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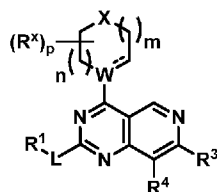
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(54) Title: HETEROCYCLIC COMPOUNDS AND METHODS OF USE

FORMULA (i)



(57) Abstract: The present disclosure provides compounds useful for the inhibition of KRAS G12D. The compounds have a general Formula (I) : wherein the variables of Formula I are defined herein. This disclosure also provides pharmaceutical compositions comprising the compounds, uses of the compounds, and compositions for treatment of, for example, cancer.



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HETEROCYCLIC COMPOUNDS AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application No. 63/231,543, filed August 10, 2021 and U.S. Provisional Patent Application No. 63/289,579, filed December 14, 2021, each of which is incorporated by reference in its entirety.

FIELD

The present disclosure provides compounds having activity as inhibitors of G12D mutant KRAS protein. This disclosure also provides pharmaceutical compositions comprising the compounds, uses and methods of treating certain disorders, such as cancer, including but not limited to Non-Small Cell Lung Cancer (NSCLC), colorectal cancer and/or pancreatic cancer.

BACKGROUND

From its identification as one of the first human oncogenes in 1982 (Der et al., 1982), KRAS (the Kirsten rat sarcoma viral oncogene homologue) has been the focus of extensive academic and industrial research, as a key node in the MAPK signal transduction pathway, as a transforming factor in a network of parallel effector pathways (e.g., PI3K/AKT) (Vojtek et al., 1998) and as a potential target for anti-cancer agents (Malumbres et al., 2003). Despite progress in the development of inhibitors of upstream and downstream nodes in the MAPK pathway (e.g., EGFR (Sridhar et al., 2003), BRAF (Holderfield et al., 2014) and MOK (Caunt et al., 2015), the KRAS protein has historically proven resistant to direct inhibition.

KRAS is a G-protein that couples extracellular mitogenic signaling to intracellular, pro-proliferative responses. KRAS serves as an intracellular “on/off” switch. Mitogen stimulation induces the binding of GTP to KRAS, bringing about a conformational change which enables the interaction of KRAS with downstream effector proteins, leading to cellular proliferation. Normally, pro-proliferative signaling is regulated by the action of GTPase-activating proteins (GAPs), which return KRAS to its GDP-bound, non-proliferative state. Mutations in KRAS impair the regulated cycling of KRAS between these GDP- and GTP-bound states, leading to the accumulation of the GTP-bound active state and dysregulated cellular proliferation (Simanshu et al., 2017).

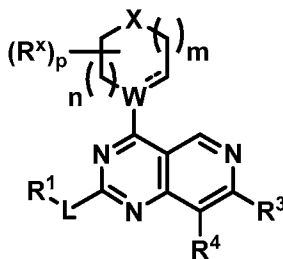
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Attempts to develop inhibitors of mutated KRAS proteins have historically been thwarted by the absence of druggable pockets on the surface of the protein (Cox et al., 2014). In 2013, Shokat and colleagues identified covalent inhibitors of a common (O'Bryan, 2019) oncogenic mutant of KRAS, KRAS G12C, which bound to a previously unrecognized
 5 allosteric pocket on GDP-KRAS G12C and prevented its subsequent activation (Ostream et al., 2013). This discovery brought about significant new efforts in the KRAS inhibitor research, which have recently culminated in the entry of KRAS inhibitors in human clinical trials.

While some progress has been made on KRAS G12C inhibitors, there is a continued
 10 interest and effort to develop inhibitors of KRAS, particularly inhibitors of other KRAS such as KRAS G12D, G12V, G12A or G12S. Thus, there is a need to develop new inhibitors for KRAS G12D, G12V, G12A, G12S or G12C for the treatment of disorders, such as cancer.

SUMMARY

In one aspect, the present application is directed to compound of formula (I):



(I)

or a pharmaceutically acceptable salt of said compound, wherein;

--- is a single bond or a double bond;

W is C, CH or N, wherein when W is CH or N, --- is a single bond;

20 X is CH₂ or CH=CH;

n is 0, 1 or 2;

m is 0, 1 or 2;

p is 0, 1, 2, 3 or 4;

each R^x is hydroxyl, halogen, oxo, cyano, -N(R^z)₂, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄

25 haloalkyl, C₁₋₄ haloalkoxy, C₃₋₆ cycloalkyl, 5-7 membered heteroaryl, -T-R^y or two R^x taken together with adjacent carbon atoms can form C₃₋₇ cycloalkyl, a 5-7 membered

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heterocycloalkyl, wherein each C₃₋₇ cycloalkyl or 5-7 membered heterocycloalkyl is further substituted with 0-3 occurrences of R^y or two R^x taken together can form a bridged ring where the bridge is selected from one of the following: -C₁₋₄ alkylene, -C₁₋₄ alkylene-O-C₁₋₄ alkylene-, -O-, -S- or -C₁₋₄ alkylene-S-C₁₋₄ alkylene- and wherein each C₁₋₄ alkylene is further substituted with 0-2 occurrences of R^y;

L is C₁₋₆ alkylene, -O-C₁₋₆ alkylene, -S-C₁₋₆ alkylene, NR^z, O or S, wherein each C₁₋₆ alkylene, -O-C₁₋₆ alkylene and -S-C₁₋₆ alkylene chain is substituted with 0-2 occurrences of R²;

R¹ is hydroxyl, aryl, heteroaryl, C₃₋₈ cycloalkyl or heterocycloalkyl substituted with 0-3 occurrences of R⁵;

R² is halogen, hydroxyl, C₁₋₄ alkyl or two R² on the same or adjacent carbon atoms can be taken together to form a C₃₋₇ cycloalkyl;

R³ is aryl or heteroaryl substituted with 0-3 occurrences of R⁶;

R⁴ is hydrogen, hydroxyl, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₇ cycloalkyl or cyano;

each R⁵ is halogen, oxo, hydroxyl, amino or C₁₋₄ alkyl;

each R⁶ is halogen, hydroxyl, cyano, -N(R^z)₂, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₂₋₄ alkynyl or C₃₋₆ cycloalkyl;

T is C₁₋₄ alkylene, -S(O)₂-, -C(O)-, -C₁₋₄ alkylene-C(O)-, -N(H)-C(O)-, -N(H)-S(O)₂-, C₁₋₄ alkylene-S(O)₂- or -S-;

R^y is halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, hydroxyl, cyano or -N(R^z)₂; and

R^z is hydrogen or C₁₋₄ alkyl.

In a second aspect, provided herein is a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt of said compound and a pharmaceutically acceptable excipient.

In a third aspect, provided herein is a compound of Formula I, or a pharmaceutically acceptable salt of said compound, or the pharmaceutical composition as described herein for use in treating cancer (e.g., NSCLC, colorectal cancer or pancreatic cancer).

Reference will now be made in detail to embodiments of the present disclosure.

While certain embodiments of the present disclosure will be described, it will be understood that it is not intended to limit the embodiments of the present disclosure to those described

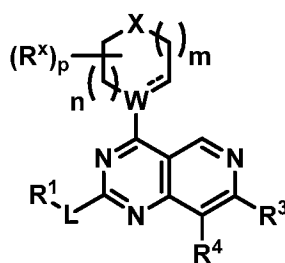
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embodiments. To the contrary, reference to embodiments of the present disclosure is intended to cover alternatives, modifications, and equivalents as may be included within the spirit and scope of the embodiments of the present disclosure as defined by the appended claims.

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DETAILED DESCRIPTION

Provided herein as embodiment 1 is a compound of formula (I):



(I)

or a pharmaceutically acceptable salt of said compound, wherein;

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--- is a single bond or a double bond;

W is C, CH or N, wherein when W is CH or N, --- is a single bond;

X is CH₂ or CH=CH;

n is 0, 1 or 2;

m is 0, 1 or 2;

15

p is 0, 1, 2, 3 or 4;

each R^x is hydroxyl, halogen, oxo, cyano, -N(R^z)₂, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄

haloalkyl, C₁₋₄ haloalkoxy, C₃₋₆ cycloalkyl, 5-7 membered heteroaryl, -T-R^y or two R^x taken

together with adjacent carbon atoms can form C₃₋₇ cycloalkyl, a 5-7 membered

heterocycloalkyl, wherein each C₃₋₇ cycloalkyl or 5-7 membered heterocycloalkyl is further

20

substituted with 0-3 occurrences of R^y or two R^x taken together can form a bridged ring

where the bridge is selected from one of the following: -C₁₋₄ alkylene, -C₁₋₄ alkylene-O-C₁₋₄

alkylene-, -O-, -S- or -C₁₋₄ alkylene-S-C₁₋₄ alkylene- and wherein each C₁₋₄ alkylene is further

substituted with 0-2 occurrences of R^y;

L is C₁₋₆ alkylene, -O-C₁₋₆ alkylene, -S-C₁₋₆ alkylene, NR^z, O or S, wherein each C₁₋₆

25

alkylene, -O-C₁₋₆ alkylene and -S-C₁₋₆ alkylene chain is substituted with 0-2 occurrences of

R^z;

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R¹ is hydroxyl, aryl, heteroaryl, C₃₋₈ cycloalkyl or heterocycloalkyl substituted with 0-3 occurrences of R⁵;

R² is halogen, hydroxyl, C₁₋₄ alkyl or two R² on the same or adjacent carbon atoms can be taken together to form a C₃₋₇ cycloalkyl;

5 R³ is aryl or heteroaryl substituted with 0-3 occurrences of R⁶;

R⁴ is hydrogen, hydroxyl, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₇ cycloalkyl or cyano;

each R⁵ is halogen, oxo, hydroxyl, amino or C₁₋₄ alkyl;

each R⁶ is halogen, hydroxyl, cyano, -N(R^z)₂, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, 10 C₁₋₄ haloalkoxy, C₂₋₄ alkynyl or C₃₋₆ cycloalkyl;

T is C₁₋₄ alkylene, -S(O)₂-, -C(O)-, -C₁₋₄ alkylene-C(O)-, -N(H)-C(O)-, -N(H)-S(O)₂-, C₁₋₄ alkylene-S(O)₂- or -S-;

R^y is halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, hydroxyl, cyano or -N(R^z)₂; and

R^z is hydrogen or C₁₋₄ alkyl.

15 Provided herein as embodiment 2 is the compound according to embodiment 1, wherein L is C₁₋₆ alkylene (e.g., methylene or ethylene) substituted with 0-2 occurrences of R². Provided herein as embodiment 3 is the compound according to embodiment 1, wherein L is -O-C₁₋₆ alkylene (e.g., -O-methylene-, -O-ethylene- or -O-*n*-propylene) substituted with 0-2 occurrences of R². Provided herein as embodiment 4 is the compound according to 20 embodiment 3, wherein L is -O-ethylene or -O-*n*-propylene substituted with 0-2 occurrences of R². Provided herein as embodiment 5 is the compound according to embodiment 4, wherein L is -O-ethylene substituted with 0 occurrences of R².

Provided herein as embodiment 6 is the compound according to any one of embodiments 1-5, wherein R¹ is heterocycloalkyl substituted with 0-3 occurrences of R⁵.

25 Provided herein as embodiment 7 is the compound according to embodiment 6, wherein R¹ is 7-(hexahydro-1H-pyrrolizine) substituted with 0-3 occurrences of R⁵. Provided herein as embodiment 8 is the compound according to embodiment 7, wherein R¹ is 7-(hexahydro-1H-pyrrolizine) substituted with 0 occurrences of R⁵. Provided herein as embodiment 9 is the compound according to embodiment 7, wherein R¹ is 7-(hexahydro-1H-pyrrolizine) 30 substituted with 1 occurrence of R⁵. Provided herein as embodiment 10 is the compound according to embodiment 9, wherein R⁵ is halogen (e.g., fluorine).

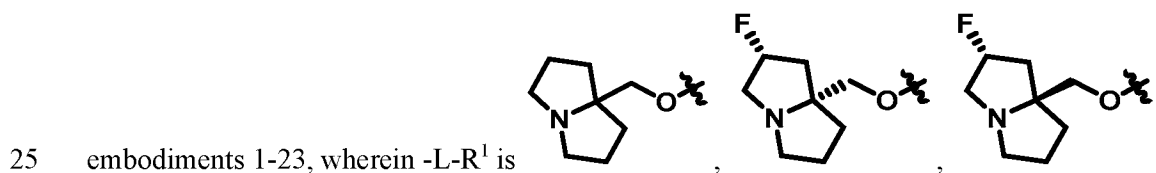
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Provided herein as embodiment 11 is the compound according to embodiment 6, wherein R^1 is 2-pyrrolidine or 3-pyrrolidine substituted with 0-3 occurrences of R^5 . Provided herein as embodiment 12 is the compound according to embodiment 11, wherein R^1 is 3-pyrrolidine substituted with 1 occurrence of R^5 . Provided herein as embodiment 13 is the compound according to embodiment 12, wherein R^5 is cyano. Provided herein as embodiment 14 is the compound according to embodiment 11, wherein R^1 is 3-pyrrolidine substituted with 2 occurrences of R^5 . Provided herein as embodiment 15 is the compound according to embodiment 14, wherein one R^5 is methyl and the other R^5 is cyano.

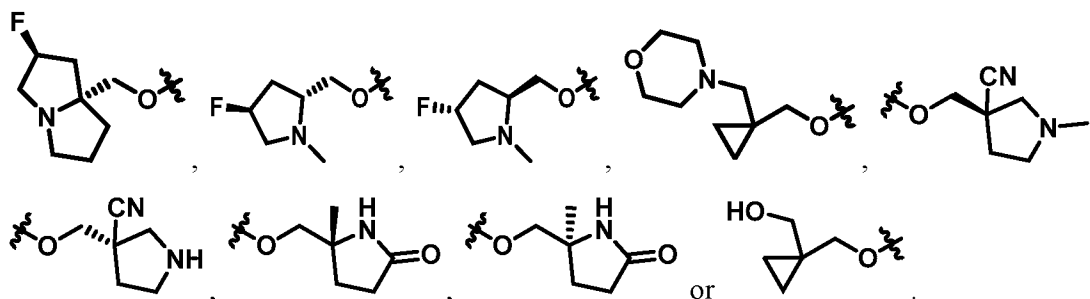
Provided herein as embodiment 16 is the compound according to embodiment 11, wherein R^1 is 2-pyrrolidine substituted with 2 occurrences of R^5 . Provided herein as embodiment 17 is the compound according to embodiment 16, wherein R^5 is C_{1-4} alkyl (e.g., methyl), oxo, cyano or halogen (e.g., fluorine). Provided herein as embodiment 18 is the compound according to embodiment 16, wherein one R^5 is methyl and the other R^5 is fluorine. Provided herein as embodiment 19 is the compound according to embodiment 16, wherein one R^5 is methyl and the other R^5 is oxo.

Provided herein as embodiment 20 is the compound according to embodiment 3, wherein L is -O-*n*-propylene substituted with 2 occurrences of R^2 . Provided herein as embodiment 21 is the compound according to embodiment 20, wherein the two R^2 are taken together with the same carbon atom to form a C_{3-7} cycloalkyl (e.g., cyclopropyl). Provided herein as embodiment 22 is the compound according to embodiment 21, wherein R^1 is heterocycloalkyl (e.g., N-morpholinyl) substituted with 0-3 occurrences of R^5 . Provided herein as embodiment 23 is the compound according to embodiment 21, wherein R^1 is hydroxyl.

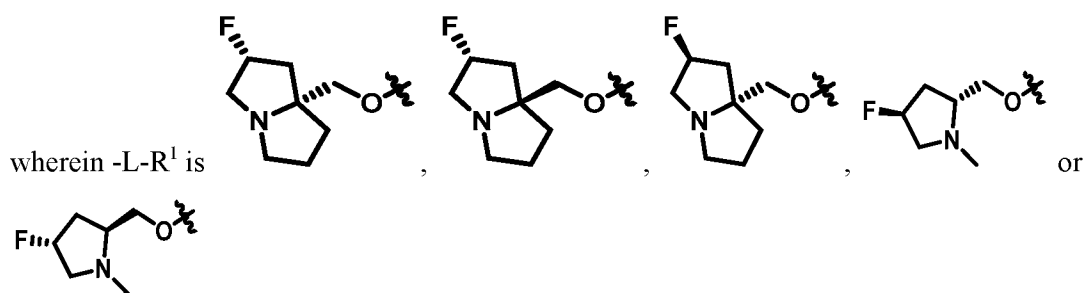
Provided herein as embodiment 24 is the compound according to any one of



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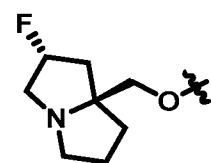
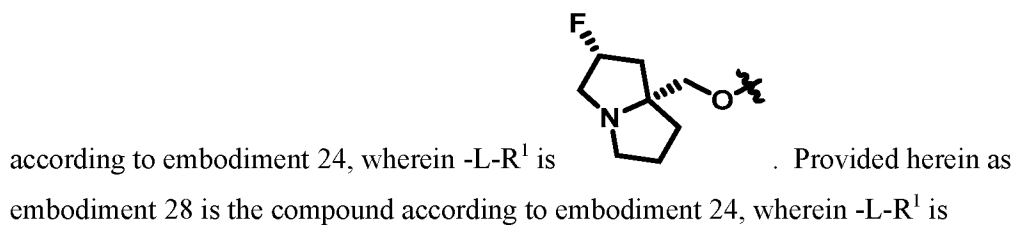
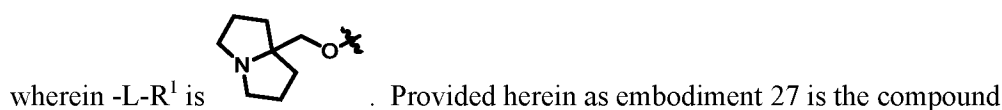


Provided herein as embodiment 25 is the compound according to embodiment 24,



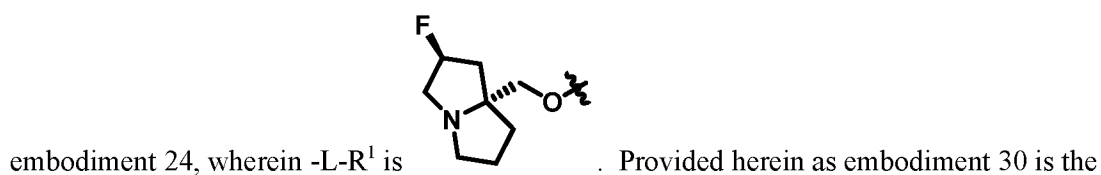
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Provided herein as embodiment 26 is the compound according to embodiment 24,



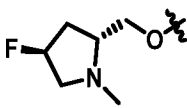
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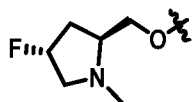
Provided herein as embodiment 29 is the compound according to



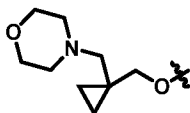
Provided herein as embodiment 30 is the

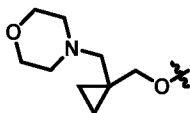
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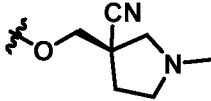
compound according to embodiment 24, wherein -L-R¹ is . Provided herein as embodiment 31 is the compound according to embodiment 24, wherein -L-R¹ is

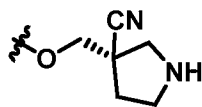


. Provided herein as embodiment 32 is the compound according to

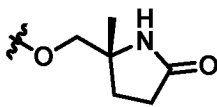


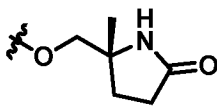
embodiment 24, wherein -L-R¹ is . Provided herein as embodiment 33 is the

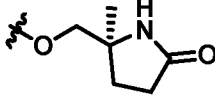
5 compound according to embodiment 24, wherein -L-R¹ is . Provided herein as embodiment 34 is the compound according to embodiment 24, wherein -L-R¹ is



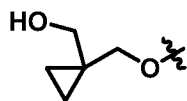
. Provided herein as embodiment 35 is the compound according to



embodiment 24, wherein -L-R¹ is . Provided herein as embodiment 36 is

the compound according to embodiment 24, wherein -L-R¹ is . Provided

10 herein as embodiment 37 is the compound according to embodiment 24, wherein -L-R¹ is



Provided herein as embodiment 38 is the compound according to any one of embodiments 1-37, wherein R³ is aryl (e.g., phenyl or naphthyl) substituted with 0-3 occurrences of R⁶.

15 Provided herein as embodiment 39 is the compound according to any one of embodiments 1-37, wherein R³ is naphthyl substituted with 1 occurrence of R⁶. Provided herein as embodiment 40 is the compound according to embodiment 39, wherein R⁶ is halogen, amino, C₁₋₄ alkyl (e.g., methyl), C₁₋₄ haloalkyl (e.g., trifluoromethyl or

difluoromethyl), hydroxyl or C₂₋₄ alkynyl (e.g., ethynyl). Provided herein as embodiment 41 is the compound according to embodiment 40, wherein R⁶ is hydroxyl.

Provided herein as embodiment 42 is the compound according to embodiment 38, wherein R³ is naphthyl substituted with 2 occurrences of R⁶. Provided herein as embodiment 43 is the compound according to embodiment 42, wherein R⁶ is C₁₋₄ alkyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, halogen, hydroxyl or -N(R^z)₂. Provided herein as embodiment 44 is the compound according to embodiment 43, wherein R⁶ is ethyl, ethynyl, cyclopropyl, fluorine, chlorine, hydroxyl or -NH₂. Provided herein as embodiment 45 is the compound according to embodiment 43, wherein one R⁶ is ethynyl and the other R⁶ is hydroxyl. Provided herein as embodiment 46 is the compound according to embodiment 43, wherein one R⁶ is ethyl and the other R⁶ is hydroxyl. Provided herein as embodiment 47 is the compound according to embodiment 43, wherein one R⁶ is ethyl and the other R⁶ is fluorine. Provided herein as embodiment 48 is the compound according to embodiment 43, wherein both R⁶ are fluorine. Provided herein as embodiment 49 is the compound according to embodiment 43, wherein one R⁶ is cyclopropyl and the other R⁶ is hydroxyl. Provided herein as embodiment 50 is the compound according to embodiment 43, wherein one R⁶ is fluorine and the other R⁶ is hydroxyl. Provided herein as embodiment 51 is the compound according to embodiment 43, wherein one R⁶ is chlorine and the other R⁶ is -NH₂. Provided herein as embodiment 52 is the compound according to embodiment 43, wherein one R⁶ is ethynyl and the other R⁶ is fluorine.

