Example 245

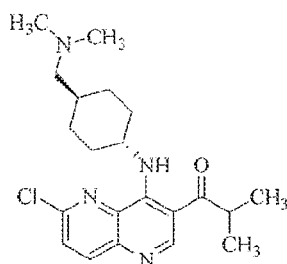
25 ethyl 2-(((6-methoxypyridin-3-yl)amino)methylene)-4-methyl-3-oxopentanoate



Ethyl 2-(((6-methoxypyridin-3-yl)amino)methylene)-4-methyl-3-oxopentanoate was prepared with conditions described in Example 99 using 2-methoxy-5-aminopyridine and ethyl 2-(ethoxymethylene)-4-methyl-3-oxopentanoate.

5 Example 246

1-(6-chloro-4-(((4-((dimethylamino)methyl)cyclohexyl)amino)-1,5-naphthyridin-3-yl)-2-methylpropan-1-one



Following general procedure I, 1-(4,6-dichloro-1,5-naphthyridin-3-yl)-2-methylpropan-1-one (500 mg, 1.85 mmol) was reacted with trans-4-
 10 ((dimethylamino)methyl)cyclohexanamine (436 mg, 2.78 mmol) to afford the product (640 mg, 89%) as a white solid: ESI MS m/z 389 $[M + H]^+$.

Compounds of the invention of this application not particularly described in the Examples above were also be synthesized by similar or analogous methods by referring to
 15 the above-mentioned Examples and such.

Next, the pharmacological activities of compound (I) will be described in the following Test Examples.

[Test Examples]

Kinase assay

20 MELK activity was determined in the presence or absence of compounds using fluorescein isothiocyanate-labeled (FITC-labeled) histone H3 peptide as a substrate. The

extent of FITC-labeled histone H3 peptide phosphorylation was measured by immobilized metal ion affinity-based fluorescence polarization (IMAP) technology (Sportsman JR, et al., Assay Drug Dev. Technol. 2: 205-14, 2004) using IMAP FP Progressive Binding System (Molecular Devices Corporation). Test compounds were dissolved in DMSO at 12.5 mM
5 and then serially diluted as the DMSO concentration in the assays to be 1%. The serially diluted compounds, 0.8 ng/micro-L PBK (Carna Biosciences) and 100 nM FITC-labeled histone H3 peptide were reacted in a reaction buffer (20 mM HEPES, 0.01% Tween-20, 0.3 mM MgCl₂, 2 mM dithiothreitol, 50micro-M ATP, pH 7.4) at room temperature for 1 hour. The reaction was stopped by the addition of three fold assay volume of progressive binding
10 solution. Following 0.5 hour incubation at room temperature, fluorescence polarization was measured by Wallac EnVision 2103 multilabel reader (PerkinElmer). IC₅₀ values were calculated by nonlinear four parameter fit using SigmaPlot, version 10.0 (Systat Software, Inc.).

IC₅₀ values of the typical compounds of the present invention are shown in the
15 following table 2:

Table 2

Example	Compound Name	IC ₅₀ (μM) (kinase assay)
1	1-(6-Chloro-4-{ <i>trans</i> -4-[(dimethylamino)methyl]-cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone	0.31
2	1-{6-(3,5-Dichloro-4-hydroxyphenyl)-4-{ <i>trans</i> -4-(dimethylamino)-cyclohexylamino}-1,5-naphthyridin-3-yl}ethanone dihydrochloride	0.0003
3	1-{6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-{ <i>trans</i> -4-(dimethylamino)-cyclohexylamino}-1,5-naphthyridin-3-yl}ethanone dihydrochloride	0.0012
4	Cyclopropyl(6-(3,5-dichloro-4-hydroxyphenyl)-4-{ <i>trans</i> -4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)methanone dihydrochloride	0.0005
5	(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-{ <i>trans</i> -4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)(cyclopropyl)methanone dihydrochloride	0.0008
6	1-{6-(3,5-Dichloro-4-hydroxyphenyl)-4-({ <i>trans</i> -4-[(dimethylamino)methyl]cyclohexyl)amino}-1,5-naphthyridin-3-yl}ethanone dihydrochloride	0.0011
7	1-{6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-({ <i>trans</i> -4-[(dimethylamino)methyl]cyclohexyl)amino}-1,5-naphthyridin-3-yl}ethanone dihydrochloride	0.0013
8	1-(6-(3-Chloro-4-hydroxy-5-methoxyphenyl)-4-{ <i>trans</i> -4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.0015
9	1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4-({ <i>trans</i> -4-[2-(dimethylamino)ethyl]cyclohexyl)amino]-1,5-naphthyridin-3-yl]ethanone dihydrochloride	0.0007
10	1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-{ <i>trans</i> -4-[2-(dimethylamino)ethyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.0014
11	1-(4-{ <i>trans</i> -4-[(Dimethylamino)methyl]cyclohexylamino}-6-[4-hydroxy-3-(trifluoromethoxy)phenyl]-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.0027
12	2,6-Dichloro-4-(8-{ <i>trans</i> -4-[(dimethylamino)methyl]cyclohexylamino}-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)phenol dihydrochloride	0.001

13	6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-({ <i>trans</i> -4-[(dimethylamino)-methyl]cyclohexyl}amino)-3-methylsulfonyl-1,5-naphthyridine dihydrochloride	0.0014
14	6-(3-Chloro-4-hydroxy-5-methoxyphenyl)-4-({ <i>trans</i> -4-[(dimethylamino)-methyl]cyclohexylamino}-3-methylsulfonyl-1,5-naphthyridine dihydrochloride	0.0009
15	2,6-Dichloro-4-{8-({ <i>trans</i> -4-(dimethylamino)cyclohexylamino}-7-(methylsulfonyl)-1,5-naphthyridin-2-yl}phenol dihydrochloride	0.0005
16	2,6-Dichloro-4-(8-(4-((dimethylamino)methyl)phenylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)phenol dihydrochloride	0.0028
17	2-Chloro-4-(8-(4-((dimethylamino)methyl)phenylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-fluorophenol dihydrochloride	0.0081
18	2-Chloro-4-(8-(4-((dimethylamino)methyl)phenylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-methoxyphenol dihydrochloride	0.005
19	1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-(3-(2-(pyrrolidin-1-yl)ethyl)-phenylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.032
20	1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-(3-(2-(pyrrolidin-1-yl)-ethyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.14
21	1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-(6-(2-(dimethylamino)-ethoxy)pyridin-3-ylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.0046
22	1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-(6-(2-(dimethylamino)-ethoxy)pyridin-3-ylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.015
23	1-(6-(3-Chloro-4-hydroxy-5-methoxyphenyl)-4-(6-(2-(dimethylamino)-ethoxy)pyridin-3-ylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.0089
24	2,6-Dichloro-4-(8-(6-(2-(dimethylamino)ethoxy)pyridin-3-ylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)phenol hydrochloride	0.0053
25	2-Chloro-4-(8-(6-(2-(dimethylamino)ethoxy)pyridin-3-ylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-fluorophenol dihydrochloride	0.019

26	2-Chloro-4-(8-(6-(2-(dimethylamino)ethoxy)pyridin-3-ylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-methoxyphenol dihydrochloride	0.01
27	1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-((1-methylpiperidin-4-yl)methylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.0007
28	1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-(<i>trans</i> -4-((dimethylamino-d6)-methyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.0004
29	1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-(4-(2-(dimethylamino)-ethyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.0026
30	1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-(4-(2-(dimethylamino)-ethyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.0059
31	1-(6-(3-Chloro-4-hydroxy-5-methoxyphenyl)-4-(4-(2-(dimethylamino)-ethyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.0037
32	2-Chloro-4-(8-(<i>trans</i> -4-(dimethylamino)cyclohexylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-fluorophenol dihydrochloride	0.0016
33	1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-(1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-ylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.0078
34	1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-(4-((4-methylpiperazin-1-yl)methyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.0061
35	1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-(4-((4-methylpiperazin-1-yl)methyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.037
36	1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-(4-(2-(pyrrolidin-1-yl)ethyl)piperidin-1-yl)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.0021
37	1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-(4-(2-(pyrrolidin-1-yl)-ethyl)piperidin-1-yl)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.01
38	1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-(6-(2-(dimethylamino)ethylamino)pyridin-3-ylamino)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.011

39	1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-(6-(2-(dimethylamino)-ethylamino)pyridin-3-ylamino)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.03
40	(S)-(4-(6-(3-Aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)-(cyclopropyl)methanone trihydrochloride	0.0012
41	1-(4-(2-(3-Aminopyrrolidin-1-yl)pyrimidin-5-ylamino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.0017
42	1-(4-{ <i>trans</i> -4-[(Dimethylamino)methyl]cyclohexylamino}-6-(1H-pyrazol-4-yl)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.017
43	1-(6-{3,5-Dichloro-4-hydroxyphenyl}-4-[<i>trans</i> -4-(hydroxymethyl)-cyclohexyl]amino)-1,5-naphthyridin-3-yl)ethanone hydrochloride	0.0031
44	1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4-{ <i>trans</i> -4-[(dimethylamino)-methyl]cyclohexylamino}-1,5-naphthyridin-3-yl]-2-hydroxyethanone dihydrochloride	0.0003
45	1-{6-(3,5-Dichloro-4-hydroxyphenyl)-4-[(1-methylpiperidin-4-yl)amino]-1,5-naphthyridin-3-yl}ethanone	0.0058
46	1-{6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-[(1-methylpiperidin-4-yl)-amino]-1,5-naphthyridin-3-yl}ethanone	0.0061
47	1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-{[4-(morpholinomethyl)-cyclohexyl]amino}-1,5-naphthyridin-3-yl)ethanone	0.01
48	1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4-(4-{[(2-hydroxyethyl)(methyl)-amino]methyl}cyclohexylamino)-1,5-naphthyridin-3-yl]-ethanone dihydrochloride	0.0006
49	1-[6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-(4-{[(2-hydroxyethyl)-(methyl)amino]methyl}cyclohexylamino)-1,5-naphthyridin-3-yl]-ethanone dihydrochloride	0.001
50	1-(6-(3,5-Difluoro-4-hydroxyphenyl)-4-{4-[(dimethylamino)methyl]-cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.0019
51	1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-{6-[3-(dimethylamino)pyrrolidin-1-yl]pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.0082
52	1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-{6-[3-(dimethylamino)-pyrrolidin-1-yl]pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.027