Provided herein as embodiment 53 is the compound according to embodiment 38, wherein R³ is naphthyl substituted with 3 occurrences of R⁶. Provided herein as embodiment 54 is the compound according to embodiment 53, wherein R⁶ is C₁₋₄ alkyl, C₂₋₄ alkynyl, halogen or hydroxyl. Provided herein as embodiment 55 is the compound according to embodiment 54, wherein R⁶ is ethyl, ethynyl, fluorine or hydroxyl. Provided herein as embodiment 56 is the compound according to embodiment 54, wherein one R⁶ is hydroxyl, another R⁶ is ethyl and the final R⁶ is fluorine. Provided herein as embodiment 57 is the compound according to embodiment 54, wherein one R⁶ is hydroxyl, another R⁶ is ethynyl and the final R⁶ is fluorine. Provided herein as embodiment 58 is the compound according to embodiment 54, wherein two R⁶ are halogen (e.g., fluorine or chlorine) and the other R⁶ is hydroxy.

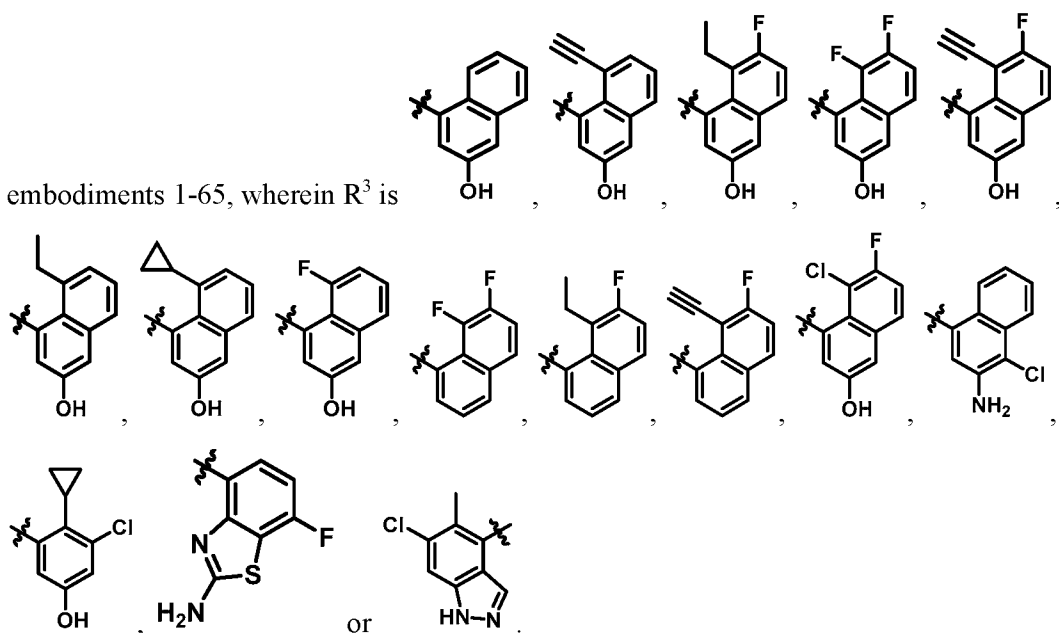
- 10 -

Provided herein as embodiment 59 is the compound according to embodiment 38, wherein R^3 is phenyl substituted with 3 occurrences of R^6 . Provided herein as embodiment 60 is the compound according to embodiment 59, wherein one R^6 is hydroxyl, another R^6 is cyclopropyl and the final R^6 is chlorine.

- 5 Provided herein as embodiment 61 is the compound according to any one of embodiments 1-37, wherein R^3 is heteroaryl (e.g., 4-(1*H*-indazole) or 4-benzo[d]thiazolyl) substituted with 0-3 occurrences of R^6 . Provided herein as embodiment 62 is the compound according to embodiment 61, wherein R^3 is 4-(1*H*-indazole) substituted with 2 occurrences of R^6 . Provided herein as embodiment 63 is the compound according to embodiment 62,
- 10 wherein one R^6 is methyl and the other R^6 is chlorine. Provided herein as embodiment 64 is the compound according to embodiment 61, wherein R^3 is 4-benzo[d]thiazolyl substituted with 2 occurrences of R^6 . Provided herein as embodiment 65 is the compound according to embodiment 64, wherein one R^6 is fluorine and the other R^6 is $-NH_2$.

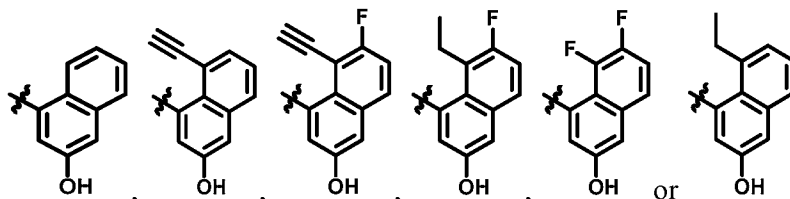
Provided herein as embodiment 66 is the compound according to any one of

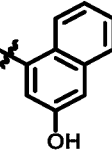
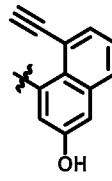
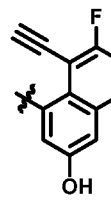
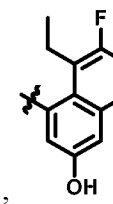
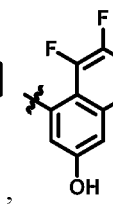
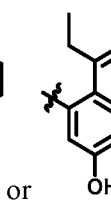
15 embodiments 1-65, wherein R^3 is

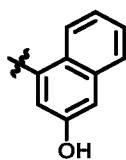


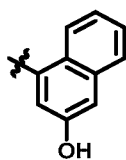
- 11 -

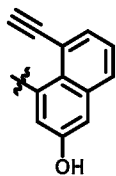
Provided herein as embodiment 67 is the compound according to embodiment 66,

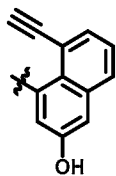


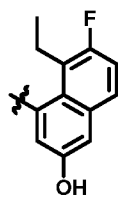
wherein R^3 is , , , ,  or . Provided herein as embodiment 68 is the compound according to embodiment 66, wherein R^3 is

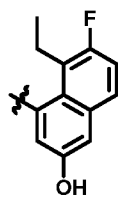


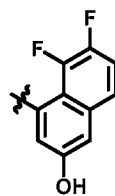
. Provided herein as embodiment 69 is the compound according to embodiment

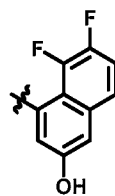


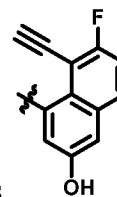
5 66, wherein R^3 is . Provided herein as embodiment 70 is the compound according

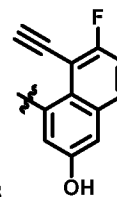


to embodiment 66, wherein R^3 is . Provided herein as embodiment 71 is the



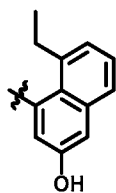
compound according to embodiment 66, wherein R^3 is . Provided herein as



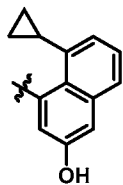
embodiment 72 is the compound according to embodiment 66, wherein R^3 is .

Provided herein as embodiment 73 is the compound according to embodiment 66, wherein R^3

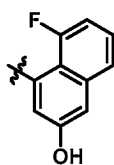
- 12 -



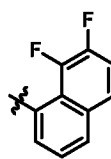
is . Provided herein as embodiment 74 is the compound according to embodiment



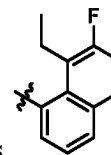
66, wherein R^3 is . Provided herein as embodiment 75 is the compound according



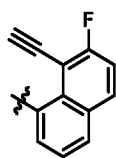
to embodiment 66, wherein R^3 is . Provided herein as embodiment 76 is the



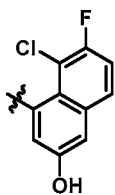
compound according to embodiment 66, wherein R^3 is . Provided herein as



- 5 embodiment 77 is the compound according to embodiment 66, wherein R^3 is .
 Provided herein as embodiment 78 is the compound according to embodiment 66, wherein R^3

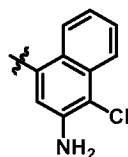


is . Provided herein as embodiment 79 is the compound according to embodiment

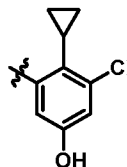


66, wherein R^3 is . Provided herein as embodiment 80 is the compound according

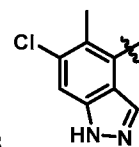
- 13 -



to embodiment 66, wherein R^3 is . Provided herein as embodiment 81 is the

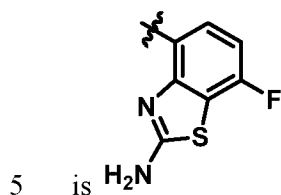


compound according to embodiment 66, wherein R^3 is . Provided herein as



embodiment 82 is the compound according to embodiment 66, wherein R^3 is

Provided herein as embodiment 83 is the compound according to embodiment 66, wherein R^3



5

is

Provided herein as embodiment 84 is the compound according to any one of
embodiments 1-83, wherein W is N and --- is a single bond.

Provided herein as embodiment 85 is the compound according to any one of
embodiments 1-84, wherein X is CH_2 .

10

Provided herein as embodiment 86 is the compound according to embodiment 85,
wherein n is 0 and m is 0. Provided herein as embodiment 87 is the compound according to
embodiment 86, wherein p is 1. Provided herein as embodiment 88 is the compound
according to embodiment 87, wherein R^x is 5-7 membered heteroaryl or $-\text{T-R}^y$. Provided
herein as embodiment 89 is the compound according to embodiment 87, wherein R^x is 5-7
15 membered heteroaryl substituted with 0-3 occurrences of R^y . Provided herein as embodiment
90 is the compound according to embodiment 89, wherein R^x is 1-imidazolyl substituted with
0 occurrences of R^y . Provided herein as embodiment 91 is the compound according to
embodiment 89, wherein $-\text{T-R}^y$ is $-\text{CH}_2\text{OH}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{S}(\text{O})_2\text{NH}_2$ or -
 $\text{S}(\text{O})_2\text{NH}_2$.

Provided herein as embodiment 92 is the compound according to embodiment 86, wherein p is 2. Provided herein as embodiment 93 is the compound according to embodiment 92, wherein each R^x is hydroxyl, C₁₋₄ alkyl, -T-R^y or two R^x taken together with adjacent carbon atoms form 5-7 membered heterocycloalkyl substituted with 0-3 occurrences of R^y. Provided herein as embodiment 94 is the compound according to embodiment 93, wherein one R^x is methyl and the other R^x is hydroxyl. Provided herein as embodiment 95 is the compound according to embodiment 93, wherein one R^x is -C(O)NH₂ and the other R^x is hydroxyl. Provided herein as embodiment 96 is the compound according to embodiment 92, wherein two R^x taken together with adjacent carbon atoms form a 1-tetrahydrofuranyl or 2-tetrahydrofuranyl substituted with 0 occurrences of R^y.

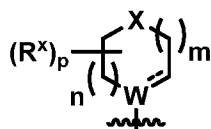
Provided herein as embodiment 97 is the compound according to embodiment 86, wherein n is 1 and m is 0 or when n is 0 and m is 1. Provided herein as embodiment 98 is the compound according to embodiment 97, wherein p is 0. Provided herein as embodiment 99 is the compound according to embodiment 97, wherein p is 1. Provided herein as embodiment 100 is the compound according to embodiment 99, wherein R^x is hydroxyl or -T-R^y. Provided herein as embodiment 101 is the compound according to embodiment 100, wherein R^x -T-R^y is -CH₂OH, -CH₂S(O)₂NH₂, -C(O)NH₂ or -S(O)₂NH₂.

Provided herein as embodiment 102 is the compound according to embodiment 97, wherein p is 2. Provided herein as embodiment 103 is the compound according to embodiment 102, wherein R^x is hydroxyl, halogen, -T-R^y or two R^x are taken together with adjacent carbon atoms form a C₃₋₇ cycloalkyl or 5-7 membered heterocycloalkyl wherein each cycloalkyl or heterocycloalkyl is substituted with 0-3 occurrences of R^y. Provided herein as embodiment 104 is the compound according to embodiment 103, wherein both R^x are hydroxyl. Provided herein as embodiment 105 is the compound according to embodiment 103, wherein one R^x is fluorine and the other is -CH₂OH. Provided herein as embodiment 106 is the compound according to embodiment 102, wherein two R^x taken together with adjacent carbon atoms form a C₃₋₇ cycloalkyl or a 5-7 membered heterocycloalkyl substituted with 0-3 occurrences of R^y. Provided herein as embodiment 107 is the compound according to embodiment 106, wherein two R^x taken together with adjacent carbon atoms form a cyclobutyl substituted with one occurrence of R^y. Provided herein as embodiment 108 is the compound according to embodiment 107, wherein R^y is hydroxyl. Provided herein as

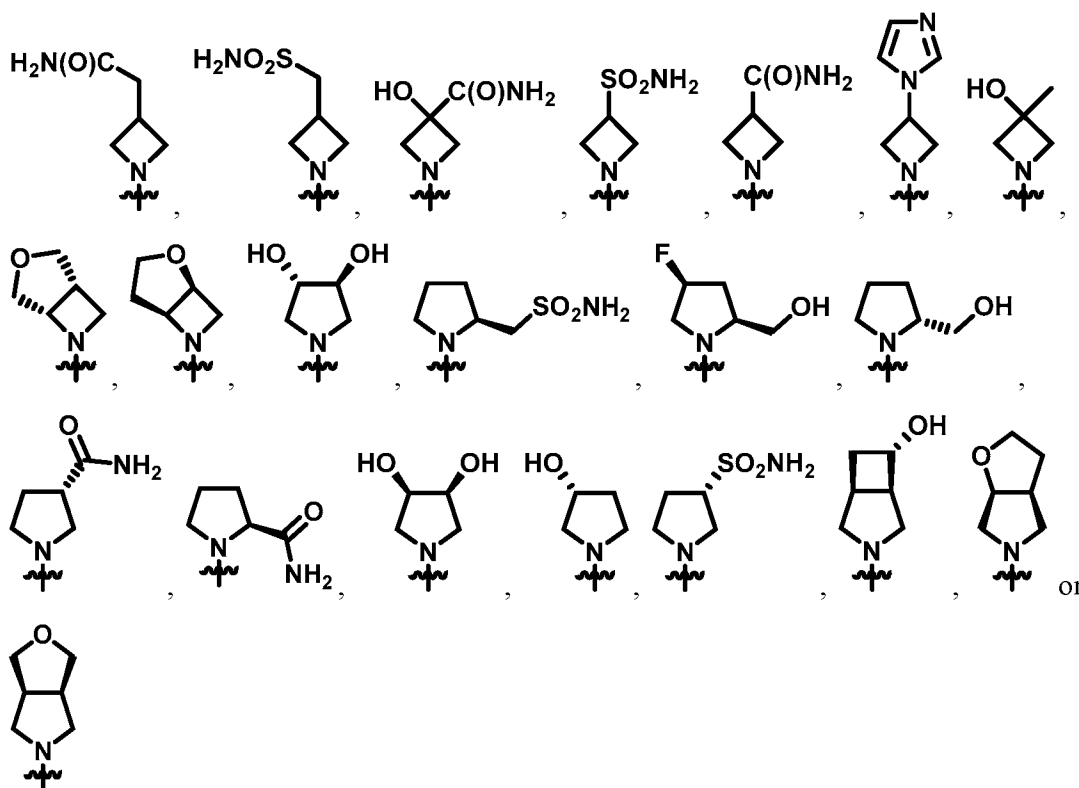
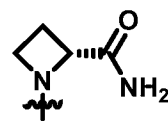
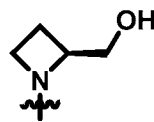
embodiment 109 is the compound according to embodiment 106, wherein two R^x taken together with adjacent carbon atoms form a 1-tetrahydrofuranyl or 2-tetrahydrofuranyl substituted with 0 occurrences of R^y.

Provided herein as embodiment 110 is the compound according to any one of

5 embodiments 1-83, wherein

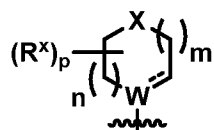


is

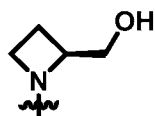


10 Provided herein as embodiment 111 is the compound according to embodiment 110,

wherein

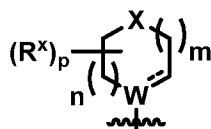


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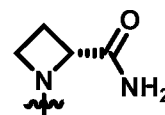


. Provided herein as embodiment 112 is the

compound according to embodiment 110, wherein

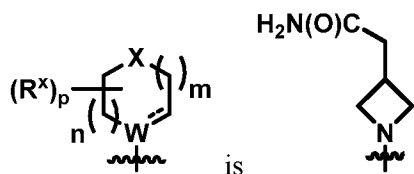


is



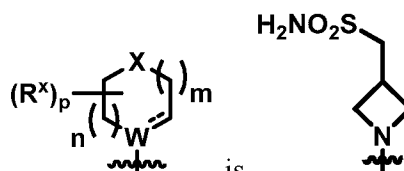
- 16 -

Provided herein as embodiment 113 is the compound according to embodiment 110, wherein



is

. Provided herein as embodiment 114 is the compound

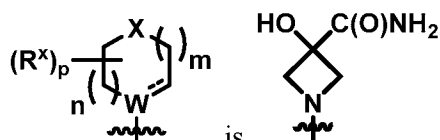


is

according to embodiment 110, wherein

. Provided herein

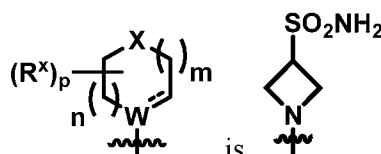
as embodiment 115 is the compound according to embodiment 110, wherein



is

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. Provided herein as embodiment 116 is the compound

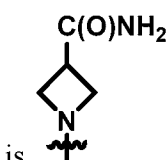


is

according to embodiment 110, wherein

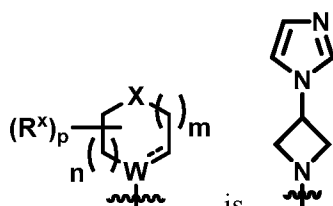
. Provided herein as

embodiment 117 is the compound according to embodiment 110, wherein



is

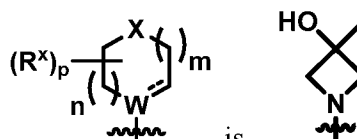
. Provided herein as embodiment 118 is the compound according to



is

embodiment 110, wherein

. Provided herein as embodiment 119

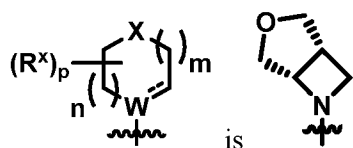


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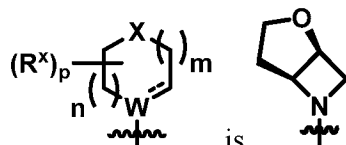
10 is the compound according to embodiment 110, wherein

- 17 -

Provided herein as embodiment 120 is the compound according to embodiment 110, wherein

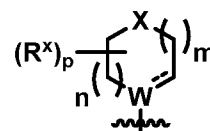


is . Provided herein as embodiment 121 is the compound

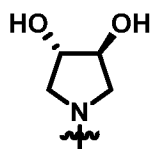


according to embodiment 110, wherein

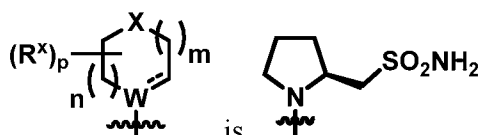
is . Provided herein as



embodiment 122 is the compound according to embodiment 110, wherein

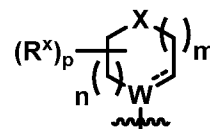


5 is . Provided herein as embodiment 123 is the compound according to

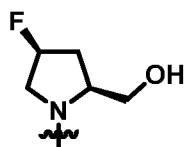


embodiment 110, wherein

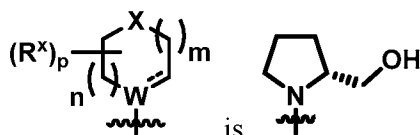
is . Provided herein as



embodiment 124 is the compound according to embodiment 110, wherein

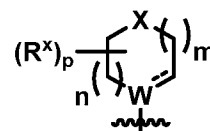


is . Provided herein as embodiment 125 is the compound according to



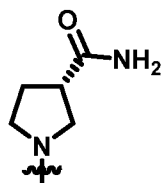
embodiment 110, wherein

is . Provided herein as

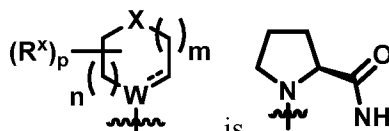


10 embodiment 126 is the compound according to embodiment 110, wherein

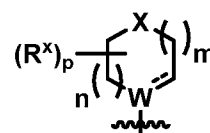
- 18 -



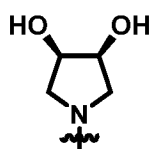
is . Provided herein as embodiment 127 is the compound according to



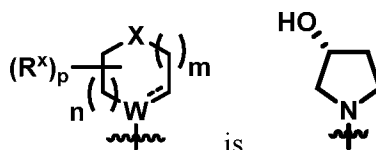
embodiment 110, wherein is . Provided herein as



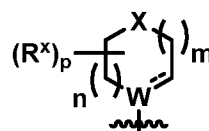
embodiment 128 is the compound according to embodiment 110, wherein



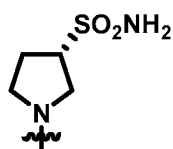
is . Provided herein as embodiment 129 is the compound according to



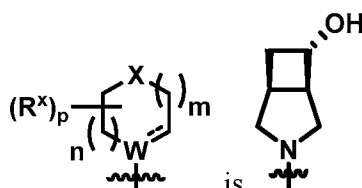
5 embodiment 110, wherein is . Provided herein as embodiment



130 is the compound according to embodiment 110, wherein is

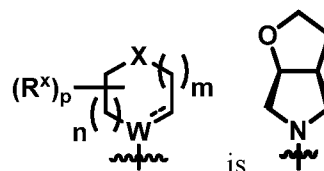


. Provided herein as embodiment 131 is the compound according to



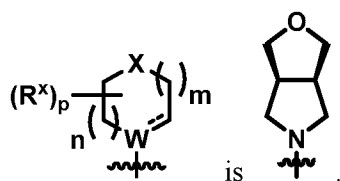
embodiment 110, wherein is . Provided herein as embodiment

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132 is the compound according to embodiment 110, wherein

Provided herein as embodiment 133 is the compound according to embodiment 110, wherein



Provided herein as embodiment 134 is the compound according to embodiment 85,
 5 wherein n is 1 and m is 1. Provided herein as embodiment 135 is the compound according to
 embodiment 134, wherein p is 0. Provided herein as embodiment 136 is the compound
 according to embodiment 134, wherein p is 1. Provided herein as embodiment 137 is the
 compound according to embodiment 136, wherein R^x is hydroxyl, cyano, C_{1-4}
 alkoxy, $-N(R^z)_2$, 5-7 membered heteroaryl or $-T-R^y$. Provided herein as embodiment 138 is
 10 the compound according to embodiment 136, wherein R^x is hydroxyl, cyano, methoxy, $-NH_2$,
 5-oxazolyl, 4-imidazolyl or 3-pyrazolyl. Provided herein as embodiment 139 is the
 compound according to embodiment 137, wherein $-T-R^y$
 is $-NHC(O)OMe$, $-S(O)_2Me$, $-NHC(O)Me$, $-NHC(O)-N(H)CH_2CH_2OMe$, $-CH_2OH$,
 $-NHS(O)_2Me$, $-CO_2H$, $-C(O)_2Me$, 1-isopropanol, $-S(O)_2NH_2$, $-C(O)NH_2$, $-S(O)_2N(H)Me$
 15 or $-C(O)N(H)Me$.

Provided herein as embodiment 140 is the compound according to embodiment 134,
 wherein p is 2. Provided herein as embodiment 141 is the compound according to
 embodiment 140, wherein R^x is halogen, hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{3-7}
 cycloalkyl, $-N(R^z)_2$ or $-T-R^y$ or two R^x taken together with the same carbon atom form a 5-7
 20 membered heterocycloalkyl substituted with 0-3 occurrences of R^y . Provided herein as
 embodiment 142 is the compound according to embodiment 141, wherein one R^x is fluorine
 and one R^x is hydroxyl. Provided herein as embodiment 143 is the compound according to
 embodiment 141, wherein one R^x is methyl and one R^x is hydroxyl. Provided herein as
 embodiment 144 is the compound according to embodiment 141, wherein one R^x
 25 is $-NHS(O)_2Me$ and one R^x is methyl. Provided herein as embodiment 145 is the compound

- 20 -

according to embodiment 141, wherein one R^x is -C(O)NH₂ and one R^x is hydroxyl.

Provided herein as embodiment 146 is the compound according to embodiment 141, wherein one R^x is methoxy and one R^x is methyl. Provided herein as embodiment 147 is the compound according to embodiment 141, wherein one R^x is -NH₂ and one R^x is methyl.

- 5 Provided herein as embodiment 148 is the compound according to embodiment 141, wherein one R^x is -NHC(O)OMe and one R^x is methyl. Provided herein as embodiment 149 is the compound according to embodiment 141, wherein one R^x is cyclopropyl and one R^x is hydroxyl. Provided herein as embodiment 150 is the compound according to embodiment 141, wherein one R^x is trifluoromethyl and one R^x is hydroxyl. Provided herein as
- 10 embodiment 151 is the compound according to embodiment 141, wherein one R^x is difluoromethyl and one R^x is hydroxyl. Provided herein as embodiment 152 is the compound according to embodiment 141, wherein one R^x is -C(O)NH₂ and one R^x is methyl. Provided herein as embodiment 153 is the compound according to embodiment 141, wherein one R^x is -CH₂OH and one R^x is chloromethyl. Provided herein as embodiment 154 is the compound
- 15 according to embodiment 141, wherein both R^x are hydroxyl.

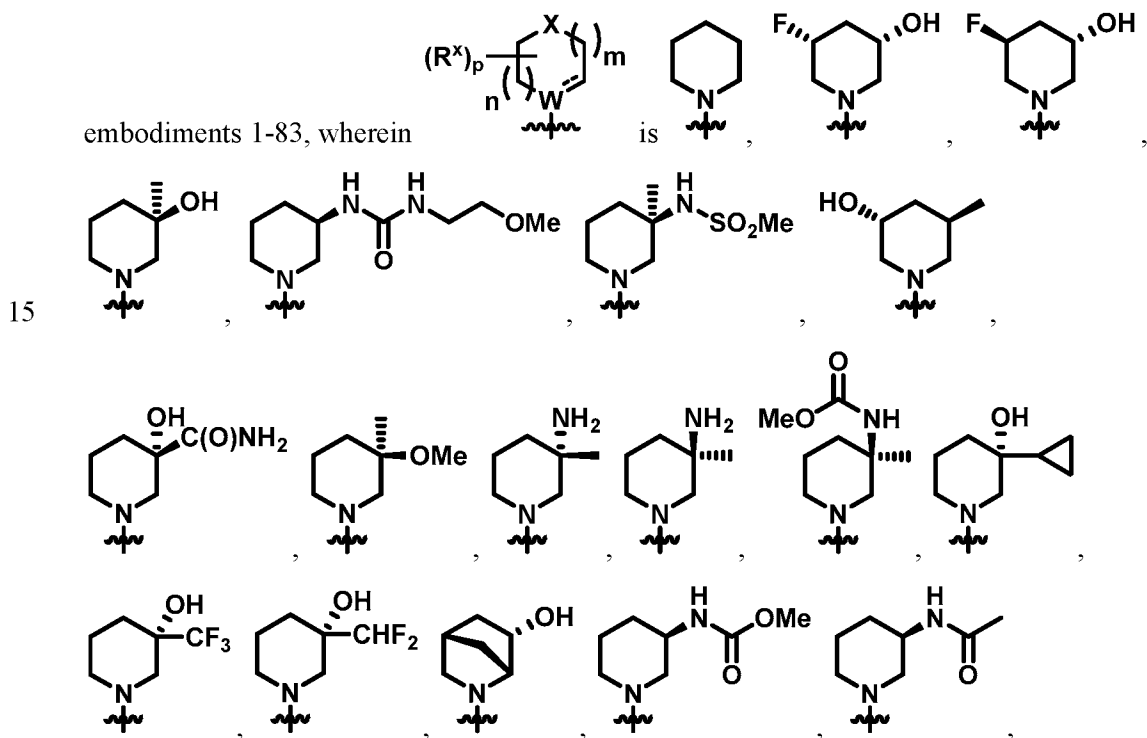
- Provided herein as embodiment 155 is the compound according to embodiment 140, wherein two R^x are taken together with adjacent carbon atoms form a 5-7 membered heterocycloalkyl substituted with 0-3 occurrences of R^y. Provided herein as embodiment 156
- 20 is the compound according to embodiment 155, wherein two R^x are taken together with adjacent carbon atoms to form 1-tetrahydrofuranyl substituted with 0 occurrences of R^y. Provided herein as embodiment 157 is the compound according to embodiment 155, wherein two R^x are taken together with adjacent carbon atoms to form 1-pyrrolidinyl or 2-pyrrolidinyl substituted with 1 occurrence of R^y. Provided herein as embodiment 158 is the compound according to embodiment 157, wherein R^y is oxo.

- 25 Provided herein as embodiment 159 is the compound according to embodiment 134, wherein p is 3. Provided herein as embodiment 160 is the compound according to embodiment 159, wherein one R^x is hydroxyl, halogen, oxo, C₁₋₄ alkyl or two R^x taken together with adjacent carbon atoms can form C₃₋₇ cycloalkyl substituted with 0-3 occurrences of R^y or two R^x taken together can form a bridged ring further substituted with 0-
- 30 2 occurrences of R^y. Provided herein as embodiment 161 is the compound according to embodiment 160, wherein one R^x is hydroxyl and the other two R^x are methyl. Provided

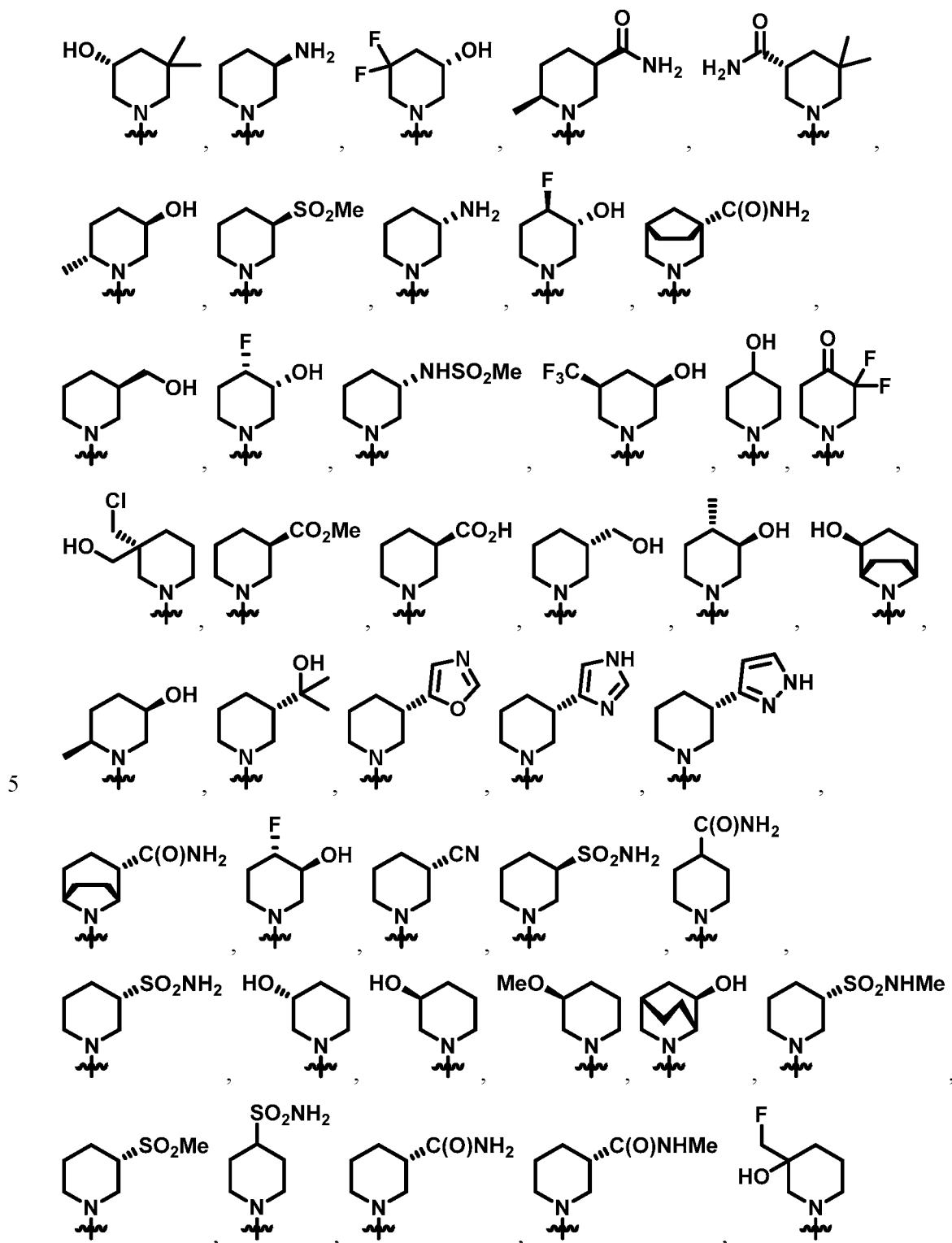
- 21 -

herein as embodiment 162 is the compound according to embodiment 160, wherein one R^x is hydroxyl and the other two R^x are fluorine. Provided herein as embodiment 163 is the compound according to embodiment 160, wherein one R^x is $-C(O)NH_2$ and the other two R^x are methyl. Provided herein as embodiment 164 is the compound according to embodiment 160, wherein one R^x is oxo and the other two R^x are fluorine. Provided herein as embodiment 165 is the compound according to embodiment 160, wherein one R^x is hydroxyl and the other two R^x taken together with adjacent carbon atoms form cyclopropyl substituted with 0 occurrences of R^y . Provided herein as embodiment 166 is the compound according to embodiment 160, wherein one R^x is hydroxyl and the other two R^x taken together form an ethylene or methylene bridge substituted with 0 occurrences of R^y . Provided herein as embodiment 167 is the compound according to embodiment 160, wherein one R^x is $C(O)NH_2$ and the other two R^x taken together form an ethylene substituted with 0 occurrences of R^y .

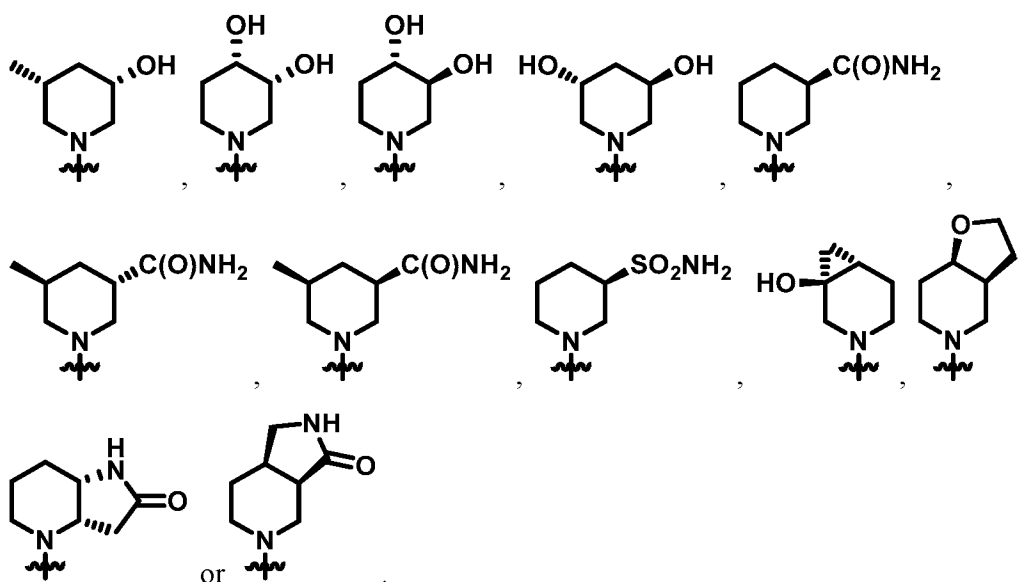
Provided herein as embodiment 168 is the compound according to any one of



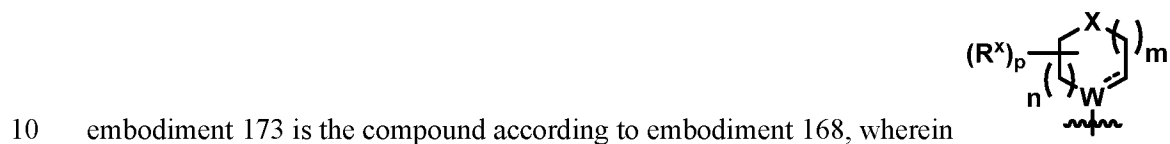
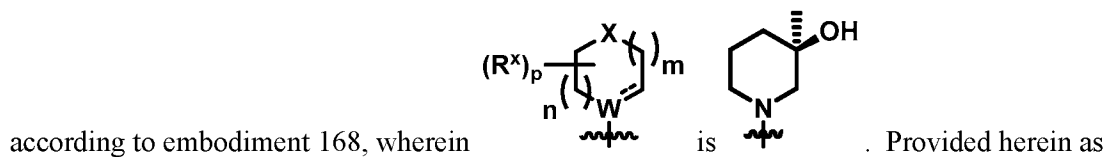
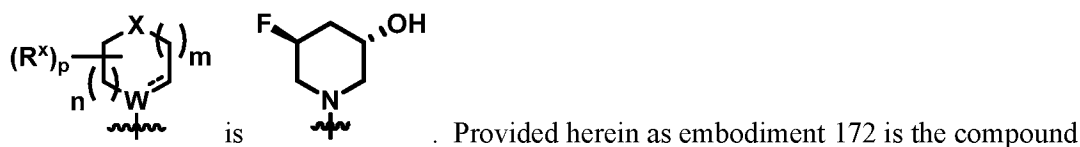
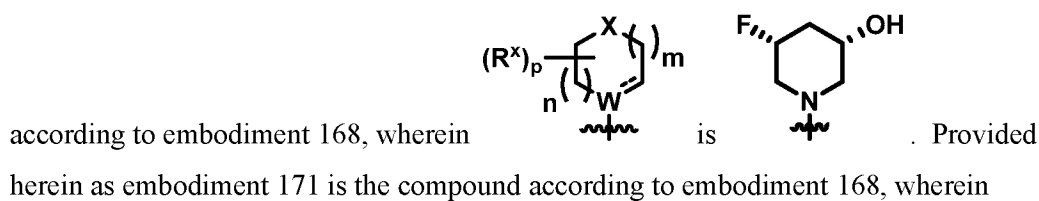
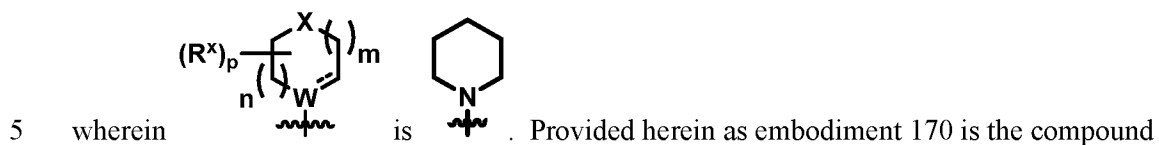
- 22 -



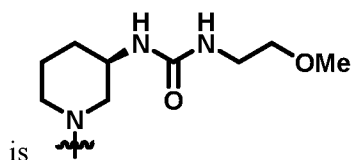
- 23 -



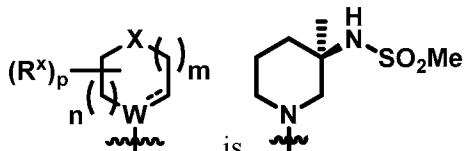
Provided herein as embodiment 169 is the compound according to embodiment 168,



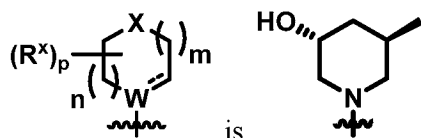
- 24 -



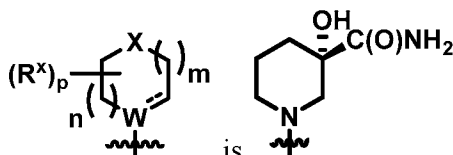
is . Provided herein as embodiment 174 is the compound



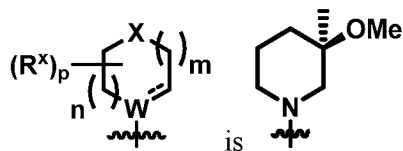
according to embodiment 168, wherein . Provided herein as embodiment 175 is the compound according to embodiment 168, wherein



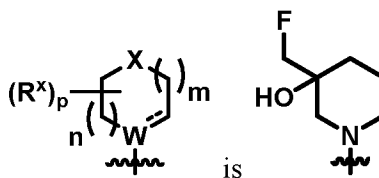
is . Provided herein as embodiment 176 is the compound



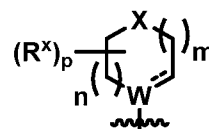
5 according to embodiment 168, wherein . Provided herein as embodiment 177 is the compound according to embodiment 168, wherein



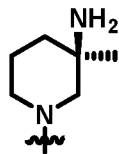
is . Provided herein as embodiment 178 is the compound



according to embodiment 168, wherein . Provided herein as

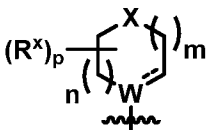
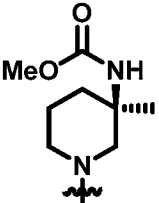


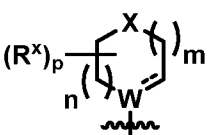
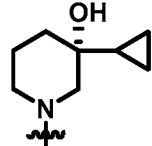
embodiment 179 is the compound according to embodiment 168, wherein

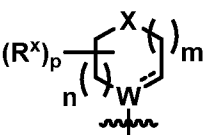
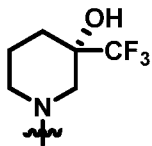


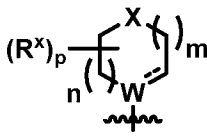
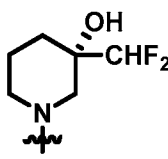
10 is . Provided herein as embodiment 180 is the compound according to embodiment