53	1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-{6-[3-(methylamino)pyrrolidin-1-yl]pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.0015
54	1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-{6-[3-(methylamino)pyrrolidin-1-yl]pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.012
55	1-(6-(1H-Benzo[d]imidazol-5-yl)-4-{ <i>trans</i> -4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.017
56	1-{4-[4-(<i>trans</i> -4-Dimethylamino)methylcyclohexylamino]-6-(pyridin-4-yl)-1,5-naphthyridin-3-yl}ethanone trihydrochloride	0.016
57	5-(7-Acetyl-8-{ <i>trans</i> -4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-2-yl)pyrimidine-2-carbonitrile	0.0012
58	1-(6-(3,5-Dimethyl-1H-pyrazol-4-yl)-4-{ <i>trans</i> -4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone trihydrochloride	1
59	1-(4-{ <i>trans</i> -4-[(DimethylaminoDimethylamino)methyl]cyclohexylamino}-6-(4-hydroxy-3,5-dimethylphenyl)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.0047
60	1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-{6-[3-(dimethylamino)pyrrolidin-1-yl]pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.0043
61	1-{6-(3,5-Dichloro-4-hydroxyphenyl)-4-{ <i>trans</i> -4-(pyrrolidin-1-ylmethyl)cyclohexylamino}-1,5-naphthyridin-3-yl}ethanone dihydrochloride	0.0004
62	1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-{ <i>trans</i> -4-(pyrrolidin-1-ylmethyl)cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.0009
63	1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-{4-[(4-methylpiperazin-1-yl)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.0008
64	1-(4-{[6-(3-Aminopiperidin-1-yl)pyridin-3-yl]amino}-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.0012
65	1-(4-{[6-(3-Aminopiperidin-1-yl)pyridin-3-yl]amino}-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.0031

66	1-{4-[(4-Aminocyclohexyl)amino]-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}ethanone dihydrochloride	0.0018
67	1-{4-[<i>trans</i> -(4-Aminocyclohexyl)amino]-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}ethanone dihydrochloride	0.0012
68	1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-{4-[(4-methylpiperazin-1-yl)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.0026
69	N-(<i>trans</i> -4-{[3-Acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl]amino}cyclohexyl)-2-amino-3-methylbutanamide dihydrochloride	0.0012
70	1-{6-(3,5-Dichloro-4-hydroxyphenyl)-4-[<i>trans</i> -4-(piperazin-1-ylmethyl)-cyclohexylamino]-1,5-naphthyridin-3-yl}ethanone trihydrochloride	0.0006
71	(S)-1-(4-{[6-(3-Aminopiperidin-1-yl)pyridin-3-yl]amino}-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.0005
72	(S)-1-(4-{[6-(3-Aminopiperidin-1-yl)pyridin-3-yl]amino}-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.0043
73	N-{ <i>trans</i> -4-[3-Acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino]cyclohexyl}-2-aminopropanamide dihydrochloride	0.0075
74	N-{4-[3-Acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin- <i>trans</i> -4-ylamino]cyclohexyl}-2-aminopropanamide dihydrochloride	0.0026
75	(S)-N-{4-[3-Acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin- <i>trans</i> -4-ylamino]cyclohexyl}pyrrolidine-2-carboxamide dihydrochloride	0.001
76	(S)-N-{4-[3-Acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin- <i>trans</i> -4-ylamino]cyclohexyl}pyrrolidine-2-carboxamide dihydrochloride	0.0024
77	1-(6-(3-Hydroxypyrrolidin-1-yl)-4-{ <i>trans</i> -4-[(3-hydroxypyrrolidin-1-yl)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone	0.74
78	1-{6-(Pyrrolidin-1-yl)-4-[<i>trans</i> -4-(pyrrolidin-1-ylmethyl)-cyclohexylamino]-1,5-naphthyridin-3-yl}ethanone	2

79	N-{ <i>trans</i> -4-[3-Acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino]cyclohexyl}-2-amino-3-methylbutanamide dihydrochloride	0.0016
80	Cyclopropyl{6-(3,5-dichloro-4-hydroxyphenyl)-4-[<i>trans</i> -4-(dimethylamino)cyclohexylamino]-1,5-naphthyridin-3-yl}methanone dihydrochloride	0.0006
81	1-[6-(3-Chloro-5-fluoro-4-methoxyphenyl)-4-{ <i>trans</i> -4-[(dimethylamino)-methyl]cyclohexylamino}-1,5-naphthyridin-3-yl]ethanone dihydrochloride	0.0005
82	1-(4-{ <i>trans</i> -4-[(Dimethylamino)methyl]cyclohexylamino}-6-(1H-pyrrolo[2,3-b]pyridin-5-yl)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.013
83	(S)-{4-[6-(3-Aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}(cyclopropyl)methanone	0.001
84	1-(4-{ <i>trans</i> -4-[(Dimethylamino)methyl]cyclohexylamino}-6-(4-methoxyphenyl)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.031
85	1-[6-(3,5-Dichloro-4-methoxyphenyl)-4-{ <i>trans</i> -4-[(dimethylamino)-methyl]cyclohexylamino}-1,5-naphthyridin-3-yl]ethanone dihydrochloride	0.12
86	1-(4-{ <i>trans</i> -4-[(Dimethylamino)methyl]cyclohexylamino}-6-(6-hydroxypyridin-3-yl)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.011
87	5-(7-Acetyl-8-{ <i>trans</i> -4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-2-yl)picolinonitrile dihydrochloride	0.0045
88	1-(4-{ <i>trans</i> -4-[(Dimethylamino)methyl]cyclohexylamino}-6-(4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.0045
89	1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4-{[<i>trans</i> -4-(dimethylamino)-cyclohexyl]methylamino}-1,5-naphthyridin-3-yl]ethanone dihydrochloride	0.0006
90	1-[6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-{[<i>trans</i> -4-(dimethylamino)-cyclohexyl]methylamino}-1,5-naphthyridin-3-yl]ethanone dihydrochloride	0.0024
91	1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4-(4-hydroxycyclohexylamino)-1,5-naphthyridin-3-yl]ethanone hydrochloride	0.015

92	1-[6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-(4-hydroxycyclohexylamino)-1,5-naphthyridin-3-yl]ethanone hydrochloride	0.012
93	1-[6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-({ <i>cis</i> -4-[(dimethylamino)methyl]cyclohexyl}amino)-1,5-naphthyridin-3-yl]ethanone dihydrochloride	0.0011
94	1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4-({ <i>cis</i> -4-[(dimethylamino)methyl]cyclohexyl}amino)-1,5-naphthyridin-3-yl]ethanone dihydrochloride	0.0006
95	(R)-1-[4-[6-(3-aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl]ethanone trihydrochloride	0.002
96	(R)-1-[4-[6-(3-Aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl]ethanone	0.0036
201	(R)-(4-{{6-(3-aminopiperidin-1-yl)pyridin-3-yl}amino}-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl) (cyclopropyl)methanone	0.00093
202	(R)-(4-{{6-(3-aminopiperidin-1-yl) pyridin-3-yl}amino}-6-(3-chloro-5-fluoro -4-hydroxyphenyl)-1,5-naphthyridin-3-yl) (cyclopropyl) methanone	0.00046
203	1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-({ <i>trans</i> -4-(dimethylamino)cyclohexyl} amino)-1,5-naphthyridin-3-yl]-2-hydroxyethanone dihydrochloride	0.0015
204	1-[6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-({ <i>trans</i> -4-[(dimethylamino)methyl]cyclohexyl} amino)-1,5-naphthyridin-3-yl]-2-hydroxyethanone dihydrochloride	0.0013
205	1-[6-(3-chloro-5-fluoro-4-hydroxyphenyl) -4-({ <i>trans</i> -4-[(dimethylamino)methyl] cyclohexyl} amino)-1,5-naphthyridin-3-yl)]propan-1-one dihydrochloride	0.0028
206	1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-({ <i>trans</i> -4-[(dimethylamino)methyl] cyclohexyl}amino)- 1,5-naphthyridin-3-yl)]propan-1-one dihydrochloride	0.0013
207	(S)-1-(4-{{6-(3-aminopiperidin-1-yl)pyridin-3-yl}amino}-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)propan-1-one trihydrochloride	0.0016
208	(S)-1-(4{{6-(3-aminopiperidin-1-yl)pyridin-3-yl}amino}-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)propan-1-one trihydrochloride	0.0026
209	1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-({4-[(R)-3-fluoropyrrolidin-1-yl]methyl} cyclohexyl} amino)-1,5-naphthyridin-3-yl]ethanone dihydrochloride	0.002

210	(S)-4-((6-(3-aminopiperidin-1-yl)pyridin-3-yl)amino)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl(cyclobutyl)methanone dihydrochloride	0.0014
211	(6-(3,5-dichloro-4-hydroxyphenyl)-4-((4-((dimethylamino)methyl)cyclohexyl)amino)-1,5-naphthyridin-3-yl)(cyclobutyl)methanone dihydrochloride	0.0027
212	(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-((4-((dimethylamino)methyl)cyclohexyl)amino)-1,5-naphthyridin-3-yl)(cyclobutyl)methanone dihydrochloride	0.0016
213	(S)-4-({6-(3-aminopiperidin-1-yl)pyridin-3-yl}amino)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl(cyclobutyl)methanone	0.0011
214	(R)-1-(4-((6-(3-aminopiperidin-1-yl)pyridin-3-yl)amino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)propan-1-one trihydrochloride	0.0013
215	(R)-1-(4-({6-(3-aminopiperidin-1-yl)pyridin-3-yl}amino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)-2-methylpropan-1-one trihydrochloride	0.0065
216	1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-({trans-4-((dimethylamino)methyl)cyclohexyl}amino)-1,5-naphthyridin-3-yl]-2-methylpropan-1-one dihydrochloride	0.0019
217	1-[6-chloro-4-({trans-4-((dimethylamino)methyl)cyclohexyl}amino)-1,5-naphthyridin-3-yl]-2-methylpropan-1-one dihydrochloride	0.0018

Western blot analysis

To evaluate the expression status of MELK in several cell lines, western blot analysis was performed using crude cell lysate collected from those cells. Anti-MELK antibody (clone 31, BD Biosciences) was used to visualize the expression. Breast cancer cell lines, 22Rv1, T47D, A549 and DU4475 expressed MELK significantly although Bladder cancer cell line and HT1197 showed no expression of MELK.