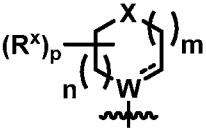
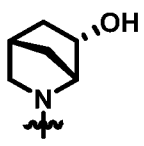
- 25 -

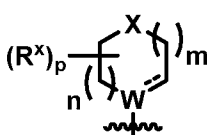
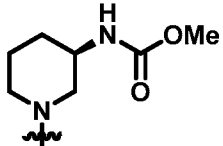
168, wherein  is . Provided herein as embodiment 181 is the

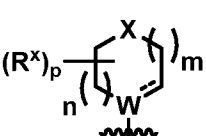
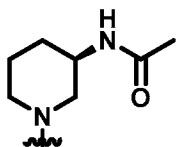
compound according to embodiment 168, wherein  is . Provided herein as embodiment 182 is the compound according to embodiment 168, wherein

 is . Provided herein as embodiment 183 is the compound

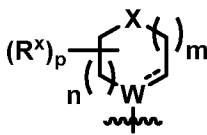
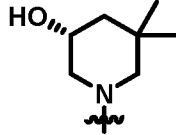
5 according to embodiment 168, wherein  is . Provided herein as embodiment 184 is the compound according to embodiment 168, wherein

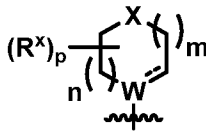
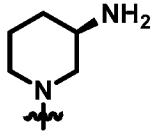
 is . Provided herein as embodiment 185 is the compound

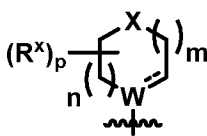
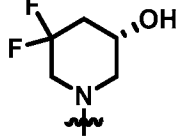
according to embodiment 168, wherein  is . Provided herein as embodiment 186 is the compound according to embodiment 168, wherein

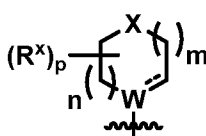
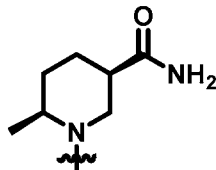
10  is . Provided herein as embodiment 187 is the compound

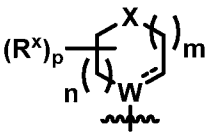
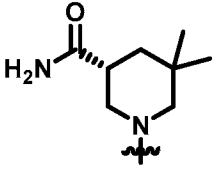
- 26 -

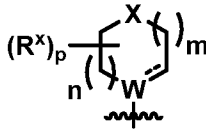
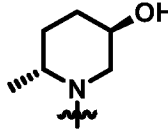
according to embodiment 168, wherein  is . Provided herein as embodiment 188 is the compound according to embodiment 168, wherein

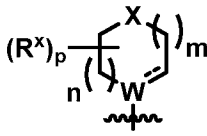
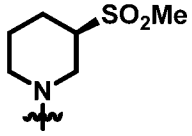
 is . Provided herein as embodiment 189 is the compound

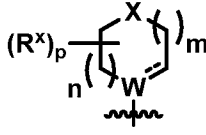
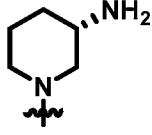
according to embodiment 168, wherein  is . Provided herein as embodiment 190 is the compound according to embodiment 168, wherein

 is . Provided herein as embodiment 191 is the

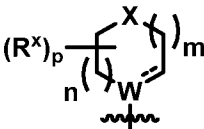
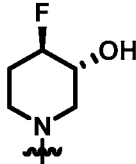
compound according to embodiment 168, wherein  is . Provided herein as embodiment 192 is the compound according to embodiment 168, wherein

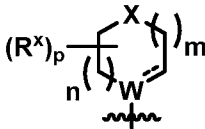
 is . Provided herein as embodiment 193 is the compound

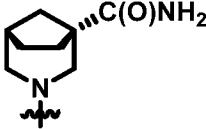
according to embodiment 168, wherein  is . Provided herein as embodiment 194 is the compound according to embodiment 168, wherein

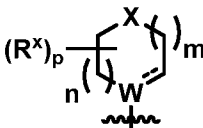
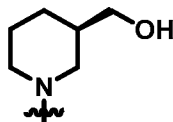
 is . Provided herein as embodiment 195 is the compound

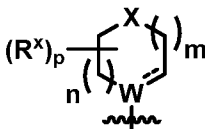
- 27 -

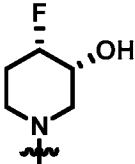
according to embodiment 168, wherein  is . Provided herein as

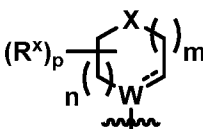
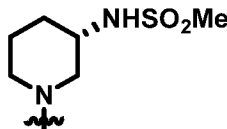
embodiment 196 is the compound according to embodiment 168, wherein 

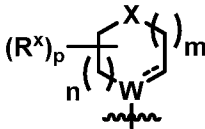
is . Provided herein as embodiment 197 is the compound according to

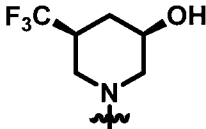
embodiment 168, wherein  is . Provided herein as

5 embodiment 198 is the compound according to embodiment 168, wherein 

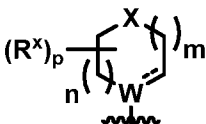
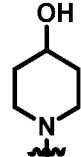
is . Provided herein as embodiment 199 is the compound according to

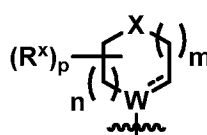
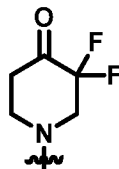
embodiment 168, wherein  is . Provided herein as

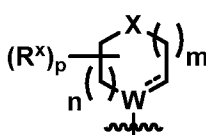
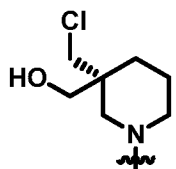
embodiment 200 is the compound according to embodiment 168, wherein 

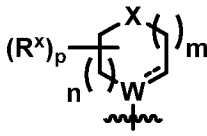
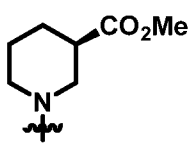
is . Provided herein as embodiment 201 is the compound according to

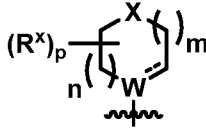
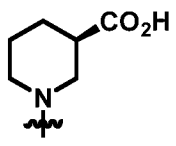
- 28 -

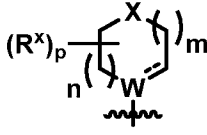
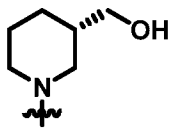
embodiment 168, wherein  is . Provided herein as embodiment 202

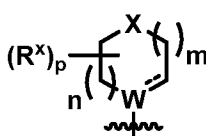
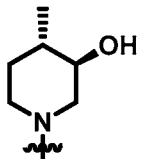
is the compound according to embodiment 168, wherein  is . Provided herein as embodiment 203 is the compound according to embodiment 168, wherein

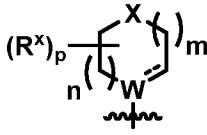
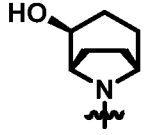
 is . Provided herein as embodiment 204 is the compound

5 according to embodiment 168, wherein  is . Provided herein as embodiment 205 is the compound according to embodiment 168, wherein

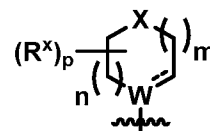
 is . Provided herein as embodiment 206 is the compound

according to embodiment 168, wherein  is . Provided herein as embodiment 207 is the compound according to embodiment 168, wherein

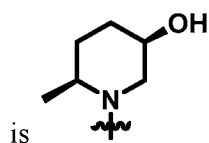
10  is . Provided herein as embodiment 208 is the compound

according to embodiment 168, wherein  is . Provided herein as

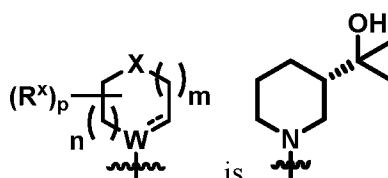
- 29 -



embodiment 209 is the compound according to embodiment 168, wherein

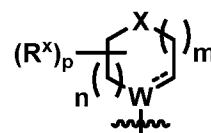


is . Provided herein as embodiment 210 is the compound according to



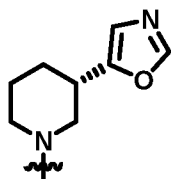
embodiment 168, wherein

is . Provided herein as embodiment



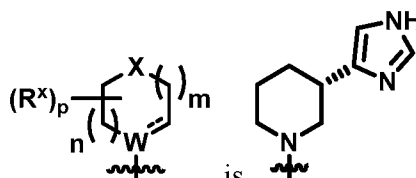
211 is the compound according to embodiment 168, wherein

is



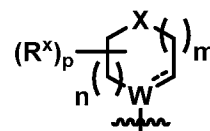
5

. Provided herein as embodiment 212 is the compound according to

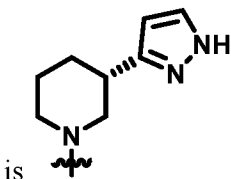


embodiment 168, wherein

is . Provided herein as

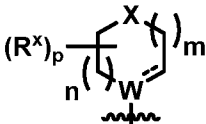
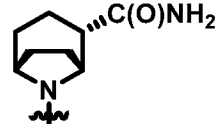


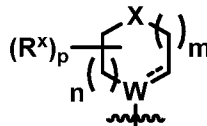
embodiment 213 is the compound according to embodiment 168, wherein

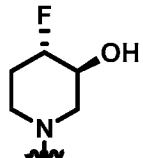


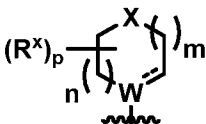
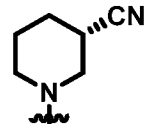
is . Provided herein as embodiment 214 is the compound according to

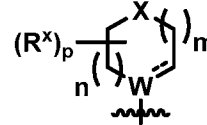
- 30 -

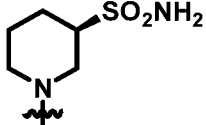
embodiment 168, wherein  is . Provided herein as

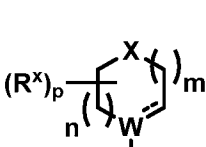
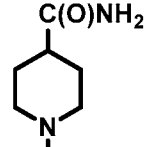
embodiment 215 is the compound according to embodiment 168, wherein 

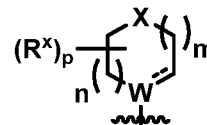
is . Provided herein as embodiment 216 is the compound according to

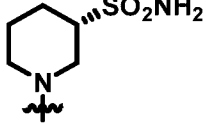
embodiment 168, wherein  is . Provided herein as embodiment

5 217 is the compound according to embodiment 168, wherein  is

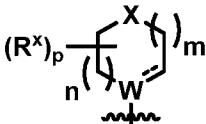
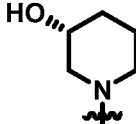
. Provided herein as embodiment 218 is the compound according to

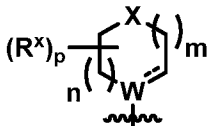
embodiment 168, wherein  is . Provided herein as embodiment

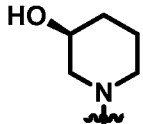
219 is the compound according to embodiment 168, wherein  is

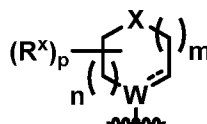
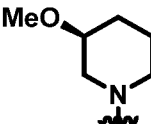
. Provided herein as embodiment 220 is the compound according to

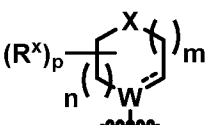
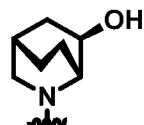
- 31 -

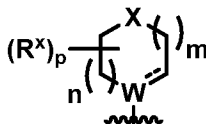
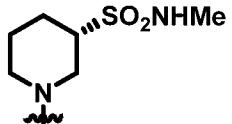
embodiment 168, wherein  is . Provided herein as embodiment

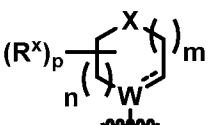
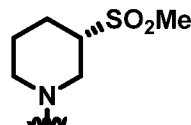
221 is the compound according to embodiment 168, wherein  is

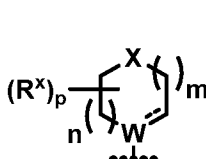
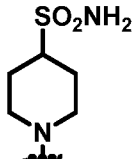
. Provided herein as embodiment 222 is the compound according to embodiment

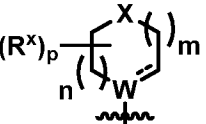
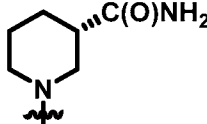
168, wherein  is . Provided herein as embodiment 223 is the

5 compound according to embodiment 168, wherein  is . Provided herein as embodiment 224 is the compound according to embodiment 168, wherein

 is . Provided herein as embodiment 225 is the

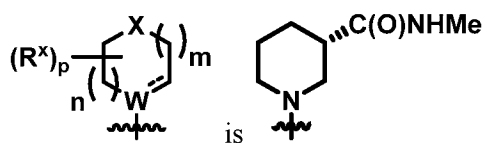
compound according to embodiment 168, wherein  is . Provided herein as embodiment 226 is the compound according to embodiment 168, wherein

10  is . Provided herein as embodiment 227 is the compound

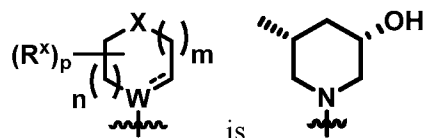
according to embodiment 168, wherein  is . Provided

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herein as embodiment 228 is the compound according to embodiment 168, wherein

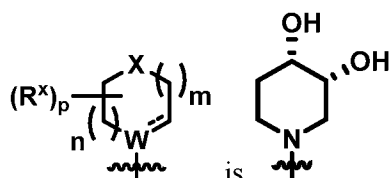


. Provided herein as embodiment 229 is the



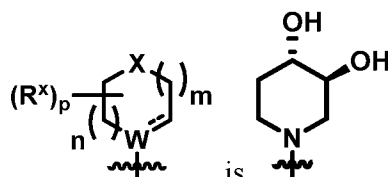
compound according to embodiment 168, wherein

Provided herein as embodiment 230 is the compound according to embodiment 168, wherein



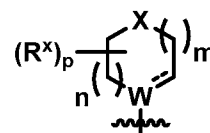
5

. Provided herein as embodiment 231 is the compound

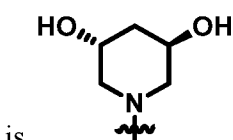


according to embodiment 168, wherein

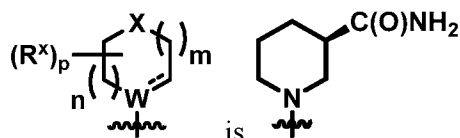
. Provided herein as



embodiment 232 is the compound according to embodiment 168, wherein

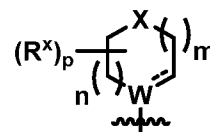


. Provided herein as embodiment 233 is the compound according to



embodiment 168, wherein

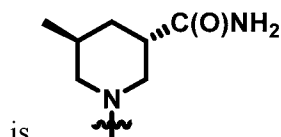
. Provided herein as



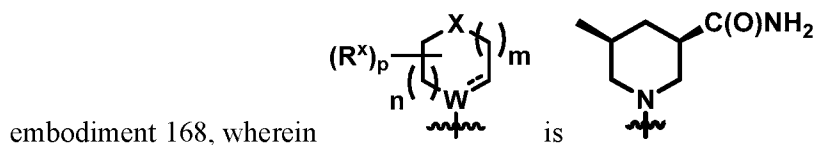
10

embodiment 234 is the compound according to embodiment 168, wherein

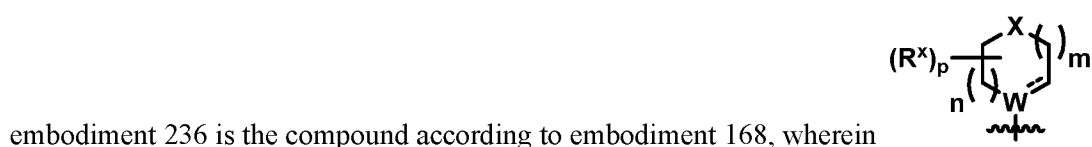
- 33 -



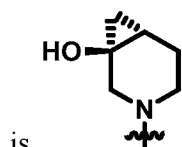
is . Provided herein as embodiment 235 is the compound according to



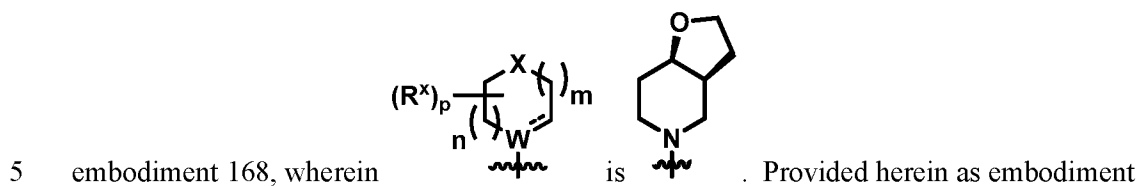
embodiment 168, wherein is . Provided herein as



embodiment 236 is the compound according to embodiment 168, wherein



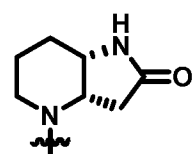
is . Provided herein as embodiment 237 is the compound according to



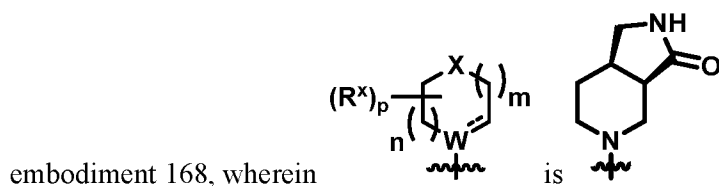
embodiment 168, wherein is . Provided herein as embodiment



238 is the compound according to embodiment 168, wherein is



. Provided herein as embodiment 239 is the compound according to



embodiment 168, wherein

Provided herein as embodiment 240 is the compound according to embodiment 85,
 10 wherein n is 1 and m is 2 or n is 2 and m is 1. Provided herein as embodiment 241 is the
 compound according to embodiment 240, wherein p is 0. Provided herein as embodiment
 242 is the compound according to embodiment 420, wherein p is 1. Provided herein as

- 34 -

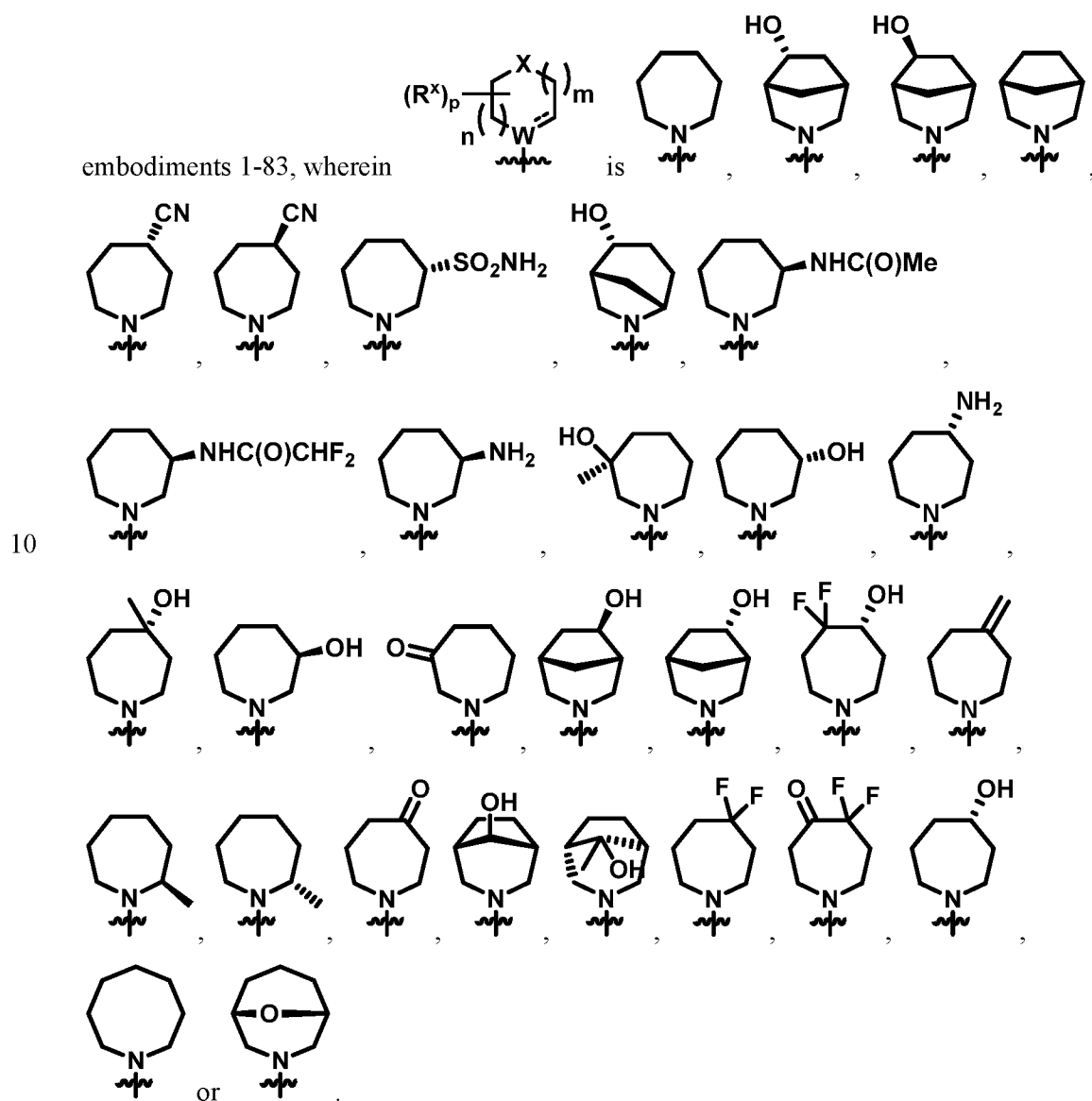
embodiment 243 is the compound according to embodiment 242, wherein R^x is C_{1-4} alkyl, C_{1-4} alkenyl, cyano, hydroxyl, oxo, $-N(R^z)_2$ or $-T-R^y$. Provided herein as embodiment 244 is the compound according to embodiment 243, wherein R^x is cyano, methyl, oxo, hydroxyl, $-NH_2$, methenyl, $-SO_2NH_2$, $-NHC(O)Me$ or $-NHC(O)CF_2H$.

5 Provided herein as embodiment 245 is the compound according to embodiment 240, wherein p is 2. Provided herein as embodiment 246 is the compound according to embodiment 245, wherein R^x is hydroxy, C_{1-4} alkyl, halogen or two R^x are taken together to form a C_{1-4} alkylene bridged ring further substituted with 0-2 occurrences of R^y . Provided herein as embodiment 247 is the compound according to embodiment 246, wherein both R^x
10 are fluorine. Provided herein as embodiment 248 is the compound according to embodiment 246, wherein one R^x is hydroxyl and the other R^x is methyl. Provided herein as embodiment 249 is the compound according to embodiment 246, wherein two R^x are taken together to form a bridged ring wherein the bridge is methylene further substituted with 0 occurrences of R^y . Provided herein as embodiment 250 is the compound according to embodiment 246,
15 wherein two R^x are taken together to form a bridged ring wherein the bridge is methylene further substituted with one occurrence of R^y . Provided herein as embodiment 251 is the compound according to embodiment 250, wherein R^y is hydroxyl. Provided herein as embodiment 252 is the compound according to embodiment 246, wherein two R^x are taken together to form a bridged ring wherein the bridge is methylene further substituted with 2
20 occurrences of R^y . Provided herein as embodiment 253 is the compound according to embodiment 252, wherein each R^y is methyl or hydroxyl.

 Provided herein as embodiment 254 is the compound according to embodiment 240, wherein p is 3. Provided herein as embodiment 255 is the compound according to embodiment 254, wherein R^x is hydroxy, oxo, halogen or two R^x are taken together to form a
25 C_{1-4} alkylene bridged ring further substituted with 0-2 occurrences of R^y . Provided herein as embodiment 256 is the compound according to embodiment 255, wherein one R^x is oxo and the other two R^x are fluorine. Provided herein as embodiment 257 is the compound according to embodiment 255, wherein one R^x is hydroxyl and the other two R^x are fluorine. Provided herein as embodiment 258 is the compound according to embodiment 255, wherein
30 one R^x is hydroxy and the other two R^x are taken together to form a bridged ring wherein the bridge is methylene further substituted with 0 occurrences of R^y .

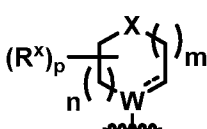
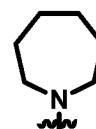
Provided herein as embodiment 259 is the compound according to embodiment 85, wherein n is 2 and m is 2. Provided herein as embodiment 260 is the compound according to embodiment 259, wherein p is 0. Provided herein as embodiment 261 is the compound according to embodiment 259, wherein p is 2. Provided herein as embodiment 262 is the compound according to embodiment 261, wherein two R^x are taken together to form a bridged ring wherein the bridge is -O-.

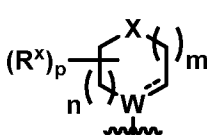
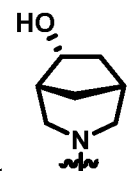
Provided herein as embodiment 263 is the compound according to any one of

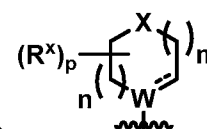


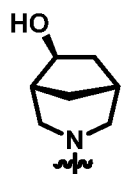
- 36 -

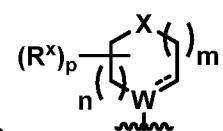
Provided herein as embodiment 264 is the compound according to embodiment 263,

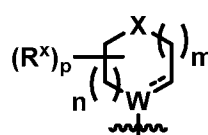
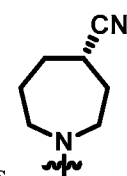
wherein  is . Provided herein as embodiment 265 is the compound

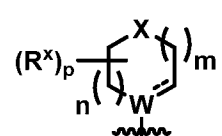
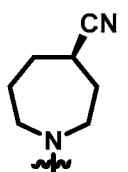
according to embodiment 263, wherein  is . Provided herein as

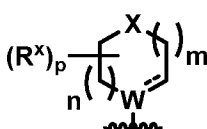
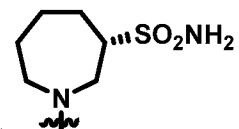
embodiment 266 is the compound according to embodiment 263, wherein 

5 is . Provided herein as embodiment 267 is the compound according to embodiment

263, wherein  is . Provided herein as embodiment 268 is the

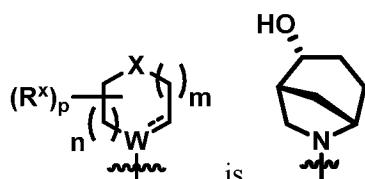
compound according to embodiment 263, wherein  is . Provided herein as embodiment 269 is the compound according to embodiment 263, wherein

 is . Provided herein as embodiment 270 is the compound

10 according to embodiment 263, wherein  is . Provided

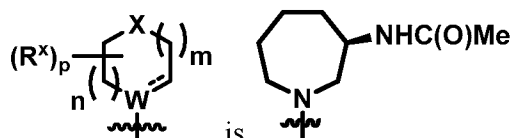
- 37 -

herein as embodiment 271 is the compound according to embodiment 263, wherein



is

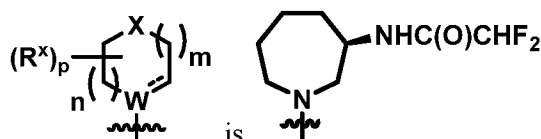
. Provided herein as embodiment 272 is the compound



according to embodiment 263, wherein

is

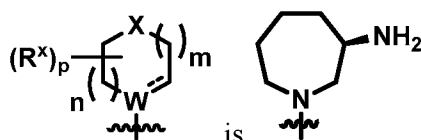
Provided herein as embodiment 273 is the compound according to embodiment 263, wherein



5

is

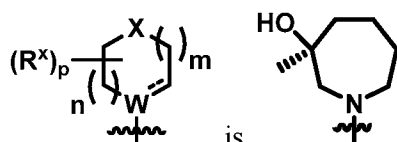
. Provided herein as embodiment 274 is the



compound according to embodiment 263, wherein

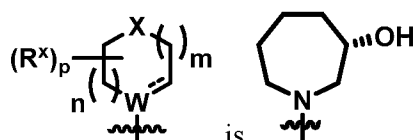
is

Provided herein as embodiment 275 is the compound according to embodiment 263, wherein



is

. Provided herein as embodiment 276 is the compound

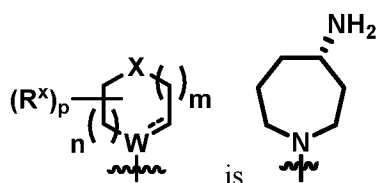


according to embodiment 263, wherein

is

10

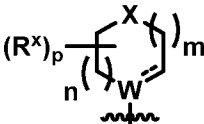
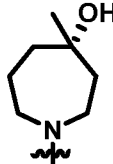
as embodiment 277 is the compound according to embodiment 263, wherein

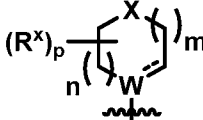


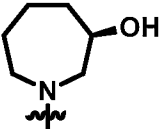
is

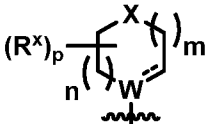
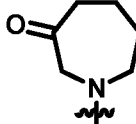
. Provided herein as embodiment 278 is the compound

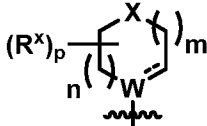
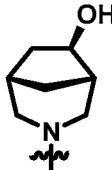
- 38 -

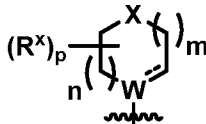
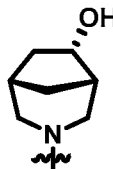
according to embodiment 263, wherein  is . Provided herein as

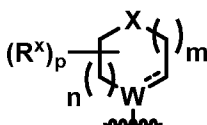
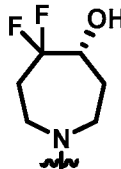
embodiment 279 is the compound according to embodiment 263, wherein 

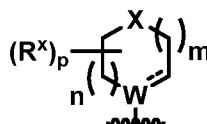
is . Provided herein as embodiment 280 is the compound according to

embodiment 263, wherein  is . Provided herein as embodiment

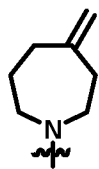
5 281 is the compound according to embodiment 263, wherein  is . Provided herein as embodiment 282 is the compound according to embodiment 263, wherein

 is . Provided herein as embodiment 283 is the compound

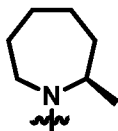
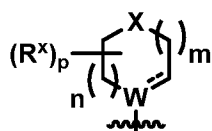
according to embodiment 263, wherein  is . Provided herein as

embodiment 284 is the compound according to embodiment 263, wherein 

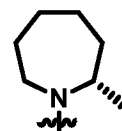
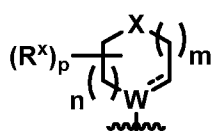
- 39 -



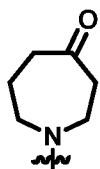
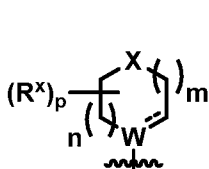
is . Provided herein as embodiment 285 is the compound according to embodiment



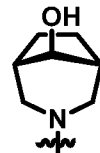
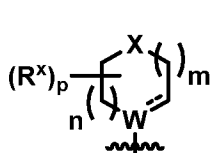
263, wherein is . Provided herein as embodiment 286 is the



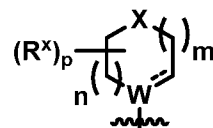
compound according to embodiment 263, wherein is . Provided herein as embodiment 287 is the compound according to embodiment 263, wherein



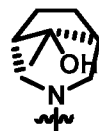
5 is . Provided herein as embodiment 288 is the compound



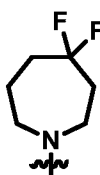
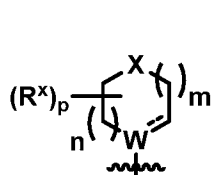
according to embodiment 263, wherein is . Provided herein as



embodiment 289 is the compound according to embodiment 263, wherein

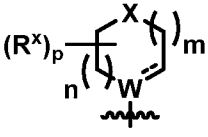
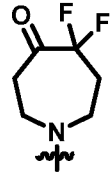


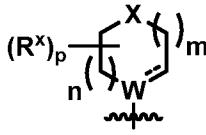
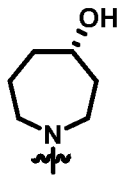
is . Provided herein as embodiment 290 is the compound according to embodiment

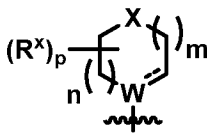
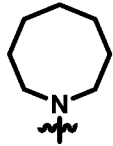


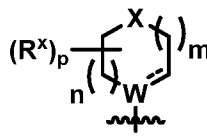
263, wherein is . Provided herein as embodiment 291 is the

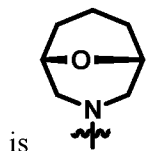
- 40 -

compound according to embodiment 263, wherein  is . Provided herein as embodiment 292 is the compound according to embodiment 263, wherein

 is . Provided herein as embodiment 293 is the compound

according to embodiment 263, wherein  is . Provided herein as

embodiment 294 is the compound according to embodiment 263, wherein 



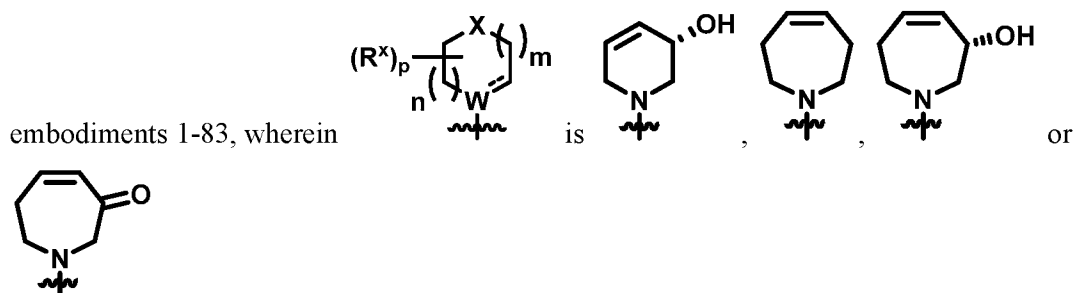
Provided herein as embodiment 295 is the compound according to any one of embodiments 1-84, wherein X is CH=CH.

Provided herein as embodiment 296 is the compound according to embodiment 295, wherein n is 0 and m is 1. Provided herein as embodiment 297 is the compound according to embodiment 296, wherein p is 1. Provided herein as embodiment 298 is the compound according to embodiment 297, wherein R^x is hydroxyl.

Provided herein as embodiment 299 is the compound according to embodiment 295, wherein n is 1 and m is 1. Provided herein as embodiment 300 is the compound according to embodiment 299, wherein p is 0. Provided herein as embodiment 301 is the compound according to embodiment 299, wherein p is 1. Provided herein as embodiment 302 is the compound according to embodiment 301, wherein R^x is oxo or hydroxyl.

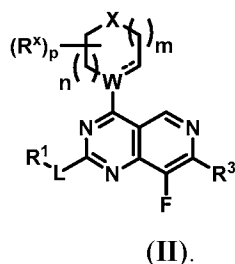
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Provided herein as embodiment 303 is the compound according to any one of

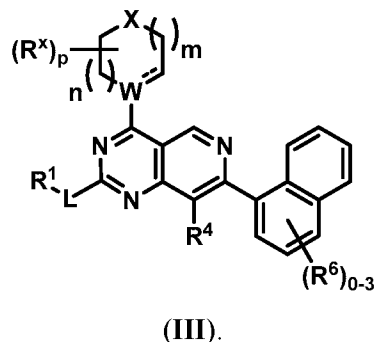


Provided herein as embodiment 304 is the compound according to any one of
 5 embodiments 1-303, wherein R^4 is C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl, halogen or C_{1-4} haloalkyl. Provided herein as embodiment 305 is the compound according to embodiment 304, wherein R^4 is C_{1-4} alkyl or halogen. Provided herein as embodiment 306 is the compound according to embodiment 305, wherein R^4 is fluorine.

Provided herein as embodiment 307 is the compound according to embodiment 1,
 10 wherein is the compound is a compound of formula (II):



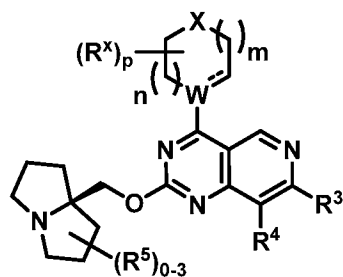
Provided herein as embodiment 308 is the compound according to embodiment 1,
 wherein is the compound is a compound of formula (III):



15

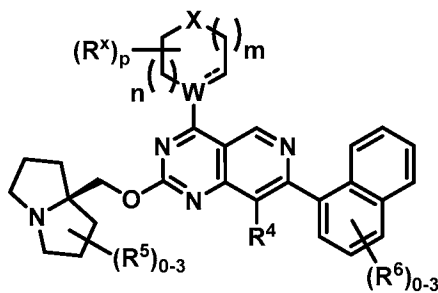
Provided herein as embodiment 309 is the compound according to embodiment 1,
 wherein is the compound is a compound of formula (IV):

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(IV).

Provided herein as embodiment 310 is the compound according to embodiment 1, wherein the compound is a compound of formula (V):



(V).

Provided herein as embodiment 311 is the compound according to embodiment 1, wherein the compound is not:

- 10 1-(7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (S)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 15 (R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (3R,5S)-5-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)-1-methylpyrrolidin-3-ol;
- 20 (2R,7aS)-7a-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)hexahydro-1H-pyrrolizin-2-ol;

- 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-4-ol;
[(3R,5S)-5-[[7-(8-ethyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-4-[(3S)-3-hydroxy-3-methyl-1-piperidyl]pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1-methylpyrrolidin-3-yl] N-methylcarbamate;
- 5 (S)-1-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-4-ol;
- 10 (3R,5S)-5-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-4-((R)-3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)-1-methylpyrrolidin-3-yl methylcarbamate;
- (R)-1-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 15 (R)-1-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (R)-1-(6-(8-ethyl-7-fluoronaphthalen-1-yl)-5-fluoro-3-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-1-yl)-3-methylpiperidin-3-ol;
- 20 (R)-1-(7-(8-ethyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 25 4-((1R,5S)-3-azabicyclo[3.2.1]octan-3-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine;
- 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine;
- 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidine;
- 30

- 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol;
1-(7-(5,6-dimethyl-1H-indazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrroliziri-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 5 (R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
(3R)-1-[7-(8-ethyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-2-[(2S)-1-methylpyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3-methylpiperidin-3-ol;
4-(3-(1H-1,2,4-triazol-3-yl)piperidin-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-
- 10 ((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine;
4-(2-azabicyclo[4.1.0]heptan-2-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine;
8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-
- 15 (octahydro-1H-cyclopenta[b]pyridin-1-yl)pyrido[4,3-d]pyrimidine;
(3R,5S)-1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5-methylpiperidin-3-ol;
1-(7-(2-amino-5,6-dimethylbenzo[d]thiazol-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-
- 1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
1-(7-(2-amino-5,6-dimethylbenzo[d]thiazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-
- 20 yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
4-(azocan-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine;
1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-
- 25 yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-3-ol;
(R)-1-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
4-(3,3-dimethylpiperidin-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-
- pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine;
1-(7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-
- 30 yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;

- 1-(7-(8-ethynynaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
8-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)-1-naphthonitrile;
- 5 6-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-3-ol;
(3R,5R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3,5-diol;
- 10 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylazepan-3-ol;
1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(quinolin-8-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
1-(7-(2-aminobenzo[d]thiazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 15 1-(7-(benzo[d]thiazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 20 1-(7-(3-chloro-2-cyclopropyl-5-hydroxyphenyl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
4-(3-(1H-imidazol-1-yl)azetidin-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine;
- 25 6-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-3-ol;
3-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol;
3-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol;
- 30 ol;

- 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3-carboxamide;
1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepane-4-carbonitrile;
- 5 (3S,5R)-1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3,5-diol;
4-(3-(1H-imidazol-1-yl)azetidin-1-yl)-7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine;
4-(2-(1H-pyrazol-4-yl)pyrrolidin-1-yl)-7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine;
- 10 6-(7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-3-ol;
4-(3-(1H-1,2,3-triazol-4-yl)piperidin-1-yl)-7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine;
- 15 4-(3-(1H-pyrazol-1-yl)piperidin-1-yl)-7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine;
(3R,5R)-1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5-methylpiperidin-3-ol;
(1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanol;
- 20 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methylazepan-4-ol;
1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-(hydroxymethyl)piperidin-4-ol;
- 25 2-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)isoindolin-4-ol;
4-(3,6-dihydropyridin-1(2H)-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine;
1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-4-ol;
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- (1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-3-yl)methanol;
4-(3-(1H-pyrazol-3-yl)piperidin-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine;
- 5 1-(7-(3-chloro-5-hydroxy-2-((1S,2R)-2-methylcyclopropyl)phenyl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
4-(4-(3-(1H-imidazol-1-yl)azetidin-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
4-(4-(3-(1H-1,2,4-triazol-5-yl)piperidin-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5,6-difluoronaphthalen-2-ol;
- 10 5,6-difluoro-4-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(3-methyl-1H-1,2,4-triazol-5-yl)piperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol;
3-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol;
- 15 1-(7-(5-cyclopropyl-6-methyl-1H-indazol-4-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
4-(4-(3-(1H-1,2,4-triazol-5-yl)piperidin-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3-carboxamide;
- 20 1-(8-fluoro-7-(3-hydroxynaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
(3R)-1-(7-(6-chloro-5-(2-methylcyclopropyl)-1H-indazol-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 25 (3R)-1-(7-(1H-benzo[f]indazol-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
1-(1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide;
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- 5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(pyridin-4-yl)azetidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol;
1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepane-4-carbonitrile;
- 5 (3R,5R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5-fluoropiperidin-3-ol;
(3S,4S)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-4-fluoropiperidin-3-ol;
- 10 (3R,5S)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5-methylpiperidin-3-ol;
(2R,3R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperidin-3-ol;
- 15 (3R,6R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methylpiperidin-3-ol;
- 20 1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-(trifluoromethyl)piperidin-3-ol;
3-(difluoromethyl)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol;
(2S,3R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperidin-3-ol;
- 25 (3R,6S)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methylpiperidin-3-ol;

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(3R,5R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5-methylpiperidin-3-ol;

(3R,4S)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-4-methylpiperidin-3-ol;

(3R,4R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-4-methylpiperidin-3-ol;