Cell-based assay

Active candidate inhibitors against MELK were evaluated for their target-specific cytotoxicity using 22Rv1, T47D, A549, DU4475 and HT-1197 cells was used for negative control. 100 micro-L of cell suspension was seeded onto 96-well microtiter plate (ViewPlate-96FTC, PerkinElmer). The initial cell concentration of 22Rv1, T47D, A549,

DU4475, and HT1197 were 3,000 cells/well, 2,000 cells/well and 2,500 cells/well, respectively. Cellular growth was determined using Cell Counting Kit-8 (DOJINDO) at 72 hours after the exposure of the candidate inhibitors. IC₅₀ was used as an indicator of the anti-proliferative activity of the inhibitors, and calculated by serial dilution method (0, 1.5625, 3.125, 6.25, 12.5, 25, 50, and 100 micro-M). Accurate IC₅₀ values were calculated as described previously.

IC₅₀ values of the typical compounds of the present invention are shown in the following table 3:

Table 3;

Ex.	Compound Name	IC ₅₀ (μM) (22Rv1)	IC ₅₀ (μM) (T47D)	IC ₅₀ (μM) (A549)	IC ₅₀ (μM) (DU4475)	IC ₅₀ (μM) (HT1197)
1	1-(6-Chloro-4-{ <i>trans</i> -4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone	5	5.3	2.7	2.5	10
2	1-{6-(3,5-Dichloro-4-hydroxyphenyl)-4-[<i>trans</i> -4-(dimethylamino)cyclohexylamino]-1,5-naphthyridin-3-yl}ethanone dihydrochloride	0.0032	0.0018	0.004	0.0015	0.19
3	1-{6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-[<i>trans</i> -4-(dimethylamino)cyclohexylamino]-1,5-naphthyridin-3-yl}ethanone Dihydrochloride	0.006	0.0026	0.0091	0.0033	0.39
4	Cyclopropyl(6-(3,5-dichloro-4-hydroxyphenyl)-4-{ <i>trans</i> -4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)methanone dihydrochloride	0.0064	0.0055	0.0062	0.0026	0.036
5	(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-{ <i>trans</i> -4-[(dimethylamino)methyl]cyclohexylamino]-1,5-naphthyridin-3-yl)(cyclopropyl)methanone dihydrochloride	0.0057	0.0029	0.0061	0.003	0.018
6	1-{6-(3,5-Dichloro-4-hydroxyphenyl)-4-[(<i>trans</i> -4-[(dimethylamino)methyl]cyclohexylamino)-1,5-naphthyridin-3-yl]ethanone dihydrochloride	0.0052	0.0053	0.0089	0.0033	0.12

7	1-{6-(3-Chloro-5-fluoro-4-hydroxy-phenyl)-4-({ <i>trans</i> -4-[(dimethylamino)methyl]cyclohexyl}amino)-1,5-naphthyridin-3-yl}ethanone dihydrochloride	0.0061	0.0035	0.0097	0.0036	0.11
8	1-{6-(3-Chloro-4-hydroxy-5-methoxyphenyl)-4-({ <i>trans</i> -4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.044	0.013	0.024	0.0064	0.24
9	1-{6-(3,5-Dichloro-4-hydroxy-phenyl)-4-({ <i>trans</i> -4-[2-(dimethylamino)ethyl]cyclohexyl}amino)-1,5-naphthyridin-3-yl}ethanone dihydrochloride	0.011	0.0066	0.013	0.0055	0.27
10	1-{6-(3-Chloro-5-fluoro-4-hydroxy-phenyl)-4-({ <i>trans</i> -4-[2-(dimethylamino)ethyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.01	0.0039	0.012	0.0049	0.2
11	1-(4-({ <i>trans</i> -4-[(Dimethylamino)methyl]cyclohexylamino}-6-[4-hydroxy-3-(trifluoromethoxy)-phenyl]-1,5-naphthyridin-3-yl)-ethanone dihydrochloride	0.066	0.027	0.042	0.049	0.14
12	2,6-Dichloro-4-{8-({ <i>trans</i> -4-[(dimethylamino)methyl]cyclohexylamino}-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)phenol dihydrochloride	0.019	0.019	0.053	0.0045	0.46
13	6-(3-Chloro-5-fluoro-4-hydroxy-phenyl)-4-({ <i>trans</i> -4-[(dimethylamino)methyl]cyclohexyl}amino)-3-methylsulfonyl-1,5-naphthyridine dihydrochloride	0.019	0.013	0.073	0.0068	0.32
14	6-(3-Chloro-4-hydroxy-5-methoxy-phenyl)-4-({ <i>trans</i> -4-[(dimethylamino)methyl]cyclohexylamino}-3-methylsulfonyl-1,5-naphthyridine dihydrochloride	0.05	0.027	0.033	0.0096	0.14
15	2,6-Dichloro-4-{8-({ <i>trans</i> -4-(dimethylamino)cyclohexylamino}-7-(methylsulfonyl)-1,5-naphthyridin-2-yl}phenol dihydrochloride	0.026	0.018	0.092	0.0027	2.2

16	2,6-Dichloro-4-(8-(4-((dimethylamino)methyl)phenylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)phenol dihydrochloride	0.17	0.078	0.47	0.031	4.4
17	2-Chloro-4-(8-(4-((dimethylamino)methyl)phenylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-fluorophenol dihydrochloride	0.33	0.13	0.83	0.064	6.6
18	2-Chloro-4-(8-(4-((dimethylamino)methyl)phenylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-methoxyphenol dihydrochloride	1	0.32	0.69	0.31	3.8
19	1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-(3-(2-(pyrrolidin-1-yl)ethyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.63	0.59	0.14	0.11	7
20	1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-(3-(2-(pyrrolidin-1-yl)ethyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.81	0.5	0.31	0.21	4.8
21	1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-(6-(2-(dimethylamino)ethoxy)pyridin-3-ylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.27	0.1	0.21	0.096	2.3
22	1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-(6-(2-(dimethylamino)ethoxy)pyridin-3-ylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.35	0.1	0.29	0.31	3.5
23	1-(6-(3-Chloro-4-hydroxy-5-methoxyphenyl)-4-(6-(2-(dimethylamino)ethoxy)pyridin-3-ylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	1.3	0.38	0.47	0.41	8.9

24	2,6-Dichloro-4-(8-(6-(2-(dimethylamino)ethoxy)pyridin-3-ylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)phenol hydrochloride	1.8	0.58	5.1	0.38	15
25	2-Chloro-4-(8-(6-(2-(dimethylamino)ethoxy)pyridin-3-ylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-fluorophenol dihydrochloride	2.8	0.7	5.9	0.74	21
26	2-Chloro-4-(8-(6-(2-(dimethylamino)ethoxy)pyridin-3-ylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-methoxyphenol dihydrochloride	4.1	1	3.1	1.6	15
27	1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-((1-methylpiperidin-4-yl)methylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.1	0.079	0.11	0.1	2
28	1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-(<i>trans</i> -4-((dimethylamino-d6)methyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.0052	0.004	0.006	0.0022	0.14
29	1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-(4-(2-(dimethylamino)ethyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.084	0.085	0.11	0.028	0.68
30	1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-(4-(2-(dimethylamino)ethyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.17	0.11	0.14	0.041	1.2
31	1-(6-(3-Chloro-4-hydroxy-5-methoxyphenyl)-4-(4-(2-(dimethylamino)ethyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.65	0.41	0.31	0.19	4.4

32	2-Chloro-4-(8-(<i>trans</i> -4-(dimethylamino)cyclohexylamino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-fluorophenol dihydrochloride	0.046	0.024	0.2	0.0063	3.1
33	1-(6-(3,5-Dichloro-4-hydroxy-phenyl)-4-(1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-ylamino)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.64	0.35	0.93	0.34	100
34	1-(6-(3,5-Dichloro-4-hydroxy-phenyl)-4-(4-((4-methylpiperazin-1-yl)methyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.21	0.11	0.19	0.096	1.6
35	1-(6-(3-Chloro-5-fluoro-4-hydroxy-phenyl)-4-(4-((4-methyl-piperazin-1-yl)methyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.65	0.22	0.41	0.31	3.8
36	1-(6-(3,5-Dichloro-4-hydroxy-phenyl)-4-(4-(2-(pyrrolidin-1-yl)-ethyl)piperidin-1-yl)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.36	0.21	0.63	0.22	4.7
37	1-(6-(3-Chloro-5-fluoro-4-hydroxy-phenyl)-4-(4-(2-(pyrrolidin-1-yl)-ethyl)piperidin-1-yl)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.49	0.25	1.2	0.42	7.2
38	1-(6-(3,5-Dichloro-4-hydroxy-phenyl)-4-(6-(2-(dimethylamino)-ethylamino)pyridin-3-ylamino)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.24	0.11	0.26	0.069	9.5
39	1-(6-(3-Chloro-5-fluoro-4-hydroxy-phenyl)-4-(6-(2-(dimethylamino)-ethylamino)pyridin-3-ylamino)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.38	0.12	0.44	0.19	10
40	(S)-(4-(6-(3-Aminopiperidin-1-yl)-pyridin-3-ylamino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)(cyclopropyl)-methanone trihydrochloride	0.034	0.025	0.29	0.02	4.2

41	1-(4-(2-(3-Aminopyrrolidin-1-yl)-pyrimidin-5-ylamino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.052	0.027	0.27	0.026	100
42	1-(4-{4-[(Dimethylamino)methyl]cyclohexylamino}-6-(1H-pyrazol-4-yl)-1,5-naphthyridin-3-yl)-ethanone trihydrochloride	0.063	0.036	0.049	0.045	0.06
43	1-(6-{3,5-Dichloro-4-hydroxyphenyl}-4-[4-(hydroxymethyl)cyclohexyl]amino)-1,5-naphthyridin-3-yl)ethanone hydrochloride	0.085	0.024	0.057	0.019	0.64
44	1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4-{trans-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl]-2-hydroxyethanone dihydrochloride	0.006	0.0029	0.0067	0.0017	0.2
45	1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-[(1-methylpiperidin-4-yl)amino]-1,5-naphthyridin-3-yl)-ethanone	0.096	0.086	0.065	0.096	0.45
46	1-[6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-[(1-methylpiperidin-4-yl)amino]-1,5-naphthyridin-3-yl]-ethanone	0.14	0.092	0.098	0.14	0.53
47	1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-[[4-(morpholinomethyl)cyclohexyl]amino]-1,5-naphthyridin-3-yl)ethanone	0.034	0.015	0.02	0.009	0.16
48	1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4-(4-{[(2-hydroxyethyl)(methyl)amino]methyl}cyclohexylamino)-1,5-naphthyridin-3-yl]-ethanone dihydrochloride	0.0092	0.0068	0.02	0.0034	0.57
49	1-[6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-(4-{[(2-hydroxyethyl)(methyl)amino]methyl}cyclohexylamino)-1,5-naphthyridin-3-yl]-ethanone dihydrochloride	0.0087	0.0039	0.021	0.0039	0.49

50	1-(6-(3,5-Difluoro-4-hydroxyphenyl)-4-{4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.017	0.0061	0.015	0.0053	0.08
51	1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-{6-[3-(dimethylamino)pyrrolidin-1-yl]pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.36	0.19	0.32	0.32	2.8
52	1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-{6-[3-(dimethylamino)pyrrolidin-1-yl]pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.44	0.18	0.39	0.4	2
53	1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-{6-[3-(methylamino)pyrrolidin-1-yl]pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.078	0.042	0.2	0.071	100
54	1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-{6-[3-(methylamino)pyrrolidin-1-yl]pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.086	0.04	0.17	0.11	3.9
55	1-(6-(1H-Benzo[d]imidazol-5-yl)-4-{trans-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.3	0.084	0.25	0.65	2
56	1-{4-[4-(trans-4-Dimethylamino)methylcyclohexylamino]-6-(pyridin-4-yl)-1,5-naphthyridin-3-yl}ethanone trihydrochloride	0.86	0.38	0.52	0.46	1.7
57	5-(7-Acetyl-8-{trans-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-2-yl)pyrimidine-2-carbonitrile	0.24	0.089	0.56	0.22	0.38
58	1-(6-(3,5-Dimethyl-1H-pyrazol-4-yl)-4-{trans-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone trihydrochloride	6.1	1.6	3	5.9	10

59	1-(4-{ <i>trans</i> -4-[(Dimethylamino)-methyl]cyclohexylamino}-6-(4-hydroxy-3,5-dimethylphenyl)-1,5-naphthyridin-3-yl)ethanone dichloride	2.5	0.39	0.23	0.21	7.5
60	1-(6-(3,5-Dichloro-4-hydroxy-phenyl)-4-{6-[3-(dimethylamino)-pyrrolidin-1-yl]pyridin-3-ylamino}-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.1	0.066	0.11	0.041	1.1
61	1-(6-(3,5-Dichloro-4-hydroxy-phenyl)-4-{ <i>trans</i> -4-(pyrrolidin-1-ylmethyl)cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.011	0.0069	0.012	0.0044	0.15
62	1-(6-(3-Chloro-5-fluoro-4-hydroxy-phenyl)-4-{[<i>trans</i> -4-(pyrrolidin-1-ylmethyl)cyclohexyl]amino}-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.0073	0.0034	0.011	0.0037	0.091
63	1-(6-(3,5-Dichloro-4-hydroxy-phenyl)-4-{4-[(4-methylpiperazin-1-yl)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.025	0.016	0.02	0.0092	0.13
64	1-(4-{[6-(3-Aminopiperidin-1-yl)-pyridin-3-yl]amino}-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.016	0.0064	0.07	0.016	2.9
65	1-(4-{[6-(3-Aminopiperidin-1-yl)-pyridin-3-yl]amino}-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.013	0.0047	0.021	0.015	0.74
66	1-(4-{[4-(4-Aminocyclohexyl)amino]-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}ethanone dihydrochloride	0.0045	0.0018	0.016	0.001	10
67	1-(4-{ <i>trans</i> -(4-Aminocyclohexyl)-amino}-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.0061	0.0019	0.022	0.0012	2.8

68	1-(6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-{{4-(4-methylpiperazin-1-yl)methyl}cyclohexylamino})-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.039	0.012	0.026	0.012	0.11
69	N-(<i>trans</i> -4-{{3-Acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl}amino}cyclohexyl)-2-amino-3-methylbutanamide dihydrochloride	0.025	0.007	0.064	0.013	2.5
70	1-(6-(3,5-Dichloro-4-hydroxyphenyl)-4-{{ <i>trans</i> -4-(piperazin-1-yl-methyl)cyclohexylamino}-1,5-naphthyridin-3-yl}ethanone trihydrochloride	0.031	0.021	0.084	0.011	3.9
71	(S)-1-(4-{{[6-(3-Aminopiperidin-1-yl)pyridin-3-yl]amino}-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}ethanone trihydrochloride	0.014	0.0074	0.09	0.008	3.4
72	(S)-1-(4-{{[6-(3-Aminopiperidin-1-yl)pyridin-3-yl]amino}-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}ethanone trihydrochloride	0.014	0.0053	0.047	0.014	1.2
73	N-{{ <i>trans</i> -4-[3-Acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino]cyclohexyl}-2-aminopropanamide dihydrochloride	0.027	0.0086	0.18	0.0043	100
74	N-{4-[3-Acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin- <i>trans</i> -4-ylamino]-cyclohexyl}-2-aminopropanamide dihydrochloride	0.025	0.0043	0.13	0.0036	100
75	(S)-N-{4-[3-Acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin- <i>trans</i> -4-ylamino]-cyclohexyl}pyrrolidine-2-carboxamide dihydrochloride	0.099	0.036	0.21	0.021	8.4
76	(S)-N-{4-[3-Acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin- <i>trans</i> -4-ylamino]-cyclohexyl}pyrrolidine-2-carboxamide dihydrochloride	0.073	0.03	0.32	0.019	8.7

77	1-(6-(3-Hydroxypyrrolidin-1-yl)-4-{ <i>trans</i> -4-[(3-hydroxypyrrolidin-1-yl)methyl] cyclohexylamino}-1,5-naphthyridin-3-yl)ethanone	10	10	10	10	10
78	1-(6-(Pyrrolidin-1-yl)-4-{ <i>trans</i> -4-(pyrrolidin-1-ylmethyl)cyclohexylamino}-1,5-naphthyridin-3-yl)-ethanone	5.6	5.4	6.8	7.7	9.8
79	N-{ <i>trans</i> -4-[3-Acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino]cyclohexyl}-2-amino-3-methylbutanamide dihydrochloride	0.038	0.018	0.11	0.016	3.9
80	Cyclopropyl{6-(3,5-dichloro-4-hydroxyphenyl)-4-{ <i>trans</i> -4-(dimethylamino)cyclohexylamino}-1,5-naphthyridin-3-yl}methanone Dihydrochloride	0.0052	0.0041	0.0076	0.002	0.084
81	1-[6-(3-Chloro-5-fluoro-4-methoxyphenyl)-4-{ <i>trans</i> -4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl]ethanone dihydrochloride	0.0049	0.002	0.0062	0.0018	0.044
82	1-(4-{ <i>trans</i> -4-[(Dimethylamino)methyl]cyclohexylamino}-6-(1H-pyrrolo[2,3-b]pyridin-5-yl)-1,5-naphthyridin-3-yl)ethanone trihydrochloride	0.37	0.32	0.33	0.65	2.3
83	(S)-{4-[6-(3-Aminopiperidin-1-yl)-pyridin-3-ylamino]-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}(cyclopropyl)-methanone	0.025	0.012	0.09	0.015	2.7
84	1-(4-{ <i>trans</i> -4-[(Dimethylamino)methyl]cyclohexylamino}-6-(4-methoxyphenyl)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.58	0.25	2.4	5.2	6
85	1-[6-(3,5-Dichloro-4-methoxyphenyl)-4-{ <i>trans</i> -4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl]ethanone dihydrochloride	0.77	0.43	2.3	2.3	6.5
86	1-(4-{ <i>trans</i> -4-[(Dimethylamino)methyl]cyclohexylamino}-6-(6-hydroxypyridin-3-yl)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	5.3	6.2	8	6.5	10

87	5-(7-Acetyl-8-{ <i>trans</i> -4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-2-yl)-picolinonitrile dihydrochloride	0.66	0.66	1.8	0.74	2
88	1-(4-{ <i>trans</i> -4-[(Dimethylamino)methyl]cyclohexylamino}-6-(4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone dihydrochloride	0.04	0.031	0.023	0.021	0.039
89	1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4-[(<i>trans</i> -4-(dimethylamino)cyclohexyl)methylamino]-1,5-naphthyridin-3-yl]ethanone dihydrochloride	0.028	0.023	0.041	0.0063	0.9
90	1-[6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-[(<i>trans</i> -4-(dimethylamino)cyclohexyl)methylamino]-1,5-naphthyridin-3-yl]ethanone Dihydrochloride	0.052	0.03	0.12	0.027	10
91	1-[6-(3,5-Dichloro-4-hydroxyphenyl)-4-(4-hydroxycyclohexylamino)-1,5-naphthyridin-3-yl]-ethanone hydrochloride	0.072	0.038	0.048	0.016	0.33
92	1-[6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-(4-hydroxycyclohexylamino)-1,5-naphthyridin-3-yl]-ethanone hydrochloride	0.061	0.036	0.053	0.018	0.53
93	1-{6-(3-Chloro-5-fluoro-4-hydroxyphenyl)-4-[(<i>cis</i> -4-[(dimethylamino)methyl]cyclohexyl)amino]-1,5-naphthyridin-3-yl}ethanone Dihydrochloride	0.032	0.02	0.039	0.011	0.19
94	1-{6-(3,5-Dichloro-4-hydroxyphenyl)-4-[(<i>cis</i> -4-[(dimethylamino)methyl]cyclohexyl)amino]-1,5-naphthyridin-3-yl}ethanone Dihydrochloride	0.028	0.02	0.039	0.0073	0.25
95	(R)-1-{4-[6-(3-Aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}ethanone trihydrochloride	0.029	0.022	0.088	0.03	1.9
96	(R)-1-{4-[6-(3-Aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}ethanone	0.026	0.018	0.035	0.024	0.43