- 5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione;
1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-N-methylpiperidine-3-sulfonamide;
5 2-(1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)isothiazolidine-1,1-dioxide;
8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-[3-(sulfamoylamino)piperidin-1-yl]pyrido[4,3-d]pyrimidine;
1-(1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)urea;
10 N-(1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)formamide;
1-(1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-4-yl)urea;
15 N-(1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-4-yl)formamide;
6-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6,7,8,9-tetrahydro-5H-pyrido[3,2-c]azepine;
1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)sulfamate;
20 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(methylsulfonyl)azepan-1-yl)pyrido[4,3-d]pyrimidine;
8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(methylsulfonyl)azocan-1-yl)pyrido[1,3-d]pyrimidine;
25 4-(3-(1H-1,2,4-triazol-1-yl)azetidin-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine;
1-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoro-7-(8-fluoronaphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((1-(pyrrolidin-1-ylmethyl)cyclopropyl)methoxy)pyrido[1,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
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- (R)-(1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanol;
- (S)-1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3-carboxamide;
- 5 5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethyl-5,6,7,8-tetrahydropyrazolo[4,3-c]azepine-2(4H)-carboxamide;
- 1-(1-(7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide;
- 10 1-(1-(7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide;
- 3-(7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol;
- 5-(7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione;
- 15 4-(3-(1H-1,2,4-triazol-3-yl)piperidin-1-yl)-7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine;
- (3R,5R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3,5-
- 20 diol;
- 1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol;
- (R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((3R,7aS)-3-(hydroxymethyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-
- 25 3-methylpiperidin-3-ol;
- (R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((3S,7aR)-3-(hydroxymethyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-
- 3-methylpiperidin-3-ol;
- (R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((3R,7aR)-3-(hydroxymethyl)hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-
- 30 3-methylpiperidin-3-ol;

- (R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((3S,7aS)-3-(hydroxymethyl)hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol;
- 5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(methylsulfonyl)azepan-1-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol;
- 5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(methylsulfonyl)azocan-1-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol;
- 10 (2R,7aS)-7a-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-4-((R)-3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)hexahydro-1H-pyrrolizin-2-ol;
- N-(1-(dimethylamino)propan-2-yl)-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-1-((R)-3-hydroxy-3-methylpiperidin-1-yl)pyrido[1,3-d]pyrimidine-2-carboxamide;
- ((3S,7aR)-7a-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-4-((R)-3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl dimethylcarbamate;
- 15 ((3S,7aS)-7a-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-4-((R)-3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl dimethylcarbamate;
- 20 (R)-1-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 4-(4-(azepan-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- (1R,5R,6R)-3-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-((1-(pyrrolidin-1-yl)methyl)cyclopropyl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol;
- 25 4-(4-(azocan-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- (3RS,5RS)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5-
- 30 (hydroxymethyl)-3-methylpiperidin-3-ol;

- (R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-((1-(piperidin-1-ylmethyl)cyclopropyl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
 (R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-((1-(morpholinomethyl)cyclopropyl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
 5 7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)hexahydro-2,7-naphthyridine-1,3(2H,4H)-dione;
 (R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-((1-(4-methylpiperazin-1-yl)methyl)cyclopropyl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
 10 1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-4-ol;
 1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-3-ol;
 2-(1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-
 15 fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)isothiazolidine-1,1-dioxide;
 4-(4-(3-azabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
 7-(8-ethyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-
 20 pyrrolizin-7a-yl)methoxy)-4-[3-(sulfamoylamino)-1-piperidyl]pyrido[4,3-d]pyrimidine;
 5-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethyl-5,6,7,8-tetrahydropyrazolo[4,3-c]azepine-2(4H)-carboxamide;
 (1R,5R,6R)-3-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-7-(8-ethyl-7-fluoro-3-
 25 hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol;
 (((3R,7aR)-7a-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-4-((R)-3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl dimethylcarbamate;

- (4aR,7aS)-6-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)hexahydro-1H-pyrrolo[3,4-d]pyridazine-1,4(4aH)-dione;
- (R)-1-(2-(3-(dimethylamino)-2,2-dimethylpropoxy)-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 5 1-(2-(2-(dimethylamino)ethoxy)-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol;
- (1R,5R,6R)-3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-
- 10 azabicyclo[3.2.1]octan-6-ol;
- 5-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione;
- 6-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-
- 15 azabicyclo[3.2.1]octan-3-ol;
- (R)-1-(7-(8-bromo-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 20 3-(7-(8-bromo-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol;
- 6-(7-(8-bromo-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-
- 25 azabicyclo[3.2.1]octan-3-ol;
- 5-(7-(8-bromo-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione;
- 1-(1-(7-(8-chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide;
- 30

- (R)-1-(7-(8-chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 3-(7-(8-chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol;
- 6-(7-(8-chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-3-ol;
- 5-(7-(8-chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione;
- 1-(8-fluoro-7-(2-fluoro-5-hydroxyphenyl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(5-methyl-1H-indazol-4-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 1-(8-fluoro-7-(6-methyl-1H-indazol-4-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(5-hydroxy-2-methylphenyl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (R)-1-(7-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (1-(8-fluoro-7-(naphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide;
- 1-(1-(7-(8-ethynynaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide;
- 1-(1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-methylnaphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide;
- 1-(1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-(hydroxymethyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide;

- 1-(7-(8-cyclopropylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
4-(3-(1H-1,2,4-triazol-3-yl)piperidin-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-methylnaphthalen-1-yl)pyrido[4,3-d]pyrimidine;
5 8-(4-(3-(1H-1,2,4-triazol-3-yl)piperidin-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-1-naphthonitrile;
(3aR,6aS)-5-(7-(8-ethynylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione;
1-(7-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-fluoro-2-(((2R,7aS)-2-
10 fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
1-(1-(8-fluoro-7-(8-(fluoromethyl)naphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide;
1-(1-(8-fluoro-7-(7-fluoro-3-hydroxy-8-methylnaphthalen-1-yl)-2-(((2R,7aS)-2-
15 fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide;
1-(1-(7-(8-(difluoromethyl)naphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide;
1-(1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-
20 (trifluoromethyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide;
1-(7-(5,6-dimethyl-1H-indazol-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
(3R)-1-(7-(8-ethyl-2-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-
25 fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
(3R)-1-(7-(5-ethyl-1H-benzo[f]indazol-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
5-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-
30 1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-N-isopropyl-5,6,7,8-tetrahydropyrazolo[4,3-c]azepine-2(4H)-carboxamide;

- 5-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3a-methyltetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione;
- (1R,5R,6S,7R)-3-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-7-(hydroxymethyl)-3-azabicyclo[3.2.1]octan-6-ol;
- 5-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)hexahydro-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione;
- (3R,3aR,6aS)-5-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-(hydroxymethyl)hexahydropyrrolo[3,4-c]pyrrol-1(2H)-one;
- (3R,6R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepane-3,6-diol;
- (3R,6S)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepane-3,6-diol;
- ((3S,7aS)-7a-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-4-((R)-3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl morpholine-4-carboxylate;
- ((3R,7aS)-7a-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-4-((R)-3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl dimethylcarbamate;
- (R)-1-(7-(7,8-difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (R)-1-(7-(3-chloro-2-cyclopropyl-5-hydroxyphenyl)-2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 5-(7-(3-chloro-2-cyclopropyl-5-hydroxyphenyl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione; or

(3R)-1-(7-(5,6-dimethyl-1H-indazol-4-yl)-2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol.

- Provided herein as embodiment 312 is the compound according to embodiment 1,
- 5 wherein the compound is not:
- 1-(7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (S)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-
- 10 methylpiperidin-3-ol;
- (R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (3R,5S)-5-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-4-(piperidin-1-
- 15 yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)-1-methylpyrrolidin-3-ol;
- (2R,7aS)-7a-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)hexahydro-1H-pyrrolizin-2-ol;
- 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-4-ol;
- 20 [(3R,5S)-5-[[7-(8-ethyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-4-[(3S)-3-hydroxy-3-methyl-1-piperidyl]pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1-methyl-pyrrolidin-3-yl] N-methylcarbamate;
- (S)-1-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-
- 25 methylpiperidin-3-ol;
- 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-4-ol;
- (3R,5S)-5-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-4-((R)-3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)-1-methylpyrrolidin-3-yl
- 30 methylcarbamate;

- (R)-1-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (R)-1-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (R)-1-(6-(8-ethyl-7-fluoronaphthalen-1-yl)-5-fluoro-3-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-1-yl)-3-methylpiperidin-3-ol;
- (R)-1-(7-(8-ethyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 4-((1R,5S)-3-azabicyclo[3.2.1]octan-3-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine;
- 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine;
- 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidine;
- 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol;
- 1-(7-(5,6-dimethyl-1H-indazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrroliziri-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (3R)-1-[7-(8-ethyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-2-[(2S)-1-methylpyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 4-(3-(1H-1,2,4-triazol-3-yl)piperidin-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine;
- 4-(2-azabicyclo[4.1.0]heptan-2-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine;
- 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(octahydro-1H-cyclopenta[b]pyridin-1-yl)pyrido[4,3-d]pyrimidine;

- (3R,5S)-1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5-methylpiperidin-3-ol;
1-(7-(2-amino-5,6-dimethylbenzo[d]thiazol-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
5 1-(7-(2-amino-5,6-dimethylbenzo[d]thiazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
4-(azocan-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine;
1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-3-ol;
10 (R)-1-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
4-(3,3-dimethylpiperidin-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine;
15 1-(7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
1-(7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
8-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)-1-naphthonitrile;
20 6-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-3-ol;
(3R,5R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3,5-diol;
25 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylazepan-3-ol;
1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(quinolin-8-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
30 1-(7-(2-aminobenzo[d]thiazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;

- 1-(7-(benzo[d]thiazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 5 1-(7-(3-chloro-2-cyclopropyl-5-hydroxyphenyl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 4-(3-(1H-imidazol-1-yl)azetidin-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine;
- 6-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-3-ol;
- 10 3-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol;
- 3-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol;
- 15 ol;
- 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3-carboxamide;
- 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepane-4-carbonitrile;
- 20 (3S,5R)-1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3,5-diol;
- 4-(3-(1H-imidazol-1-yl)azetidin-1-yl)-7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine;
- 4-(2-(1H-pyrazol-4-yl)pyrrolidin-1-yl)-7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine;
- 25 6-(7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-3-ol;
- 4-(3-(1H-1,2,3-triazol-4-yl)piperidin-1-yl)-7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine;
- 30 4-(3-(1H-pyrazol-1-yl)piperidin-1-yl)-7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine;

- (3R,5R)-1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5-methylpiperidin-3-ol;
(1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanol;
5 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methylazepan-4-ol;
1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-(hydroxymethyl)piperidin-4-ol;
2-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)isoindolin-4-ol;
10 4-(3,6-dihydropyridin-1(2H)-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine;
1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-4-ol;
15 (1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-3-yl)methanol;
4-(3-(1H-pyrazol-3-yl)piperidin-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine;
1-(7-(3-chloro-5-hydroxy-2-((1S,2R)-2-methylcyclopropyl)phenyl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
20 4-(4-(3-(1H-imidazol-1-yl)azetidin-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
4-(4-(3-(1H-1,2,4-triazol-5-yl)piperidin-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5,6-difluoronaphthalen-2-ol;
25 5,6-difluoro-4-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(3-methyl-1H-1,2,4-triazol-5-yl)piperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol;
3-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol;
1-(7-(5-cyclopropyl-6-methyl-1H-indazol-4-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
30

- 4-(4-(3-(1H-1,2,4-triazol-5-yl)piperidin-1-yl)-8-fluoro-2-(((2R, 7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R, 7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3-carboxamide;
- 5 1-(8-fluoro-7-(3-hydroxynaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
(3R)-1-(7-(6-chloro-5-(2-methylcyclopropyl)-1H-indazol-4-yl)-8-fluoro-2-(((2R, 7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 10 (3R)-1-(7-(1H-benzo[f]indazol-4-yl)-8-fluoro-2-(((2R, 7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
1-(1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R, 7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide;
- 15 5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R, 7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(pyridin-4-yl)azetidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol;
1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R, 7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepane-4-carbonitrile;
(3R,5R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R, 7aS)-2-
- 20 fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5-fluoropiperidin-3-ol;
(3S,4S)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R, 7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-4-fluoropiperidin-3-ol;
- 25 (3R,5S)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R, 7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5-methylpiperidin-3-ol;
(2R,3R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R, 7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-
- 30 methylpiperidin-3-ol;

- (3R,6R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methylpiperidin-3-ol;
- 1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-(trifluoromethyl)piperidin-3-ol;
- 5 3-(difluoromethyl)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol;
- (2S,3R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[1,3-d]pyrimidin-4-yl)-2-methylpiperidin-3-ol;
- 10 ol;
- (3R,6S)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methylpiperidin-3-ol;
- (3R,5R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5-methylpiperidin-3-ol;
- 15 methylpiperidin-3-ol;
- (3R,4S)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-4-methylpiperidin-3-ol;
- 20 (3R,4R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-4-methylpiperidin-3-ol;
- 1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5,5-difluoropiperidin-3-ol;
- 25 1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-4,4-difluoropiperidin-3-ol;
- (3R,5S)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5-fluoropiperidin-3-ol;

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(R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol;

5 5-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione;

(3R)-1-[7-(8-ethyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-2-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3-methylpiperidin-3-ol;
 1-(1-(7-(8-di-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide; or

8-fluoro-7-(8-fluoronaphthalen-1-yl)-4-(3-(pyridin-4-yl)azetidin-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine.

Provided herein as embodiment 313 is the compound according to embodiment 1,
 15 wherein the compound is selected from one of the following compounds:

1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-3-one;

(R)-1-(7-(8-Ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;

20 (R)-1-(7-(8-Cyclopropyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;

3-(Difluoromethyl)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol (Isomer 1);

(R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aR)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;

3-(Difluoromethyl)-1-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol (Isomer 1);

- (1*R*,5*R*,6*R*)-3-(7-(8-ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 1);
- (1*R*,5*R*,6*R*)-3-(7-(8-ethynyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 1);
- (*R*)-1-(7-(8-Chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (*R*)-1-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 2);
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylazepan-3-ol (Isomer 2);
- (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-4-one;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2,3,6,7-tetrahydro-1*H*-azepin-3-ol;
- 4-(4-((*R*)-5-Amino-3,3-difluoropiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- rac*-(3*S*,5*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-fluoropiperidin-3-ol;
- 4-(4-(Azepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5,6-difluoronaphthalen-2-ol;

- 4-(4-(Azocan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-difluoropiperidin-3-ol;
5 (R)-1-(7-(8-Ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;
4-(4-(Azepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
(R)-1-(8-Fluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
10 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-4-carbonitrile
(Isomer 1);
5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(2,3,6,7-tetrahydro-1*H*-azepin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
15 *rac*-(3*R*,5*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-methylpiperidin-3-ol;
20 *N*-((R)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-yl)-2,2-difluoroacetamide;
3-Ethyl-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;
25 ol;
(R)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-sulfonamide; or
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-(trifluoromethyl)piperidin-3-ol.
30

Provided herein as embodiment 314 is the compound according to embodiment 1, wherein the compound is selected from one of the following compounds:

- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-one;
- 5 (R)-1-(7-(8-Cyclopropyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 3-(Difluoromethyl)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-
- 10 3-ol (Isomer 1);
- (R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aR*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 3-(Difluoromethyl)-1-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-
- 15 (((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol (Isomer 1);
- (1*R*,5*R*,6*R*)-3-(7-(8-ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-
- azabicyclo[3.2.1]octan-6-ol (Isomer 1);
- 20 (1*R*,5*R*,6*R*)-3-(7-(8-ethynyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-
- azabicyclo[3.2.1]octan-6-ol (Isomer 1);
- (R)-1-(7-(8-Chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-
- 25 methylpiperidin-3-ol;
- (R)-1-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-
- 30 azabicyclo[3.2.1]octan-6-ol (Isomer 2);

- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylazepan-3-ol (Isomer 2);
- (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-4-one;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2,3,6,7-tetrahydro-1*H*-azepin-3-ol;
- 4-(4-((*R*)-5-Amino-3,3-difluoropiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- rac*-(3*S*,5*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-fluoropiperidin-3-ol;
- 4-(4-(Azepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5,6-difluoronaphthalen-2-ol;
- 4-(4-(Azocan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-difluoropiperidin-3-ol;
- (*R*)-1-(7-(8-Ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;
- 4-(4-(Azepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- (*R*)-1-(8-Fluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepane-4-carbonitrile (Isomer 1);

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5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(2,3,6,7-tetrahydro-1*H*-azepin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;

rac-(3*R*,5*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-methylpiperidin-3-ol;

N-((*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-yl)-2,2-difluoroacetamide;

3-Ethyl-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;

(*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-sulfonamide; or

1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-(trifluoromethyl)piperidin-3-ol.

Provided herein as embodiment 315 is the compound according to embodiment 1, wherein the compound is selected from one of the following compounds:

(*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-sulfonamide;

4-(4-(Azepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;

1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidine-3-carboxamide;

(*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidine-

2-carboxamide;

- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azetidine-2-carboxamide;
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide;
5 (S)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-sulfonamide;
2-(1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azetidin-3-yl)acetamide;
10 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.0]heptan-6-ol;
(*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;
15 (3*S*,4*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidine-3,4-diol;
20 (*R*)-1-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;
(*R*)-1-(7-(8-Ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;
(S)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;
25 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(3-methoxypiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidin-3-ol;
30

- (1*R*,4*S*)-2-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-azabicyclo[2.2.2]octan-6-ol;
- 3-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol;
- 5 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*S*)-2-(hydroxymethyl)azetidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 4-(4-((1*S*,5*R*)-3-Oxa-6-azabicyclo[3.2.0]heptan-6-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 10 *rel*-4-(4-((1*R*,5*R*)-2-Oxa-6-azabicyclo[3.2.0]heptan-6-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 15 4-(4-(3-(Chloromethyl)-3-(hydroxymethyl)piperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 1);
- 20 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 2);
- (1*R*,5*R*,6*R*)-3-(7-(8-ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 1);
- 25 (1*R*,5*R*,6*R*)-3-(7-(3-chloro-2-cyclopropyl-5-hydroxyphenyl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 1);

- (1*R*,5*R*,6*R*)-3-(7-(8-ethynyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 1);
- 1-(7-(8-Ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-dimethylpiperidin-3-ol;
- (3*R*,6*S*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-methylpiperidin-3-ol;
- 8-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octan-2-ol 2,2,2-trifluoroacetate;
- (3*R*,6*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-methylpiperidin-3-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(hexahydro-5*H*-furo[2,3-*c*]pyrrol-5-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 3-(Difluoromethyl)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol (Isomer 1);
- 3-(Difluoromethyl)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol (Isomer 2);
- 3-(Difluoromethyl)-1-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol (Isomer 1);
- rel*-5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((3*aR*,7*aR*)-hexahydrofuro[3,2-*b*]pyridin-4(2*H*)-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;

- (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-(fluoromethyl)piperidin-3-ol (Isomer 1);
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-(fluoromethyl)piperidin-3-ol (Isomer 2);
(3*R*)-1-(7-(8-ethyl-3-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol (Isomer 2);
(3*R*)-1-(7-(8-ethyl-3-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol (Isomer 1);
(3*R*)-1-(7-(8-Allyl-3-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-dimethylpiperidine-3-carboxamide;
4-(4-((*R*)-3-Aminopiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
4-(4-((*S*)-3-Amino-3-methylpiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
4-(4-((*R*)-3-Amino-3-methylpiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
(3*R*,4*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-4-fluoropiperidin-3-ol;
(*R*)-1-(7-(7,8-Difluoronaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;

- (*R*)-1-(7-(8-Ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
2-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-azabicyclo[2.2.1]heptan-6-ol;
5 ol;
(*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aR*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
(*R*)-1-(7-(8-Chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
10 fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
(*R*)-1-(8-Fluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
(*R*)-1-(7-(8-Ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
15 pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
(*R*)-1-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
(*R*)-1-(8-Fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-7-(3-hydroxynaphthalen-1-yl)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
20 *rel*-(3*aR*,6*aS*)-5-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)hexahydropyrrolo[3,4-*c*]pyrrol-1(2*H*)-one;
5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-*rel*-((3*aR*,7*aS*)-hexahydrofuro[3,2-*c*]pyridin-5(4*H*)-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
25 7-yl)naphthalen-2-ol;
rel-(3*aR*,7*aR*)-4-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)octahydro-2*H*-pyrrolo[3,2-*b*]pyridin-2-one;
rel-(3*S*,6*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-methylpiperidine-3-carboxamide;
30 methylpiperidine-3-carboxamide;

- 3-Ethyl-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*S*)-3-(hydroxymethyl)-3-methylpiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*R*)-3-(hydroxymethyl)-3-methylpiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 10 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidine-3-carboxamide;
- 8-(7-(8-Ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-methyl-8-
- 15 azabicyclo[3.2.1]octan-2-ol;
- 8-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-methyl-8-
- azabicyclo[3.2.1]octan-2-ol;
- 2-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-methyl-2-
- 20 azabicyclo[2.2.1]heptan-6-ol;
- 2-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-azabicyclo[2.2.1]heptan-6-one;
- 25 *N*-((*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-yl)acetamide;
- 1-((*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-
- 30 yl)-3-(2-methoxyethyl)thiourea;

- N*-((*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-yl)methanesulfonamide;
- 5 *N*-((*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-yl)acetamide;
- Methyl ((*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-yl)carbamate;
- 10 Methyl ((*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-yl)carbamate;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-*N*-methylpiperidine-3-sulfonamide;
- 15 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*R*)-2-methylazepan-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*S*)-2-methylazepan-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 20 (1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azetidin-3-yl)methanesulfonamide;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-hydroxyazetidine-3-carboxamide;
- 25 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(3-(methylsulfonyl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-4-sulfonamide;
- 30

- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidine-3-sulfonamide;
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azetidine-3-sulfonamide;
5 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azetidine-3-carboxamide;
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-*N*-methylpiperidine-3-carboxamide;
10 (*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-carboxamide;
4-(4-(3-(1*H*-Imidazol-1-yl)azetidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
15 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylazetidin-3-ol;
4-(4-(Azocan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-4-one;
20 *rac*-(3*R*,5*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-methylpiperidin-3-ol;
3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-ol;
25 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-8-methyl-3-azabicyclo[3.2.1]octan-8-ol;