201	(R)-(4-([6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)(cyclopropyl)methanone	0.0061	0.0025	0.0061	0.003	0.032
202	(R)-(4-([6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)(cyclopropyl)methanone	0.0044	0.0038	0.0054	0.001	0.047
203	1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-([trans-4-(dimethylamino)cyclohexyl]amino)-1,5-naphthyridin-3-yl]-2-hydroxyethanone dihydrochloride	0.017	0.0093	0.034	0.013	1.2
204	1-[6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-([trans-4-[(dimethylamino)methyl]cyclohexyl]amino)-1,5-naphthyridin-3-yl]-2-hydroxyethanone dihydrochloride	0.02	0.014	0.058	0.013	10
205	1-[6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-([trans-4-[(dimethylamino)methyl]cyclohexyl]amino)-1,5-naphthyridin-3-yl]propan-1-one dihydrochloride	0.022	0.0083	0.032	0.033	0.69
206	1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-([trans-4-[(dimethylamino)methyl]cyclohexyl]amino)-1,5-naphthyridin-3-yl]propan-1-one dihydrochloride	0.022	0.01	0.061	0.023	10
207	(S)-1-(4-([6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)propan-1-one trihydrochloride	0.034	0.018	0.098	0.024	3.9
208	(S)-1-(4-([6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)propan-1-one trihydrochloride	0.026	0.015	0.063	0.021	0.86
209	1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-([4-([(R)-3-fluoropyrrolidin-1-yl)methyl]cyclohexyl]amino)-1,5-naphthyridin-3-yl]ethanone dihydrochloride	0.032	0.036	0.037	0.01	0.12
210	(S)-(4-((6-(3-aminopiperidin-1-yl)pyridin-3-yl)amino)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)(cyclobutyl)methanone dihydrochloride	0.017	0.0093	0.042	0.022	1.4

211	(6-(3,5-dichloro-4-hydroxyphenyl)-4-((4-((dimethylamino)methyl)cyclohexyl)amino)-1,5-naphthyridin-3-yl)(cyclobutyl)methanone dihydrochloride	0.0072	0.0034	0.0076	0.003	0.0077
212	(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-((4-((dimethylamino)methyl)cyclohexyl)amino)-1,5-naphthyridin-3-yl)(cyclobutyl)methanone dihydrochloride	0.013	0.0074	0.014	0.003	0.014
213	(S)-(4-([6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)(cyclobutyl)methanone	0.0071	0.0043	0.029	0.003	1.7
214	(R)-1-(4-([6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)propan-1-one trihydrochloride	0.0059	0.0028	0.013	0.004	0.34
215	(R)-1-(4-([6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)-2-methylpropan-1-one trihydrochloride	0.032	0.016	0.083	0.014	1.7
216	1-[6-(3,5-dichloro-5-4-hydroxyphenyl)-4-((trans-4-((dimethylamino)methyl)cyclohexyl)amino)-1,5-naphthyridin-3-yl]-2-methylpropan-1-one dihydrochloride	NT	NT	0.012	NT	0.025
217	1-[6-chloro-4-((trans-4-((dimethylamino)methyl)cyclohexyl)amino)-1,5-naphthyridin-3-yl]-2-methylpropan-1-one dihydrochloride	NT	NT	0.021	NT	0.055

NT: Not tested

The growth inhibitory effect of Compound Example 6 was further examined on the growth of various cancer cell lines. *In vitro* anti-proliferative assay using A549 (lung), T47D (breast), DU4475 (breast), and 22Rv1 (prostate) cancer cells, in which MELK was highly expressed, revealed IC₅₀ values of 6.7, 4.3, 2.3, and 6.0 nM, respectively (Fig. 1a-d). On the other hand, HT1197 (bladder) cancer cells, in which MELK expression was hardly detectable, revealed IC₅₀ value of 97 nM (Fig. 1e), clearly implying the MELK-dependent growth inhibition effect of this compound.

10 Xenograft Model Antitumor Assay

MDA-MB-231 cells were injected into the mammary fat pads of NOD.CB17-*Prkdc^{scid}*/J mice (Charles River Laboratory). A549, MIAPaCa-2 and PC-14 cells (1×10^7 cells) were injected subcutaneously in the left flank of female BALB/cSLC-nu/nu mice (Japan SLC, Inc.). DU145 cells were injected subcutaneously in the left flank of male

5 BALB/cSLC-nu/nu mice (Japan SLC, Inc.). When MDA-MB-231, A549, DU145, MIAPaCa-2, and PC-14 xenografts had reached an average volume of 100, 210, 110, 250, and 250 mm³, respectively, animals were randomized into groups of 6 mice (except for PC-14, for which groups of 3 mice were used). For oral administration, compounds were prepared in a vehicle of 0.5% methylcellulose and given by oral gavage at the indicated

10 dose and schedule. For intravenous administration, compounds were formulated in 5% glucose and injected into the tail vein. An administration volume of 10 mL per kg of body weight was used for both administration routes. Concentrations were indicated in main text and Figures. Tumor volumes were determined every other day using a caliper. The results were converted to tumor volume (mm³) by the formula $\text{length} \times \text{width}^2 \times 1/2$. The weight of the mice was determined as an indicator of tolerability on the same days. The animal experiments using A549 xenografts were conducted by contract with KAC Co., Ltd. (Shiga, Japan) in accordance with their Institutional Guidelines for the Care and Use of Laboratory Animals. The other animal experiments were conducted at OncoTherapy Science, Inc. in accordance with their Institutional Guidelines for the Care and Use of

20 Laboratory Animals. Tumor growth inhibition (TGI) was calculated according to the formula $\{1 - (T - T_0) / (C - C_0)\} \times 100$, where T and T_0 are the mean tumor volumes at day 14 and day 0, respectively, for the experimental group, and $C - C_0$ are those for the vehicle control group. All values were presented as means $\pm$ SD. Statistical significance was computed using student's t-test, and the level of significance was set at $p < 0.05$.

25 The present inventors subsequently examined *in vivo* anti-tumor effect of Compound Example 6 by a xenograft model using MDA-MB-231 cells (MELK-positive, triple-negative breast cancer cells). The compound was administered to mice bearing xenografts for 14 days after the tumor size reached about 100 mm³. The tumor size was

measured as a surrogate marker of drug response (tumor growth inhibition (TGI)) (see **Methods**). Intravenous administration of Example 6 at 20 mg/kg once every two days resulted in TGI of 73% (**Fig. 2a**). Since the bioavailability of this compound was expected to be very high (data not shown), oral administration of this compound was attempted.

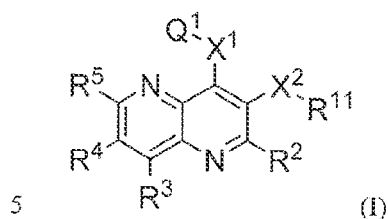
5 The oral administration at 10 mg/kg once a day revealed TGI of 72% (**Fig. 2b**). Due to the high growth-suppressive effect on various cancer cell lines, *in vivo* growth-suppressive effect using cancer cell lines of other types was further investigated and found significant tumor growth suppression by Example 6 for multiple cancer types in dose-dependent manners with no or a little body-weight loss (**Fig. 2** and **Fig. 3**). For example, mice
10 carrying A549 (lung cancer) xenografts that were treated with 1, 5, and 10 mg/kg once a day of Example 6 by intravenous administration revealed TGI of 51, 91, and 108, respectively (**Fig. 2c**) and those by oral administration of 5 and 10 mg/kg once a day revealed TGI of 95 and 124%, respectively (**Fig. 2d**). In addition, the present inventors examined DU145 (prostate cancer) and MIAPaCa-2 (pancreatic cancer) xenograft models
15 by oral administration of 10 mg/kg once a day, and observed TGI of 106 and 87%, respectively (**Fig. 2e and f**). To further validate the MELK-specific *in vivo* tumor suppressive effect, the inventors examined PC-14 lung cancer cells in which MELK expression was hardly detectable (**Fig. 2g**). Oral administration of 10 mg/kg Example 6 once a day for 14 days showed no tumor growth suppressive effect on PC-14 xenografts
20 (**Fig. 2h**), further supporting the MELK-dependent antitumor activity of Example 6.

INDUSTRIAL APPLICABILITY

The present invention provides a novel quinoline derivative having MELK inhibitory effect. The compounds of the present invention may be used for pharmaceutical
25 composition for inhibiting MELK. Such pharmaceutical compositions are suitable for treating or preventing cancer.

CLAIMS

1. A compound represented by formula (I) or a pharmaceutically acceptable salt thereof;



wherein,

X¹ is selected from the group consisting of a direct bond, -NR¹²-, -O-, and -S-;

R¹² is selected from the group consisting of a hydrogen atom, C₁-C₆ alkyl and C₃-C₁₀ cycloalkyl;

10 Q¹ is selected from the group consisting of C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, 3- to 10-membered non-aromatic heterocyclyl, (C₃-C₁₀ cycloalkyl)-C₁-C₆ alkyl, (C₆-C₁₀ aryl)-C₁-C₆ alkyl, (5- to 10-membered heteroaryl)-C₁-C₆ alkyl, and (3- to 10-membered non-aromatic heterocyclyl)-C₁-C₆ alkyl; wherein Q¹ is optionally substituted with one or more substituents independently selected from A¹;

15 X² is selected from the group consisting of -CO-, -S-, -SO-, and -SO₂-;

R¹¹ is selected from the group consisting of C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein R¹¹ is optionally substituted with one or more substituents independently selected from A²;

20 R⁵ is selected from the group consisting of a halogen atom, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein the cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A³;

R², R³, and R⁴ are independently selected from the group consisting of a hydrogen

atom, a halogen atom, and C₁-C₅ alkyl;

A¹ and A³ are independently selected from the group consisting of a halogen atom, cyano, -COOR¹³, -CONR¹⁴R¹⁵, formyl, (C₁-C₆ alkyl)carbonyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, nitro, -NR¹⁶R¹⁷, -OR¹⁸, -S(O)_nR¹⁹, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-
5 membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein the alkylcarbonyl, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A⁴;

A² is independently selected from the group consisting of a halogen atom, cyano, C₃-C₁₀ cycloalkyl, carboxy, formyloxy, (C₁-C₆ alkyl)carbonyloxy, hydroxy, C₁-C₆ alkoxy,
10 amino, C₁-C₆ alkylamino, and di(C₁-C₆ alkyl)amino;

R¹³, R¹⁴, and R¹⁵ are independently selected from the group consisting of a hydrogen atom, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally
15 substituted with one or more substituents independently selected from A⁴; or R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form 3- to 10-membered nitrogen-containing heterocyclyl, which is optionally substituted with one or more substituents independently selected from A⁴;

R¹⁶ and R¹⁸ are independently selected from the group consisting of a hydrogen atom, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-
20 membered heteroaryl, 3- to 10-membered non-aromatic heterocyclyl, and -COR²⁰; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A⁴; R¹⁷ is selected from the group consisting of a hydrogen atom, and C₁-C₆ alkyl that is optionally substituted
25 with one or more substituents independently selected from A⁴; or R¹⁶ and R¹⁷ together with the nitrogen atom to which they are attached form 3- to 10-membered nitrogen-containing heterocyclyl, which is optionally substituted with one or more substituents independently selected from A⁴;

R^{19} is selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, C_6 - C_{10} aryl, and 5- to 10-membered heteroaryl; wherein the alkyl, cycloalkyl, aryl, and heteroaryl are optionally substituted with one or more substituents independently selected from A^4 ;

R^{20} is selected from the group consisting of a hydrogen atom, $-NR^{14}R^{15}$, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_{10} cycloalkyl, C_6 - C_{10} aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A^4 ;

n is an integer independently selected from 0 to 2;

A^4 is independently selected from consisting of a halogen atom, cyano, $-COOR^{21}$, $-CONR^{22}R^{23}$, formyl, $(C_1$ - C_6 alkyl)carbonyl, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, nitro, $-NR^{24}R^{25}$, $-OR^{26}$, $-S(O)_nR^{27}$, C_3 - C_{10} cycloalkyl, C_6 - C_{10} aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein the alkylcarbonyl, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A^5 ;

R^{21} , R^{22} , and R^{23} are independently selected from the group consisting of a hydrogen atom, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_{10} cycloalkyl, C_6 - C_{10} aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A^5 ; or R^{22} and R^{23} together with the nitrogen atom to which they are attached form 3- to 10-membered nitrogen-containing heterocyclyl, which is optionally substituted with one or more substituents independently selected from A^5 ;

R^{24} and R^{26} are independently selected from the group consisting of a hydrogen atom, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_{10} cycloalkyl, C_6 - C_{10} aryl, 5- to 10-membered heteroaryl, 3- to 10-membered non-aromatic heterocyclyl, and $-COR^{28}$; wherein the alkyl, alkenyl, alkynyl cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A^5 ; R^{25} is selected

from the group consisting of a hydrogen atom, and C₁-C₆ alkyl that is optionally substituted with one or more substituents independently selected from A⁵; or R²⁴ and R²⁵ together with the nitrogen atom to which they are attached form 3- to 10-membered nitrogen-containing heterocyclyl, which is optionally substituted with one or more substituents independently
 5 selected from A⁵;

R²⁷ is selected from the group consisting of C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, and 5- to 10-membered heteroaryl; wherein the alkyl, cycloalkyl, aryl, and heteroaryl are optionally substituted with one or more substituents independently selected from A⁵;

R²⁸ is independently selected from the group consisting of a hydrogen atom, -
 10 NR²²R²³, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A⁵;

A⁵ is independently selected from consisting of a halogen atom, cyano, -COOR³¹, -
 15 CONR³²R³³, formyl, (C₁-C₆ alkyl)carbonyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, nitro, -NR³⁴R³⁵, -OR³⁶, -S(O)_nR³⁷, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein the alkylcarbonyl, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A⁶;

R³¹, R³², and R³³ are independently selected from the group consisting of a
 20 hydrogen atom, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A⁶; or R³² and R³³
 25 together with the nitrogen atom to which they are attached form 3- to 10-membered nitrogen-containing heterocyclyl, which is optionally substituted with one or more substituents independently selected from A⁶;

R³⁴ and R³⁶ are independently selected from the group consisting of a hydrogen

atom, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, 3- to 10-membered non-aromatic heterocyclyl, and -COR³⁸; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A⁶; R³⁵ is selected

5 from the group consisting of a hydrogen atom, and C₁-C₆ alkyl that is optionally substituted with one or more substituents independently selected from A⁶; or R³⁴ and R³⁵ together with the nitrogen atom to which they are attached form 3- to 10-membered nitrogen-containing heterocyclyl, which is optionally substituted with one or more substituents independently selected from A⁶;

10 R³⁷ is selected from the group consisting of C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, and 5- to 10-membered heteroaryl; wherein the alkyl, cycloalkyl, aryl, and heteroaryl are optionally substituted with one or more substituents independently selected from A⁶;

R³⁸ is independently selected from the group consisting of a hydrogen atom, -NR³²R³³, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to

15 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from A⁶;

A⁶ is independently selected from consisting of a halogen atom, cyano, carboxy, -COOR⁴¹, -CONR⁴²R⁴³, formyl, (C₁-C₆ alkyl)carbonyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, nitro, -NR⁴⁴R⁴⁵, -OR⁴⁶, S(O)_nR⁴⁷, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-

20 membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein the alkylcarbonyl, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from the group consisting of a halogen atom, hydroxy, C₁-C₆ alkoxy, amino, C₁-C₆ alkylamino, and di(C₁-

25 C₆ alkyl)amino;

R⁴¹, R⁴², and R⁴³ are independently selected from the group consisting of a hydrogen atom, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl; wherein

the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents independently selected from the group consisting of a halogen atom, hydroxy, C₁-C₆ alkoxy, amino, C₁-C₆ alkylamino, and di(C₁-C₆ alkyl)amino;

5 R⁴⁴ and R⁴⁶ are independently selected from the group consisting of a hydrogen atom, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, 3- to 10-membered non-aromatic heterocyclyl, and -COR⁴⁸;

 R⁴⁵ is selected from the group consisting of a hydrogen atom, and C₁-C₆ alkyl;

 R⁴⁷ is selected from the group consisting of C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₆-C₁₀
10 aryl, and 5- to 10-membered heteroaryl; and

 R⁴⁸ is independently selected from the group consisting of C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered non-aromatic heterocyclyl.

2. The compound or a pharmaceutically acceptable salt thereof according to claim 1,
15 wherein Q¹ is selected from the group consisting of C₅-C₇ cycloalkyl, phenyl, pyridyl, pyrazolyl, pyrimidinyl, and piperidyl; wherein Q¹ is optionally substituted with one or more substituents independently selected from A¹.

3. The compound or a pharmaceutically acceptable salt thereof according to claim 1
or 2, wherein X² is selected from the group consisting of -CO- and -SO₂-; and R¹¹ is
20 selected from the group consisting of C₁-C₆ alkyl and C₃-C₇ cycloalkyl, which are optionally substituted with one or more substituents independently selected from the group consisting of hydroxy and a halogen atom.

4. The compound or a pharmaceutically acceptable salt thereof according to any one
of claims 1 to 3, wherein R⁵ is phenyl substituted with one to three substituents
25 independently selected from the group consisting of hydroxy, a halogen atom, C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein the alkyl and alkoxy are optionally substituted with one or more halogen atoms.

5. The compound or a pharmaceutically acceptable salt thereof according to any one

of claims 1 to 4, wherein R^2 is a hydrogen atom.

6. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein R^3 is a hydrogen atom.

7. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 6, wherein R^4 is a hydrogen atom.

8. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 7, wherein X^1 is -NH-.

9. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 8, wherein the optional substituent of Q^1 is selected from the group consisting of hydroxy, amino, C_1 - C_6 alkoxy, C_1 - C_6 alkylamino, di(C_1 - C_6 alkyl)amino, amino- C_1 - C_6 alkyl, (C_1 - C_6 alkylamino)- C_1 - C_6 alkyl, di(C_1 - C_6 alkyl)amino- C_1 - C_6 alkyl, amino- C_1 - C_6 alkoxy, (C_1 - C_6 alkylamino)- C_1 - C_6 alkoxy, di(C_1 - C_6 alkyl)amino- C_1 - C_6 alkoxy, hydroxy- C_1 - C_6 alkyl, (C_1 - C_6 alkoxy)- C_1 - C_6 alkyl, carboxy- C_1 - C_6 alkyl, [(C_1 - C_6 alkoxy)carbonyl]- C_1 - C_6 alkyl, carbamoyl- C_1 - C_6 alkyl, [N-(C_1 - C_6 alkyl) carbamoyl]- C_1 - C_6 alkyl, [N,N-di(C_1 - C_6 alkyl)carbamoyl]- C_1 - C_6 alkyl, (C_1 - C_6 alkyl)carbonylamino, N-(C_1 - C_6 alkyl)carbonyl-N-(C_1 - C_6 alkyl)amino, pyrrolidinyl, piperidyl, piperazinyl;

wherein the pyrrolidinyl, piperidyl, and piperazinyl defined as the optional substituent of Q^1 are optionally substituted with a substituent selected from the group consisting of C_1 - C_6 alkyl, amino, C_1 - C_6 alkylamino, di(C_1 - C_6 alkyl)amino, hydroxy, C_1 - C_6 alkoxy, pyrrolidinyl, piperidyl, and piperazinyl; and

wherein the alkyl moiety of the group defined as the optional substituent of Q^1 is optionally substituted with a substituent selected from the group consisting of amino, C_1 - C_6 alkylamino, di(C_1 - C_6 alkyl)amino, hydroxy, C_1 - C_6 alkoxy, pyrrolidinyl, piperidyl, and piperazinyl.

10. The compound or a pharmaceutically acceptable salt thereof according to claim 9, wherein the optional substituent of Q^1 is selected from the group consisting of hydroxy, amino, di(C_1 - C_6 alkyl)amino, C_1 - C_6 alkyl, di(C_1 - C_6 alkyl)amino- C_1 - C_6 alkyl, di(C_1 - C_6 alkyl)amino- C_1 - C_6 alkoxy, di(C_1 - C_6 alkyl)amino, [(amino- C_1 - C_6 alkyl)carbonyl]amino, N-

(C₁-C₆ alkyl)piperidyl, di(C₁-C₆ alkyl)amino-pyrrolidin-1-yl, amino-pyrrolidin-1-yl, (pyrrolidin-1-yl)-C₁-C₆ alkyl, (C₁-C₆ alkyl)amino-piperidin-1-yl, amino-piperidin-1-yl, hydroxy-C₁-C₆ alkyl, [di(C₁-C₆ alkyl)amino-C₁-C₆ alkyl]amino, [4-(C₁-C₆ alkyl)-piperazin-1-yl]-C₁-C₆ alkyl, (piperazin-1-yl)-C₁-C₆ alkyl, pyrrolidinylcarbonyl-amino, (hydroxy-pyrrolidin-1-yl)-C₁-C₆ alkyl, morpholino-C₁-C₆ alkyl, [N-(hydroxy-C₁-C₆ alkyl)-N-(C₁-C₆ alkyl)amino]-C₁-C₆ alkyl, and (CD₃)₂N-C₁-C₆ alkyl.