- 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[4.1.0]heptan-1-ol;
- rel*-(3*R*,4*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3,4-diol;
- rel*-(3*S*,4*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3,4-diol;
- rel*-(3*aR*,7*aR*)-5-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)octahydro-3*H*-pyrrolo[3,4-*c*]pyridin-3-one;
- 4-(4-((*S*)-3-Aminopiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 4-(4-(3-Azabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 4-(4-(3-(1*H*-Imidazol-4-yl)piperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 4-(4-(3-(1*H*-Pyrazol-5-yl)piperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(3-(oxazol-5-yl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-1,2,3,6-tetrahydropyridin-3-ol;
- N*-(1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide;
- 5-Ethyl-6-fluoro-4-(8-fluoro-4-((2*S*,4*S*)-4-fluoro-2-(hydroxymethyl)pyrrolidin-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;

- (3*R*,4*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-4-fluoropiperidin-3-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*R*)-2-(hydroxymethyl)pyrrolidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- rac*-(3*S*,5*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-fluoropiperidin-3-ol;
- 10 (3*S*,4*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidine-3,4-diol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-difluoropiperidin-3-ol;
- 15 ((*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidin-2-yl)methanesulfonamide;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-difluoroazepan-4-ol;
- 20 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octane-1-carboxamide;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((3*aR*,6*aS*)-tetrahydro-1*H*-furo[3,4-*c*]pyrrol-5(3*H*)-yl)pyrido[4,3-*d*]pyrimidin-
- 25 7-yl)naphthalen-2-ol;
- rac*-(1*S*,5*S*)-8-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octane-2-carboxamide;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(3-(2-hydroxypropan-2-yl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-
- 30 yl)naphthalen-2-ol;

- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*S*)-3-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- Methyl (*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-carboxylate;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-one;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*R*)-3-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-ol;
- (*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-ol;
- 4-(4-((*R*)-3-Aminoazepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- N*-((*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-yl)-2,2-difluoroacetamide;
- N*-((*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-yl)acetamide;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-1,2,6,7-tetrahydro-3*H*-azepin-3-one;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2,3,6,7-tetrahydro-1*H*-azepin-3-ol;

- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylazepan-3-ol (Isomer 1);
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylazepan-3-ol (Isomer 2);
- (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-carboxylic acid;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(2,3,6,7-tetrahydro-1*H*-azepin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 4-(4-((*R*)-5-Amino-3,3-difluoropiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-4-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-4-methylazepan-4-ol;
- 4-(4-(4-Aminoazepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(4-methyleneazepan-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octane-6-carbonitrile (Isomer Mix 1);
- 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octane-6-carbonitrile (Isomer Mix 2);
- 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.2]nonane-6-carbonitrile;

- (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-(methyl-*d*3)piperidin-3-ol;
- (*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-(methyl-*d*3)piperidin-3-ol;
- 5 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(3-methoxy-3-methylpiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 10 4-(4-(4,4-Difluoroazepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-difluoroazepan-4-one;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-carbonitrile;
- 15 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3,3-difluoropiperidin-4-one;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-4-ol;
- 20 (3*R*,5*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-(trifluoromethyl)piperidin-3-ol;
- 6-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-2-
- 25 ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-(trifluoromethyl)piperidin-3-ol;
- 3-Cyclopropyl-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-
- 30 ol;

- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepane-3-sulfonamide;
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-hydroxypiperidine-3-
5 carboxamide;
4-(4-(3-((Difluoromethyl)sulfonyl)piperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-methylpiperidine-3-
10 carboxamide;
(*R*)-1-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-sulfonamide;
4-(4-(Azepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-
15 yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5,6-difluoronaphthalen-2-ol;
(*R*)-1-(7-(8-Cyclopropyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
(*R*)-1-(8-Chloro-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-
20 methylpiperidin-3-ol;
(*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-8-methylpyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
(*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*S*,7*aR*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol bis(2,2,2-trifluoroacetate);
(*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol; or
30 (*R*)-1-(2-((1-((Dimethylamino)methyl)cyclopropyl)methoxy)-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol.

Provided herein as embodiment 316 is the compound according to embodiment 1, wherein the compound is selected from one of the following compounds:

- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-one;
- 5 (R)-1-(7-(8-Cyclopropyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 3-(Difluoromethyl)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-
- 10 3-ol (Isomer 1);
- (R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aR*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 3-(Difluoromethyl)-1-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-
- 15 (((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol (Isomer 1);
- (1*R*,5*R*,6*R*)-3-(7-(8-ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-
- azabicyclo[3.2.1]octan-6-ol (Isomer 1);
- 20 (1*R*,5*R*,6*R*)-3-(7-(8-ethynyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-
- azabicyclo[3.2.1]octan-6-ol (Isomer 1);
- (R)-1-(7-(8-Chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-
- 25 methylpiperidin-3-ol;
- (R)-1-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-
- 30 azabicyclo[3.2.1]octan-6-ol (Isomer 2);

- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylazepan-3-ol (Isomer 2);
- (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-4-one;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2,3,6,7-tetrahydro-1*H*-azepin-3-ol;
- 4-(4-((*R*)-5-Amino-3,3-difluoropiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- rac*-(3*S*,5*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-fluoropiperidin-3-ol;
- 4-(4-(Azepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5,6-difluoronaphthalen-2-ol;
- 4-(4-(Azocan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-difluoropiperidin-3-ol; or
- (*R*)-1-(7-(8-Ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol.

- Provided herein as embodiment 317 is the compound according to embodiment 1,
- wherein the compound is selected from one of the following compounds:
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-one;
- (*R*)-1-(7-(8-Cyclopropyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;

- 3-(Difluoromethyl)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol (Isomer 1);
- (*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aR*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 3-(Difluoromethyl)-1-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol (Isomer 1);
- (1*R*,5*R*,6*R*)-3-(7-(8-ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 1);
- (1*R*,5*R*,6*R*)-3-(7-(8-ethynyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 1);
- (*R*)-1-(7-(8-Chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (*R*)-1-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol; or
- 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 2).

- Provided herein as embodiment 318 is the compound according to embodiment 1,
- wherein the compound is selected from one of the following compounds:
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-one;
- (*R*)-1-(7-(8-Cyclopropyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;

3-(Difluoromethyl)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol (Isomer 1);

(*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aR*)-2-

5 fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol; or

3-(Difluoromethyl)-1-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol (Isomer 1).

10 Provided herein as embodiment 319 is the compound according to embodiment 1, wherein the compound is selected from one of the following compounds:

1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-(fluoromethyl)piperidin-3-ol (Isomer 1);

15 (*R*)-1-(7-(8-Ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;

(3*R*)-1-(7-(8-Allyl-3-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;

20 (*R*)-1-(7-(8-Cyclopropyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;

(*R*)-1-(2-((1-((Dimethylamino)methyl)cyclopropyl)methoxy)-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;

25 3-(Difluoromethyl)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol (Isomer 1);

(*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aR*)-2-

fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-

30 methylpiperidin-3-ol;

- (3R)-1-(7-(8-ethyl-3-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (Isomer 2);
- 3-(Difluoromethyl)-1-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol (Isomer 1);
- (1R,5R,6R)-3-(7-(8-ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 1);
- (1R,5R,6R)-3-(7-(8-ethynyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 1);
- (R)-1-(7-(8-Chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (R)-1-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (R)-1-(8-Chloro-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 2);
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylazepan-3-ol (Isomer 2);
- (R)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8-methylpyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (R)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-3-ol;

- 4-(4-((*R*)-5-Amino-3,3-difluoropiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
rac-(3*S*,5*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-fluoropiperidin-3-ol;
 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-difluoropiperidin-3-ol;
 4-(4-(Azepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
 10 *rac*-(3*R*,5*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-methylpiperidin-3-ol; or
N-((*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-yl)-2,2-difluoroacetamide.

- Provided herein as embodiment 320 is the compound according to embodiment 1, wherein the compound is selected from one of the following compounds:
- (*R*)-1-(7-(8-Ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
 20 (*R*)-1-(7-(8-Cyclopropyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
 3-(Difluoromethyl)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol (Isomer 1);
 25 3-(Difluoromethyl)-1-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol (Isomer 1);
 (1*R*,5*R*,6*R*)-3-(7-(8-ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 1);
 30

- (*R*)-1-(7-(8-Chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (*R*)-1-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (*R*)-1-(8-Chloro-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 2);
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylazepan-3-ol (Isomer 2);
- (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-8-methylpyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-ol;
- 4-(4-(((*R*)-5-Amino-3,3-difluoropiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- rac*-(3*S*,5*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-fluoropiperidin-3-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-difluoropiperidin-3-ol;
- 4-(4-(Azepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- rac*-(3*R*,5*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-methylpiperidin-3-ol; or

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N-((R)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-3-yl)-2,2-difluoroacetamide.

Provided herein as embodiment 321 is the compound according to embodiment 1,
5 wherein the compound is not example 1, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 21, 22, 23, 25, 27, 28, 30, 31, 32, 33, 39, 40, 41, 44, 51, 53, 54, 55, 56, 58, 59, 65, 66, 67, 68, 69, 71, 75, 76, 81, 82, 86, 87, 89, 101, 104, 106, 108, 109, 112, 113, 116, 117, 120, 123, 129, 130, 131, 132, 134, 137, 138, 140, 144, 145, 147, 151, 153, 154, 170, 172, 173, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 197, 202, 203, 213,
10 221, 228, 237, 239, 240, 241, 242, 243, 244, 246, 248, 250, 251, 253, 256, 257, 268, 273, 274, 281, 285, 290, 292, 295, 296, 299, 301, 302, 303, 304, 306, 308, 309, 311, 312, 313, 314, 316, 317, 320, 325, 327, 331, 332, 335, 336, 346, 347, 348, 350, 352, 353, 360, 362, 363, 366, 387, 388, 389, 390, 399, 402, 403, 404, 414, 418, 421, 422, 423, 429, 430, 431, 432, 435, 436, 437, 438, 439, 440, 455, 456, 458, 459, 460, 461, 463, 465, 471, 472, 473,
15 479, 482, 486, 487, 488, 490, 491, 511, 512, 514, 517, 519 or 520 from international publication No. WO 2022/132200 (International Application No. PCT/US2021/010065).

Provided herein as embodiment 322 is the compound according to embodiment 1,
wherein the compound is not example 1, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 21,
22, 23, 25, 27, 28, 30, 31, 32, 33, 39, 40, 41, 44, 51, 53, 54, 55, 56, 58, 59, 65, 66, 67, 68, 69,
20 71, 75, 76, 81, 82, 86, 87, 89, 101, 104, 106, 108, 109, 112, 113, 116, 117, 120, 123, 129, 130, 131, 132, 134, 137, 138, 140, 144, 145, 147, 151, 153, 154, 170, 172, 173, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 197, 202 or 203 from international publication No. WO 2022/132200 (International Application No. PCT/US2021/010065).

25 The foregoing merely summarizes certain aspects of this disclosure and is not intended, nor should it be construed, as limiting the disclosure in any way.

Formulation, and Route of Administration

While it may be possible to administer a compound disclosed herein alone in the uses described, the compound administered normally will be present as an active ingredient in a
30 pharmaceutical composition. Thus, in one embodiment, provided herein is a pharmaceutical

composition comprising a compound disclosed herein in combination with one or more pharmaceutically acceptable excipients, such as diluents, carriers, adjuvants and the like, and, if desired, other active ingredients. *See, e.g.*, Remington: The Science and Practice of Pharmacy, Volume I and Volume II, twenty-second edition, edited by Loyd V. Allen Jr., Philadelphia, PA, Pharmaceutical Press, 2012; Pharmaceutical Dosage Forms (Vol. 1-3), Liberman et al., Eds., Marcel Dekker, New York, NY, 1992; Handbook of Pharmaceutical Excipients (3rd Ed.), edited by Arthur H. Kibbe, American Pharmaceutical Association, Washington, 2000; Pharmaceutical Formulation: The Science and Technology of Dosage Forms (Drug Discovery), first edition, edited by GD Tovey, Royal Society of Chemistry, 2018. In one embodiment, a pharmaceutical composition comprises a therapeutically effective amount of a compound disclosed herein.

The compound(s) disclosed herein may be administered by any suitable route in the form of a pharmaceutical composition adapted to such a route and in a dose effective for the treatment intended. The compounds and compositions presented herein may, for example, be administered orally, mucosally, topically, transdermally, rectally, pulmonarily, parentally, intranasally, intravascularly, intravenously, intraarterial, intraperitoneally, intrathecally, subcutaneously, sublingually, intramuscularly, intrasternally, vaginally or by infusion techniques, in dosage unit formulations containing conventional pharmaceutically acceptable excipients.

The pharmaceutical composition may be in the form of, for example, a tablet, chewable tablet, minitab, caplet, pill, bead, hard capsule, soft capsule, gelatin capsule, granule, powder, lozenge, patch, cream, gel, sachet, microneedle array, syrup, flavored syrup, juice, drop, injectable solution, emulsion, microemulsion, ointment, aerosol, aqueous suspension, or oily suspension. The pharmaceutical composition is typically made in the form of a dosage unit containing a particular amount of the active ingredient.

Provided herein as embodiment 323 is a pharmaceutical composition comprising the compound according to any one of embodiments 1-322, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, and a pharmaceutically acceptable excipient.

Provided herein as embodiment 324 is a compound according to any one of Embodiments 1-322, or a tautomer thereof, or a pharmaceutically acceptable salt of said

compound or said tautomer, or the pharmaceutical composition according to embodiment 323 for use as a medicament.

Methods of Use

As discussed herein (see, section entitled “Definitions”), the compounds described
5 herein are to be understood to include all stereoisomers, tautomers, or pharmaceutically acceptable salts of any of the foregoing or solvates of any of the foregoing. Accordingly, the scope of the methods and uses provided in the instant disclosure is to be understood to encompass also methods and uses employing all such forms.

Besides being useful for human treatment, the compounds provided herein may be
10 useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. For example, animals including horses, dogs, and cats may be treated with compounds provided herein.

In one embodiment, the disclosure provides methods of using the compounds or pharmaceutical compositions of the present disclosure to treat disease conditions, including
15 but not limited to conditions implicated by KRAS G12D, G12V, G12A, G12S or G12C mutation (e.g., cancer). The cancer types are non-small cell lung cancer, colorectal cancer, pancreatic cancer, appendiceal cancer, endometrial cancer, esophageal cancer, cancer of unknown primary, ampullary cancer, gastric cancer, small bowel cancer, sinonasal cancer, bile duct cancer, or melanoma.

20 KRAS G12D mutations occur with the alteration frequencies shown in the table below (TCGA data sets; ¹⁻³ For example, the table shows that 32.4% of subjects with pancreatic cancer have a cancer wherein one or more cells express KRAS G12D mutant protein. Accordingly, the compounds provided herein, which bind to KRAS^{G12D} (see Section entitled “Biological Evaluation” below) are useful for treatment of subjects having a cancer,
25 including, but not limited to the cancers listed in the table below.

Cancer Type	Alteration Frequency
Pancreatic Adenocarcinoma (PAAD)	32.4
Colon Adenocarcinoma (COAD)	12.25
Rectal adenocarcinoma (READ)	8.03

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Uterine corpus endometrial carcinoma (UCEC)	6.04
Lung Adenocarcinoma (LUAD)	3.53
Plasma Cell Tumors	2.92
Stomach Adenocarcinoma (STAD)	2.27
Bladder urothelial carcinoma (BLCA)	1.46
Cervical Squamous carcinoma (CESC)	1.38
Kidney Adenocarcinoma	1.07
Thymic Cancer	0.81
Myeloid Leukemia (LAML)	0.69
Liver Hepatocellular Carcinoma (LIHC)	0.55
Glioblastoma multiforme (GBM)	0.51
Skin Cutaneous Melanoma (SKCM)	0.43
Bladder Cancer	0.4
Prostate Adenocarcinoma (PRAD)	0.2
Breast Invasive Carcinoma (BRCA)	0.1

Provided herein as embodiment 325 is a compound according to any one of embodiments 1-322 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to embodiment 323 for use in treating cancer.

- 5 Provided herein as Embodiment 326 is a compound according to any one of Embodiments 1-322 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to Embodiment 323 for use in treating cancer, wherein one or more cells express KRAS G12D, G12V, G12A, G12S or G12C mutant protein.

- 10 Provided herein as Embodiment 327 is the compound or pharmaceutical composition for use of Embodiment 325 or 326, wherein the cancer is pancreatic cancer, colorectal cancer, non-small cell lung cancer, small bowel cancer, appendiceal cancer, cancer of unknown primary, endometrial cancer, mixed cancer types, hepatobiliary cancer, small cell lung cancer, cervical cancer, germ cell cancer, ovarian cancer, gastrointestinal neuroendocrine cancer, bladder cancer, myelodysplastic/myeloproliferative neoplasms, head and neck cancer, esophagogastric cancer, soft tissue sarcoma, mesothelioma, thyroid cancer, leukemia, or
15 melanoma.

Provided herein as Embodiment 328 is a use of the compound according to any one of Embodiments 1-322 or a pharmaceutically acceptable salt thereof, or the pharmaceutical

composition according to Embodiment 323 in the preparation of a medicament for treating cancer.

Provided herein as Embodiment 329 is a use of the compound according to any one of Embodiments 1-322 or a pharmaceutically acceptable salt thereof, or the pharmaceutical
5 composition according to Embodiment 323 in the preparation of a medicament for treating cancer, wherein one or more cells express KRAS G12D, G12V, G12A, G12S or G12C mutant protein.

Provided herein as Embodiment 330 is the use according to Embodiment 328 or 329, wherein the cancer is non-small cell lung cancer, small bowel cancer, appendiceal cancer,
10 colorectal cancer, cancer of unknown primary, endometrial cancer, mixed cancer types, pancreatic cancer, hepatobiliary cancer, small cell lung cancer, cervical cancer, germ cell cancer, ovarian cancer, gastrointestinal neuroendocrine cancer, bladder cancer, myelodysplastic/myeloproliferative neoplasms, head and neck cancer, esophagogastric cancer, soft tissue sarcoma, mesothelioma, thyroid cancer, leukemia, or melanoma.

Provided herein as Embodiment 331 is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective
15 amount of the compound according to any one of to any one of Embodiments 1-322 or a pharmaceutically acceptable salt thereof.

Provided herein as Embodiment 332 is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective
20 amount of the compound according to any one of to any one of Embodiments 1-322 or a pharmaceutically acceptable salt thereof, wherein one or more cells express KRAS G12D, G12V, G12A, G12S or G12C mutant protein.

Provided herein as Embodiment 333 is the method according to Embodiment 331 or
25 332, wherein the cancer is non-small cell lung cancer, small bowel cancer, appendiceal cancer, colorectal cancer, cancer of unknown primary, endometrial cancer, mixed cancer types, pancreatic cancer, hepatobiliary cancer, small cell lung cancer, cervical cancer, germ cell cancer, ovarian cancer, gastrointestinal neuroendocrine cancer, bladder cancer, myelodysplastic/myeloproliferative neoplasms, head and neck cancer, esophagogastric
30 cancer, soft tissue sarcoma, mesothelioma, thyroid cancer, leukemia, or melanoma.

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Provided herein as Embodiment 334 is the method according to Embodiment 332 or 333, wherein the cancer is non-small cell lung cancer, colorectal cancer, pancreatic cancer, appendiceal cancer, endometrial cancer, esophageal cancer, cancer of unknown primary, ampullary cancer, gastric cancer, small bowel cancer, sinonasal cancer, bile duct cancer, or
5 melanoma.

Provided herein as Embodiment 335 is the method according to Embodiment 334, wherein the cancer is non-small cell lung cancer.

Provided herein as Embodiment 336 is the method according to Embodiment 334, wherein the cancer is colorectal cancer.

10 Provided herein as Embodiment 337 is the method according to Embodiment 334, wherein the cancer is pancreatic cancer.

Provided herein as Embodiment 338 is the method according to anyone of Embodiments 331-337, wherein the subject has a cancer that was determined to have one or more cells expressing the KRAS G12D, G12V, G12A, G12S or G12C mutant protein prior to
15 administration of the compound or a pharmaceutically acceptable salt thereof.

Combination Therapy

The present disclosure also provides methods for combination therapies in which an agent known to modulate other pathways, or other components of the same pathway, or even
20 overlapping sets of target enzymes are used in combination with a compound of the present disclosure or a pharmaceutically acceptable salt thereof. In one aspect, such therapy includes but is not limited to the combination of one or more compounds of the disclosure with chemotherapeutic agents, therapeutic antibodies, and radiation treatment, to provide a synergistic or additive therapeutic effect. *See, e.g.*, U.S. Patent No. 10,519,146 B2, issued
25 December 31, 2019; specifically, the sections from column 201 (line 37) to column 212 (line 46) and column 219 (line 64) to column 220 (line 39), which are herewith incorporated by reference.

Provided herein as Embodiment 339 is the method according to anyone of Embodiments 331-338, which further comprises simultaneous, separate, or sequential
30 administration of an effective amount of a second compound, wherein the second compound is an Aurora kinase A inhibitor, AKT inhibitor, arginase inhibitor, CDK4/6 inhibitor, ErbB

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family inhibitor, ERK inhibitor, FAK inhibitor, FGFR inhibitor, glutaminase inhibitor, IGF-1R inhibitor, KIF18A inhibitor, MCL-1 inhibitor, MEK inhibitor, mTOR inhibitor, PD-1 inhibitor, PD-L1 inhibitor, PI3K inhibitor, Raf kinase inhibitor, SHP2 inhibitor, SOS1 inhibitor, Src kinase inhibitor, or one or more chemotherapeutic agent.

5 In one embodiment, the second compound is administered as a pharmaceutically acceptable salt. In another embodiment the second compound is administered as a pharmaceutical composition comprising the second compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

10 Aurora Kinase A Inhibitors

Provided herein is the method according to anyone of Embodiments 331-338, which further comprises simultaneous, separate, or sequential administration of an effective amount of a second compound, wherein the second compound is an Aurora kinase A inhibitor.