11. The compound or a pharmaceutically acceptable salt thereof according to claims 1 to 10, which is selected from the group consisting of the following compounds:

1-(6-chloro-4-(4-((dimethylamino)methyl) cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;

1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((4-(dimethylamino)cyclohexyl)amino)-1,5-naphthyridin-3-yl)ethanone;

1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-((4-(dimethylamino)cyclohexyl)amino)-1,5-naphthyridin-3-yl)ethanone;

cyclopropyl(6-(3,5-dichloro-4-hydroxyphenyl)-4-(4-((dimethylamino)methyl)-cyclohexylamino)-1,5-naphthyridin-3-yl)methanone;

(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(4-((dimethylamino)methyl)-cyclohexylamino)-1,5-naphthyridin-3-yl)(cyclopropyl)methanone;

1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((4-((dimethylamino)methyl)cyclohexyl)-amino)-1,5-naphthyridin-3-yl)ethanone;

1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-((4-((dimethylamino)methyl)cyclohexyl)-amino)-1,5-naphthyridin-3-yl)ethanone;

1-(6-(3-chloro-4-hydroxy-5-methoxyphenyl)-4-((4-((dimethylamino)methyl)-cyclohexyl)amino)-1,5-naphthyridin-3-yl)ethanone;

1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((4-(2-(dimethylamino)ethyl)cyclohexyl)-amino)-1,5-naphthyridin-3-yl)ethanone;

1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(4-(2-(dimethylamino)ethyl)-cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;

1-(4-(4-((dimethylamino)methyl)cyclohexylamino)-6-(4-hydroxy-3-(trifluoromethoxy)-phenyl)-1,5-naphthyridin-3-yl)ethanone;

2,6-dichloro-4-(8-((4-((dimethylamino)methyl)cyclohexyl)amino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)phenol;

5 2-chloro-4-(8-((4-((dimethylamino)methyl)cyclohexyl)amino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-fluorophenol;

2-chloro-4-(8-((4-((dimethylamino)methyl)cyclohexyl)amino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-methoxyphenol;

10 2,6-dichloro-4-(8-((4-(dimethylamino)cyclohexyl)amino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)phenol;

2,6-dichloro-4-(8-((4-((dimethylamino)methyl)phenyl)amino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)phenol;

2-chloro-4-(8-((4-((dimethylamino)methyl)phenyl)amino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-fluorophenol;

15 2-chloro-4-(8-((4-((dimethylamino)methyl)phenyl)amino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-methoxyphenol;

1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((3-(2-(pyrrolidin-1-yl)ethyl)phenyl)amino)-1,5-naphthyridin-3-yl)ethanone;

20 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(3-(2-(pyrrolidin-1-yl)ethyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone;

1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((6-(2-(dimethylamino)ethoxy)pyridin-3-yl)-amino)-1,5-naphthyridin-3-yl)ethanone;

1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-((6-(2-(dimethylamino)ethoxy)pyridin-3-yl)amino)-1,5-naphthyridin-3-yl)ethanone;

25 1-(6-(3-chloro-4-hydroxy-5-methoxyphenyl)-4-((6-(2-(dimethylamino)ethoxy)pyridin-3-yl)amino)-1,5-naphthyridin-3-yl)ethanone;

2,6-dichloro-4-(8-((6-(2-(dimethylamino)ethoxy)pyridin-3-yl)amino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)phenol;

- 2-chloro-4-(8-((6-(2-(dimethylamino)ethoxy)pyridin-3-yl)amino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-fluorophenol;
- 2-chloro-4-(8-((6-(2-(dimethylamino)ethoxy)pyridin-3-yl)amino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-methoxyphenol;
- 5 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((1-methylpiperidin-4-yl)methylamino)-1,5-naphthyridin-3-yl)ethanone;
- 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((4-((dimethylamino-d6)methyl)cyclohexyl)-amino)-1,5-naphthyridin-3-yl)ethanone;
- 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((4-(2-(dimethylamino)ethyl)phenyl)amino)-1,5-naphthyridin-3-yl)ethanone;
- 10 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-((4-(2-(dimethylamino)ethyl)phenyl)-amino)-1,5-naphthyridin-3-yl)ethanone;
- 1-(6-(3-chloro-4-hydroxy-5-methoxyphenyl)-4-((4-(2-(dimethylamino)ethyl)phenyl)-amino)-1,5-naphthyridin-3-yl)ethanone;
- 15 2-chloro-4-(8-((4-(dimethylamino)cyclohexyl)amino)-7-(methylsulfonyl)-1,5-naphthyridin-2-yl)-6-fluorophenol;
- 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)-amino)-1,5-naphthyridin-3-yl)ethanone;
- 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(4-((4-methylpiperazin-1-yl)methyl)-phenylamino)-1,5-naphthyridin-3-yl)ethanone;
- 20 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(4-((4-methylpiperazin-1-yl)methyl)-phenylamino)-1,5-naphthyridin-3-yl)ethanone;
- 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(4-(2-(pyrrolidin-1-yl)ethyl)piperidin-1-yl)-1,5-naphthyridin-3-yl)ethanone;
- 25 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(4-(2-(pyrrolidin-1-yl)ethyl)piperidin-1-yl)-1,5-naphthyridin-3-yl)ethanone;
- 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(6-(2-(dimethylamino)ethylamino)pyridin-3-ylamino)-1,5-naphthyridin-3-yl)ethanone;

1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(6-(2-(dimethylamino)ethylamino)-pyridin-3-ylamino)-1,5-naphthyridin-3-yl)ethanone;

(S)-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)(cyclopropyl)methanone;

5 1-(4-((2-(3-aminopyrrolidin-1-yl)pyrimidin-5-yl)amino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone;

1-(4-(4-((dimethylamino)methyl)cyclohexylamino)-6-(1H-pyrazol-4-yl)-1,5-naphthyridin-3-yl)ethanone;

10 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(4-(hydroxymethyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;

1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-{4-[(dimethylamino)methyl]-cyclohexylamino}-1,5-naphthyridin-3-yl]-2-hydroxyethanone;

1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(1-methylpiperidin-4-ylamino)-1,5-naphthyridin-3-yl)ethanone;

15 1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(1-methylpiperidin-4-ylamino)-1,5-naphthyridin-3-yl)ethanone;

1-{6-[3,5-dichloro-4-hydroxyphenyl]-4-[4-(morpholinomethyl)cyclohexylamino]-1,5-naphthyridin-3-yl}ethanone;

20 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(4-((2-hydroxyethyl)(methyl)amino)methyl)-cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;

1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(4-(((2-hydroxyethyl)(methyl)amino)methyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;

1-(6-(3,5-difluoro-4-hydroxyphenyl)-4-(4-((dimethylamino)methyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;

25 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((6-(3-(dimethylamino)pyrrolidin-1-yl)pyridin-3-yl)amino)-1,5-naphthyridin-3-yl)ethanone;

1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-((6-(3-(dimethylamino)pyrrolidin-1-yl)-pyridin-3-yl)amino)-1,5-naphthyridin-3-yl)ethanone;

1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(6-(3-(methylamino)pyrrolidin-1-yl)pyridin-3-ylamino)-1,5-naphthyridin-3-yl)ethanone;

1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(6-(3-(methylamino)pyrrolidin-1-yl)pyridin-3-ylamino)-1,5-naphthyridin-3-yl)ethanone;

5 1-(6-(1H-benzo[d]imidazol-5-yl)-4-(4-((dimethylamino)methyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;

1-(4-(4-((dimethylamino)methyl)cyclohexylamino)-6-(pyridin-4-yl)-1,5-naphthyridin-3-yl)ethanone;

5-(7-acetyl-8-(4-((dimethylamino)methyl)cyclohexylamino)-1,5-naphthyridin-2-yl)-pyrimidine-2-carbonitrile;

1-(6-(3,5-dimethyl-1H-pyrazol-4-yl)-4-(4-((dimethylamino)methyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;

1-(4-(4-((dimethylamino)methyl)cyclohexylamino)-6-(4-hydroxy-3,5-dimethylphenyl)-1,5-naphthyridin-3-yl)ethanone;

15 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(4-(pyrrolidin-1-ylmethyl)phenylamino)-1,5-naphthyridin-3-yl)ethanone;

1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(4-(pyrrolidin-1-ylmethyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;

1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(4-(pyrrolidin-1-ylmethyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;

1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(4-((4-methylpiperazin-1-yl)methyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;

1-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone;

25 1-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone;

1-(4-(4-aminocyclohexylamino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone;

1-[4-(4-aminocyclohexylamino)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl]ethanone;

1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-((4-methylpiperazin-1-yl)methyl)-cyclohexylamino)-1,5-naphthyridin-3-yl]ethanone;

5 N-(4-(3-acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino)-cyclohexyl)-2-amino-3-methylbutanamide;

1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(4-(piperazin-1-ylmethyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;

10 (S)-1-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone;

(S)-1-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone;

N-(4-((3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-yl)amino)cyclohexyl)-2-aminopropanamide;

15 N-(4-(3-acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino)-cyclohexyl)-2-aminopropanamide;

(S)-N-((1R,4S)-4-(3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino)cyclohexyl)pyrrolidine-2-carboxamide;

20 (S)-N-((1R,4S)-4-(3-acetyl-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino)cyclohexyl)pyrrolidine-2-carboxamide;

1-(6-(3-hydroxypyrrolidin-1-yl)-4-((3-hydroxypyrrolidin-1-yl)methyl)cyclohexylamino)-1,5-naphthyridin-3-yl]ethanone;

1-(6-(pyrrolidin-1-yl)-4-(4-(pyrrolidin-1-ylmethyl)cyclohexylamino)-1,5-naphthyridin-3-yl)ethanone;

25 N-(4-(3-acetyl-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-4-ylamino)-cyclohexyl)-2-amino-3-methylbutanamide;

[6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-[4-(dimethylamino)cyclohexylamino]-1,5-naphthyridin-3-yl](cyclopropyl)methanone;

cyclopropyl[6-(3,5-dichloro-4-hydroxyphenyl)-4-[4-(dimethylamino)cyclohexylamino]-1,5-naphthyridin-3-yl]methanone;

1-(4-{4-[(dimethylamino)methyl]cyclohexylamino}-6-(1H-pyrrolo[2,3-b]pyridin-5-yl)-1,5-naphthyridin-3-yl)ethanone;

5 (S)-{4-[6-(3-aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}(cyclopropyl)methanone;

1-(4-{4-[(dimethylamino)methyl]cyclohexyl amino}-6-(4-methoxyphenyl)-1,5-naphthyridin-3-yl)ethanone;

1-[6-(3,5-dichloro-4-methoxyphenyl)-4-{4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl]ethanone;

1-(4-{4-[(dimethylamino)methyl]cyclohexylamino}-6-(6-hydroxypyridin-3-yl)-1,5-naphthyridin-3-yl)ethanone;

5-(7-acetyl-8-{4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-2-yl)picolinonitrile;

15 1-(4-{4-[(dimethylamino)methyl]cyclohexylamino}-6-(4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone;

1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-{[4-(dimethylamino)cyclohexyl]methylamino}-1,5-naphthyridin-3-yl)ethanone;

1-[6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-{[4-(dimethylamino)cyclohexyl]methylamino}-1,5-naphthyridin-3-yl]ethanone;

1-[6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(4-hydroxycyclohexylamino)-1,5-naphthyridin-3-yl]ethanone;

1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-(4-hydroxycyclohexylamino)-1,5-naphthyridin-3-yl]ethanone;

25 1-[6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-{*cis*-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl]ethanone;

1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-{*cis*-4-[(dimethylamino)methyl]cyclohexyl amino}-1,5-naphthyridin-3-yl]ethanone;

(R)-1-{4-[6-(3-aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}ethanone;

(R)-1-{4-[6-(3-aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl}ethanone;

5 and pharmaceutically acceptable salts thereof.

12. The compound or a pharmaceutically acceptable salt thereof according to claim 1, which is selected from the group consisting of the following compounds:

1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-(*trans*-4-(dimethylamino)cyclohexyl)amino)-1,5-naphthyridin-3-yl)ethanone;

10 cyclopropyl (6-(3,5-dichloro-4-hydroxyphenyl)-4-(*trans*-4-((dimethylamino)methyl)-cyclohexylamino)-1,5-naphthyridin-3-yl) methanone;

(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-(*trans*-4-((dimethylamino)methyl)-cyclohexylamino)-1,5-naphthyridin-3-yl) (cyclopropyl) methanone;

15 1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((*trans*-4-((dimethylamino)methyl)cyclohexyl)-amino)-1,5-naphthyridin-3-yl) ethanone;

1-(6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-((*trans*-4-((dimethylamino)methyl)-cyclohexyl)amino)-1,5-naphthyridin-3-yl) ethanone;

1-(6-(3,5-dichloro-4-hydroxyphenyl)-4-((*trans*-4-(2-(dimethylamino)ethyl)cyclohexyl)-amino)-1,5-naphthyridin-3-yl) ethanone;

20 (S)-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)(cyclopropyl)methanone;

1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-{*trans*-4-[(dimethylamino)methyl]cyclohexylamino}-1,5-naphthyridin-3-yl]-2-hydroxyethanone;

25 1-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone;

1-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)ethanone;

(S)-1-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3,5-dichloro-4-hydroxy-

phenyl)-1,5-naphthyridin-3-yl)ethanone;

(S)-1-(4-(6-(3-aminopiperidin-1-yl)pyridin-3-ylamino)-6-(3-chloro-5-fluoro-4-hydroxy-phenyl)-1,5-naphthyridin-3-yl)ethanone;

(S)-{4-[6-(3-aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3-chloro-5-fluoro-4-hydroxy-phenyl)-1,5-naphthyridin-3-yl} (cyclopropyl) methanone;

(R)-1-{4-[6-(3-aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3,5-dichloro-4-hydroxy-phenyl)-1,5-naphthyridin-3-yl} ethanone;

(R)-1-{4-[6-(3-aminopiperidin-1-yl)pyridin-3-ylamino]-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl} ethanone;

(R)-(4-[[6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino]-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl) (cyclopropyl)methanone;

(R)-(4-[[6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino]-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl) (cyclopropyl) methanone;

1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-{{trans-4-(dimethylamino)cyclohexyl} amino})-1,5-naphthyridin-3-yl]-2-hydroxyethanone dihydrochloride;

1-[6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-({trans-4-[(dimethylamino)methyl]cyclohexyl} amino)-1,5-naphthyridin-3-yl]-2-hydroxyethanone dihydrochloride;

1-[6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-({trans-4-[(dimethylamino)methyl] cyclohexyl} amino)-1,5-naphthyridin-3-yl]]propan-1-one dihydrochloride;

1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-({trans-4-[(dimethylamino)methyl] cyclohexyl} amino)-1,5-naphthyridin-3-yl]]propan-1-one dihydrochloride;

(S)-1-(4-[[6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino]-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)propan-1-one trihydrochloride;

(S)-1-(4-[[6-(3-aminopiperidin-1-yl)pyridin-3-yl]amino]-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)propan-1-one trihydrochloride;

1-[6-(3,5-dichloro-4-hydroxyphenyl)-4-({4-[(R)-3-fluoropyrrolidin-1-yl)methyl] cyclohexyl} amino)-1,5-naphthyridin-3-yl]ethanone dihydrochloride;

(S)-(4-((6-(3-aminopiperidin-1-yl)pyridin-3-yl)amino)-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)(cyclobutyl)methanone dihydrochloride;

(6-(3,5-dichloro-4-hydroxyphenyl)-4-((4-[(dimethylamino)methyl(cyclohexyl)amino)-1,5-naphthyridin-3-yl](cyclobutyl)methanone dihydrochloride;

5 (6-(3-chloro-5-fluoro-4-hydroxyphenyl)-4-((4-[(dimethylamino)methyl(cyclohexyl)amino)-1,5-naphthyridin-3-yl](cyclobutyl)methanone dihydrochloride;

(S)-(4-{{6-(3-aminopiperidin-1-yl)pyridin-3-yl}amino}-6-(3-chloro-5-fluoro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)(cyclobutyl)methanone;

10 (R)-1-(4-((6-(3-aminopiperidin-1-yl)pyridin-3-yl)amino)-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)propan-1-one trihydrochloride;

(R)-1-(4-{{6-(3-aminopiperidin-1-yl)pyridin-3-yl}amino}-6-(3,5-dichloro-4-hydroxyphenyl)-1,5-naphthyridin-3-yl)-2-methylpropan-1-one trihydrochloride;

15 1-[6-(3,5-dichloro-5,4-hydroxyphenyl)-4-({trans-4-[(dimethylamino)methyl(cyclohexyl)amino)-1,5-naphthyridin-3-yl]}-2-methylpropan-1-one dihydrochloride;

1-[6-chloro-4-({trans-4-[(dimethylamino)methyl(cyclohexyl)amino)-1,5-naphthyridin-3-yl]}-2-methylpropan-1-one dihydrochloride;

and pharmaceutically acceptable salts thereof.

20 13. A pharmaceutical composition comprising as an active ingredient a compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 12.

14. An MELK inhibitor comprising as an active ingredient a compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 12.

15. An MELK-expression modulating agent comprising as an active ingredient a
25 compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 12.

16. An antitumor agent comprising as an active ingredient a compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 12.

17. A therapeutic and/or preventive agent for a disease that involves overexpression of MELK, comprising as an active ingredient a compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 12.

18. The therapeutic and/or preventive agent according to claim 17, wherein the disease
5 is cancer.

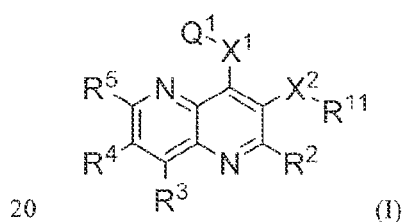
19. The therapeutic and/or preventive agent according to claim 17, wherein the cancer is selected from the group consisting of breast cancer, lung cancer, bladder cancer, lymphoma, and uterine cancer.

20. A method for treating and/or preventing a disease that involves overexpression of MELK, which comprises administering an effective amount of a compound or a
10 pharmaceutically acceptable salt thereof according to any one of claims 1 to 12 to a subject in need thereof.

21. A compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 11 for use in a treatment and/or prevention of a disease that involves
15 overexpression of MELK.

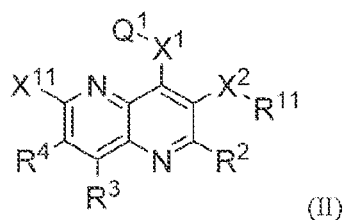
22. Use of a compound or a pharmaceutically acceptable salt thereof according to any one of above-mentioned 1 to 12 in the manufacture of a therapeutic and/or preventive agent for a disease that involves overexpression of MELK.

23. A process for preparing a compound of formula (I):

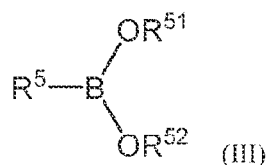


or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 12, wherein R⁵ is phenyl optionally substituted with one or more substituents independently selected from A³; and Q¹, X¹, X², R¹¹, R², R³, R⁴, and A³ are the groups as defined in any one of claims 1 to 10; which comprises:

reacting a compound represented by formula (II):



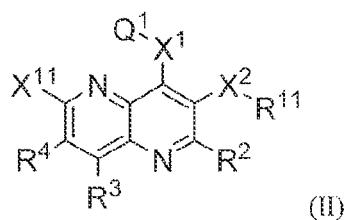
wherein Q^1 , X^1 , X^2 , R^{11} , R^2 , R^3 , and R^4 are the groups as defined above, with the proviso that the groups may have one or more protecting groups, and X^{11} is a halogen atom; with a
 5 compound represented by formula (III):



wherein R^5 is as defined above with the proviso that the group of R^5 may have one or more protecting groups; and R^{51} and R^{52} are independently selected from the group consisting of C_1 - C_6 alkyl, or R^{51} and R^{52} together with the boron atom to which they are attached forms

10 5- to 7-membered cyclic boronic acid ester optionally substituted with one or more substituents independently selected from the group consisting of C_1 - C_6 alkyl.

24. A compound represented by formula (II) or a pharmaceutically acceptable salt thereof:



15 wherein Q^1 , X^1 , X^2 , R^{11} , R^2 , R^3 , and R^4 are the groups as defined in one of claims 1 to 10 with the proviso that the groups may have one or more protecting groups, and X^{11} is a halogen atom.