Exemplary Aurora kinase A inhibitors for use in the methods provided herein
 15 include, but are not limited to, alisertib, cenisertib, danusertib, tozasertib, LY3295668 ((2R,4R)-1-[(3-chloro-2-fluorophenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]pyridin-2-yl]methyl]-2-methylpiperidine-4-carboxylic acid), ENMD-2076 (6-(4-methylpiperazin-1-yl)-N-(5-methyl-1H-pyrazol-3-yl)-2-[(E)-2-phenylethenyl]pyrimidin-4-amine), TAK-901 (5-(3-ethylsulfonylphenyl)-3,8-dimethyl-N-(1-methylpiperidin-4-yl)-9H-pyrido[2,3-b]indole-7-carboxamide), TT-00420 (4-[9-(2-chlorophenyl)-6-methyl-2,4,5,8,12-pentazatricyclo[8.4.0.0^{3,7}]tetradeca-1(14),3,6,8,10,12-hexaen-13-yl]morpholine), AMG 900 (N-[4-[3-(2-aminopyrimidin-4-yl)pyridin-2-yl]oxyphenyl]-4-(4-methylthiophen-2-yl)phthalazin-1-amine), MLN8054 (4-[[9-chloro-7-(2,6-difluorophenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-yl]amino]benzoic acid), PF-03814735 (N-[2-[(1R,8S)-4-[[4-(cyclobutylamino)-5-(trifluoromethyl)pyrimidin-2-yl]amino]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-trien-11-yl]-2-oxoethyl]acetamide), SNS-314 (1-(3-chlorophenyl)-3-[5-[2-(thieno[3,2-d]pyrimidin-4-ylamino)ethyl]-1,3-thiazol-2-yl]urea), CYC116 (4-methyl-5-[2-(4-morpholin-4-ylanilino)pyrimidin-4-yl]-1,3-thiazol-2-amine), TAS-119, BI 811283, and TTP607.

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AKT Inhibitors

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Provided herein is the method according to anyone of Embodiments 331-338, which further comprises simultaneous, separate, or sequential administration of an effective amount of a second compound, wherein the second compound is an AKT inhibitor.

Exemplary AKT inhibitors for use in the methods provided herein include, but are not limited to, afuresertib, capivasertib, ipatasertib, uprosertib, BAY1125976 (2-[4-(1-aminocyclobutyl)phenyl]-3-phenylimidazo[1,2-b]pyridazine-6-carboxamide), ARQ 092 (3-[3-[4-(1-aminocyclobutyl)phenyl]-5-phenylimidazo[4,5-b]pyridin-2-yl]pyridin-2-amine), MK2206 (8-[4-(1-aminocyclobutyl)phenyl]-9-phenyl-2H-[1,2,4]triazolo[3,4-f][1,6]naphthyridin-3-one), SR13668 (indolo[2,3-b]carbazole-2,10-dicarboxylic acid, 5,7-dihydro-6-methoxy-, 2,10-diethyl ester), ONC201 (11-benzyl-7-[(2-methylphenyl)methyl]-2,5,7,11-tetrazatricyclo[7.4.0.02,6]trideca-1(9),5-dien-8-one), ARQ 751 (N-(3-aminopropyl)-N-[(1R)-1-(3-anilino-7-chloro-4-oxoquinazolin-2-yl)but-3-ynyl]-3-chloro-2-fluorobenzamide), RX-0201, and LY2780301.

15 Arginase Inhibitors

Provided herein is the method according to anyone of Embodiments 331-338, which further comprises simultaneous, separate, or sequential administration of an effective amount of a second compound, wherein the second compound is an arginase inhibitor.

Exemplary arginase inhibitors for use in the methods provided herein include, but are not limited to, numidargistat and CB 280.

CDK4/6 Inhibitors

Provided herein is the method according to anyone of Embodiments 331-338, which further comprises simultaneous, separate, or sequential administration of an effective amount of a second compound, wherein the second compound is a CDK4/6 inhibitor.

The term “CDK 4/6” as used herein refers to cyclin dependent kinases (“CDK”) 4 and 6, which are members of the mammalian serine/threonine protein kinases.

The term “CDK 4/6 inhibitor” as used herein refers to a compound that is capable of negatively modulating or inhibiting all or a portion of the enzymatic activity of CDK 4 and/or 6.

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Exemplary CDK 4/6 inhibitors for use in the methods provided herein include, but are not limited to, abemaciclib, palbociclib, ribociclib, trilaciclib, and PF-06873600 ((pyrido[2,3-d]pyrimidin-7(8H)-one, 6-(difluoromethyl)-8-[(1R,2R)-2-hydroxy-2-methylcyclopentyl]-2-[[1-(methylsulfonyl)-4-piperidinyl]amino])).

5 In one embodiment, the CDK4/6 inhibitor is palbociclib.

ErbB Family Inhibitors

Provided herein is the method according to anyone of Embodiments 331-338, which further comprises simultaneous, separate, or sequential administration of an effective amount
10 of a second compound, wherein the second compound is an ErbB family inhibitor.

The term “ErbB family” as used herein refers to a member of a mammalian transmembrane protein tyrosine kinase family including: ErbB1 (EGFR HER1), ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4).

The term “ErbB family inhibitor” as used herein refers to an agent, *e.g.*, a compound
15 or antibody, that is capable of negatively modulating or inhibiting all or a portion of the activity of at least one member of the ErbB family. The modulation or inhibition of one or more ErbB tyrosine kinase may occur through modulating or inhibiting kinase enzymatic activity of one or more ErbB family member or by blocking homodimerization or heterodimerization of ErbB family members.

20 In one embodiment, the ErbB family inhibitor is an EGFR inhibitor, *e.g.*, an anti-EGFR antibody. Exemplary anti-EGFR antibodies for use in the methods provided herein include, but are not limited to, zalutumumab, nimotuzumab, matuzumab, necitumumab, panitumumab, and cetuximab. In one embodiment, the anti-EGFR antibody is cetuximab. In one embodiment, the anti-EGFR antibody is panitumumab.

25 In another embodiment the ErbB family inhibitor is a HER2 inhibitor, *e.g.*, an anti-HER2 antibody. Exemplary anti-HER-2 antibodies for use in the methods provided herein include, but are not limited to, pertuzumab, trastuzumab, and trastuzumab emtansine.

In yet another embodiment the ErbB family inhibitor is a HER3 inhibitor, *e.g.*, an anti-HER3 antibody, such as HMBD-001 (Hummingbird Bioscience).

30 In one embodiment, the ErbB family inhibitor is a combination of an anti-EGFR antibody and anti-HER2 antibody.

In one embodiment, the ErbB family inhibitor is an irreversible inhibitor. Exemplary irreversible ErbB family inhibitors for use in the methods provided herein include, but are not limited to, afatinib, dacomitinib, canertinib, poziotinib, AV 412 ((N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butyn-1-yl]-6-quinazoliny]-2-propenamide)), PF 6274484 ((N-[4-[(3-chloro-4-fluorophenyl)amino]-7-methoxy-6-quinazoliny]-2-propenamide), and HKI 357 ((E)-N-[4-[3-chloro-4-[(3-fluorophenyl)methoxy]anilino]-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino)but-2-enamide).

In one embodiment, the irreversible ErbB family inhibitor is afatinib. In one embodiment, the irreversible ErbB family inhibitor is dacomitinib.

In one embodiment, the ErbB family inhibitor is a reversible inhibitor. Exemplary reversible ErbB family inhibitors for use in the methods provided herein include, but are not limited to erlotinib, gefitinib, sapitinib, varlitinib, tarloxotinib, TAK-285 (N-(2-(4-((3-chloro-4-(3-(trifluoromethyl)phenoxy)phenyl)amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl)-3-hydroxy-3-methylbutanamide), AEE788 ((S)-6-(4-((4-ethylpiperazin-1-yl)methyl)phenyl)-N-(1-phenylethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine), BMS 599626 ((3S)-3-morpholinylmethyl-4-[[1-[(3-fluorophenyl)methyl]-1H-indazol-5-yl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamate), and GW 583340 (N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[2-[(2-methylsulfonyl)ethylamino)methyl]-1,3-thiazol-4-yl]quinazolin-4-amine).

In one embodiment, the reversible ErbB family inhibitor is sapitinib. In one embodiment, the reversible ErbB family inhibitor is tarloxotinib.

ERK Inhibitors

Provided herein is the method according to anyone of Embodiments 331-338, which further comprises simultaneous, separate, or sequential administration of an effective amount of a second compound, wherein the second compound is an ERK inhibitor.

Exemplary ERK inhibitors for use in the methods provided herein include, but are not limited to, ulixertinib, ravoxertinib, CC-90003 (N-[2-[[2-[(2-methoxy-5-methylpyridin-4-yl)amino]-5-(trifluoromethyl)pyrimidin-4-yl]amino]-5-methylphenyl]prop-2-enamide), LY3214996 (6,6-dimethyl-2-[2-[(2-methylpyrazol-3-yl)amino]pyrimidin-4-yl]-5-(2-

morpholin-4-ylethyl)thieno[2,3-c]pyrrol-4-one), KO-947 (1,5,6,8-tetrahydro-6-(phenylmethyl)-3-(4-pyridinyl)-7H-pyrazolo[4,3-g]quinazolin-7-one), ASTX029, LTT462, and JSI-1187.

5 **FAK Inhibitors**

Provided herein is the method according to anyone of Embodiments 331-338, which further comprises simultaneous, separate, or sequential administration of an effective amount of a second compound, wherein the second compound is a FAK inhibitor.

Exemplary FAK inhibitors for use in the methods provided herein include, but are
10 not limited to, GSK2256098 (2-[[5-chloro-2-[(5-methyl-2-propan-2-ylpyrazol-3-yl)amino]pyridin-4-yl]amino]-N-methoxybenzamide), PF-00562271 (N-methyl-N-[3-[[[2-[(2-oxo-1,3-dihydroindol-5-yl)amino]-5-(trifluoromethyl)pyrimidin-4-yl]amino]methyl]pyridin-2-yl]methanesulfonamide), VS-4718 (2-[[2-(2-methoxy-4-morpholin-4-ylanilino)-5-(trifluoromethyl)pyridin-4-yl]amino]-N-methylbenzamide), and
15 APG-2449.

FGFR Inhibitors

Provided herein is the method according to anyone of Embodiments 331-338, which further comprises simultaneous, separate, or sequential administration of an effective amount
20 of a second compound, wherein the second compound is an FGFR inhibitor.

Exemplary FGFR inhibitors for use in the methods provided herein include, but are not limited to, futibatinib, pemigatinib, ASP5878 (2-[4-[[5-[(2,6-difluoro-3,5-dimethoxyphenyl)methoxy]pyrimidin-2-yl]amino]pyrazol-1-yl]ethanol), AZD4547 (N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-[(3S,5R)-3,5-dimethylpiperazin-1-yl]benzamide), debio 1347 ([5-amino-1-(2-methyl-3H-benzimidazol-5-yl)pyrazol-4-yl]-(1H-indol-2-yl)methanone), INCB062079, H3B-6527 (N-[2-[[6-[(2,6-dichloro-3,5-dimethoxyphenyl)carbamoyl-methylamino]pyrimidin-4-yl]amino]-5-(4-ethylpiperazin-1-yl)phenyl]prop-2-enamide), ICP-105, CPL304110, HMPL-453, and HGS1036.

30 **Glutaminase Inhibitors**

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Provided herein is the method according to anyone of Embodiments 331-338, which further comprises simultaneous, separate, or sequential administration of an effective amount of a second compound, wherein the second compound is a glutaminase inhibitor.

Exemplary glutaminase inhibitors for use in the methods provided herein include, but
5 are not limited to, telaglenastat, IPN60090, and OP 330.

IGF-1R Inhibitors

Provided herein is the method according to anyone of Embodiments 331-338, which further comprises simultaneous, separate, or sequential administration of an effective amount
10 of a second compound, wherein the second compound is an IGF-1R inhibitor.

Exemplary IGF-1R inhibitors for use in the methods provided herein include, but are not limited to, cixutumumab, dalotuzumab, linsitinib, ganitumab, robatumumab, BMS-754807 ((2S)-1-[4-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]pyrrolo[2,1-f][1,2,4]triazin-2-yl]-N-(6-fluoropyridin-3-yl)-2-methylpyrrolidine-2-carboxamide), KW-2450 (N-[5-[[4-(2-
15 hydroxyacetyl)piperazin-1-yl]methyl]-2-[(E)-2-(1H-indazol-3-yl)ethenyl]phenyl]-3-methylthiophene-2-carboxamide), PL225B, AVE1642, and BIIB022.

KIF18A Inhibitors

Provided herein is the method according to anyone of Embodiments 331-338, which
20 further comprises simultaneous, separate, or sequential administration of an effective amount of a second compound, wherein the second compound is a KIF18A inhibitor.

Exemplary KIF18A inhibitors for use in the methods provided herein include, but are not limited to, the inhibitors disclosed in US 2020/0239441, WO 2020/132649, WO 2020/132651, and WO 2020/132653, each of which is herewith incorporated by reference in
25 its entirety.

MCL-1 Inhibitors

Provided herein is the method according to anyone of Embodiments 331-338, which further comprises simultaneous, separate, or sequential administration of an effective amount
30 of a second compound, wherein the second compound is an MCL-1 inhibitor.

Exemplary MEK inhibitors for use in the methods provided herein include, but are not limited to, murizatoclast, tapotoclast, AZD 5991 ((3aR)-5-chloro-2,11,12,24,27,29-hexahydro-2,3,24,33-tetramethyl-22H-9,4,8-(metheniminomethyno)-14,20:26,23-dimetheno-10H,20H-pyrazolo[4,3-l][2,15,22,18,19]benzoxadithiadiazacyclohexacosine-32-carboxylic acid), MIK 665 ((α R)- α -[[(5S)-5-[3-Chloro-2-methyl-4-[2-(4-methyl-1-piperazinyl)ethoxy]phenyl]-6-(4-fluorophenyl)thieno[2,3-d]pyrimidin-4-yl]oxy]-2-[[2-(2-methoxyphenyl)-4-pyrimidinyl]methoxy]benzenepropanoic acid), and ABBV-467.

In one embodiment, the MCL-1 inhibitor is murizatoclast. In another embodiment, the MCL-1 inhibitor is tapotoclast.

MEK Inhibitors

Provided herein is the method according to anyone of Embodiments 331-338, which further comprises simultaneous, separate, or sequential administration of an effective amount of a second compound, wherein the second compound is MEK inhibitor.

Exemplary MEK inhibitors for use in the methods provided herein include, but are not limited to, trametinib, cobimetinib, selumetinib, pimasertib, refametinib, PD-325901 (N-[(2R)-2,3-dihydroxypropoxy]-3,4-difluoro-2-(2-fluoro-4-iodoanilino)benzamide), AZD8330 (2-(2-fluoro-4-iodoanilino)-N-(2-hydroxyethoxy)-1,5-dimethyl-6-oxopyridine-3-carboxamide), GDC-0623 (5-(2-fluoro-4-iodoanilino)-N-(2-hydroxyethoxy)imidazo[1,5-a]pyridine-6-carboxamide), RO4987655 (3,4-difluoro-2-(2-fluoro-4-iodoanilino)-N-(2-hydroxyethoxy)-5-[(3-oxooxazinan-2-yl)methyl]benzamide), TAK-733 (3-[(2R)-2,3-dihydroxypropyl]-6-fluoro-5-(2-fluoro-4-iodoanilino)-8-methylpyrido[2,3-d]pyrimidine-4,7-dione), PD0325901 (N-[(2R)-2,3-dihydroxypropoxy]-3,4-difluoro-2-(2-fluoro-4-iodoanilino)benzamide), CI-1040 (2-(2-chloro-4-iodophenylamino)-N-(cyclopropylmethoxy)-3,4-difluorobenzamide), PD318088 (5-bromo-N-(2,3-dihydroxypropoxy)-3,4-difluoro-2-(2-fluoro-4-iodophenylamino)benzamide), PD98059 (2-(2-amino-3-methoxyphenyl)-4H-chromen-4-one), PD334581 (N-[5-[3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl]-1,3,4-oxadiazol-2-yl]-4-morpholineethanamine), FCN-159, CS3006, HL-085, SHR 7390, and WX-554.

In one embodiment, the MEK inhibitor is trametinib.

mTOR Inhibitors

Provided herein is the method according to anyone of Embodiments 331-338, which further comprises simultaneous, separate, or sequential administration of an effective amount of a second compound, wherein the second compound is an mTOR inhibitor.

5 Exemplary mTOR inhibitors for use in the methods provided herein include, but are not limited to, everolimus, rapamycin, zotarolimus (ABT-578), ridaforolimus (deforolimus, MK-8669), sapanisertib, buparlisib, pictilisib, vistusertib, dactolisib, Torin-1 (1-(4-(4-propionylpiperazin-1-yl)-3-(trifluoromethyl)cyclohexyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one), GDC-0349 ((S)-1-ethyl-3-(4-(4-(3-methylmorpholino)-7-(oxetan-3-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)phenyl)urea), and VS-5584 (SB2343, (5-(8-methyl-2-morpholin-4-yl-9-propan-2-ylpurin-6-yl)pyrimidin-2-amine).

In one embodiment, the mTOR inhibitor is everolimus.

15 **PD-1 Inhibitors**

Provided herein is the method according to anyone of Embodiments 331-338, which further comprises simultaneous, separate, or sequential administration of an effective amount of a second compound, wherein the second compound is a PD-1 inhibitor.

20 Exemplary PD-1 inhibitors for use in the methods provided herein include, but are not limited to, pembrolizumab, nivolumab, cemiplimab, spartalizumab (PDR001), camrelizumab (SHR1210), sintilimab (IBI308), tislelizumab (BGB-A317), toripalimab (JS001), dostarlimab (TSR-042, WBP-285), INCMGA00012 (MGA012), AMP-224, AMP-514, and the anti-PD-1 antibody as described in US 10,640,504 B2 (the "Anti-PD-1 Antibody A," column 66, line 56 to column 67, line 24 and column 67, lines 54-57), which is incorporated
25 herein by reference.

In one embodiment, the PD-1 inhibitor is pembrolizumab. In another embodiment the PD-1 inhibitor is the Anti-PD-1 Antibody A.

PD-L1 Inhibitors

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Provided herein is the method according to anyone of Embodiments 331-338, which further comprises simultaneous, separate, or sequential administration of an effective amount of a second compound, wherein the second compound is a PD-L1 inhibitor.

Exemplary PD-L1 inhibitors for use in the methods provided herein include, but are not limited to, atezolizumab, avelumab, durvalumab, ZKAB001, TG-1501, SHR-1316, MSB2311, MDX-1105, KN035, IMC-001, HLX20, FAZ053, CS1001, CK-301, CBT-502, BGB-A333, BCD-135, and A167.

In one embodiment, the PD-L1 inhibitor is atezolizumab.

10 **PI3K Inhibitors**

Provided herein is the method according to anyone of Embodiments 331-338, which further comprises simultaneous, separate, or sequential administration of an effective amount of a second compound, wherein the second compound is a PI3K inhibitor.

Exemplary PI3K inhibitors for use in the methods provided herein include, but are not limited to, idelalisib, copanlisib, duvelisib, alpelisib, taselisib, perifosine, buparlisib, umbralisib, pictilisib, dactolisib, voxalisib, sonolisib, tenalisib, serabelisib, acalisib, CUDC-907 (N-hydroxy-2-[[2-(6-methoxypyridin-3-yl)-4-morpholin-4-yl]thieno[3,2-d]pyrimidin-6-yl]methyl-methylamino]pyrimidine-5-carboxamide), ME-401 (N-[2-methyl-1-[2-(1-methylpiperidin-4-yl)phenyl]propan-2-yl]-4-(2-methylsulfonylbenzimidazol-1-yl)-6-morpholin-4-yl-1,3,5-triazin-2-amine), IPI-549 (2-amino-N-[(1S)-1-[8-[2-(1-methylpyrazol-4-yl)ethynyl]-1-oxo-2-phenylisoquinolin-3-yl]ethyl]pyrazolo[1,5-a]pyrimidine-3-carboxamide), SF1126 ((2S)-2-[[2-(2S)-3-carboxy-2-[[2-[(2S)-5-(diaminomethylideneamino)-2-[[4-oxo-4-[[4-(4-oxo-8-phenylchromen-2-yl)morpholin-4-ium-4-yl]methoxy]butanoyl]amino]pentanoyl]amino]acetyl]amino]propanoyl]amino]-3-hydroxypropanoate), XL147 (N-[3-(2,1,3-benzothiadiazol-5-ylamino)quinoxalin-2-yl]-4-methylbenzenesulfonamide), GSK1059615 ((5Z)-5-[(4-pyridin-4-ylquinolin-6-yl)methylidene]-1,3-thiazolidine-2,4-dione), and AMG 319 (N-[(1S)-1-(7-fluoro-2-pyridin-2-yl)quinolin-3-yl]ethyl]-7H-purin-6-amine).

30 **Raf Kinase Inhibitors**

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Provided herein is the method according to anyone of Embodiments 331-338, which further comprises simultaneous, separate, or sequential administration of an effective amount of a second compound, wherein the second compound is a Raf kinase inhibitor.

The term “RAF kinase” as used herein refers to a member of a mammalian
5 serine/threonine kinases composed of three isoforms (C-Raf, B-Raf and A-Raf) and includes homodimers of each isoform as well as heterodimers between isoforms, *e.g.*, C-Raf/B-Raf heterodimers.

The term “Raf kinase inhibitor” as used herein refers to a compound that is capable
of negatively modulating or inhibiting all or a portion of the enzymatic activity of one or
10 more member of the Raf family kinases, or is capable of disrupting Raf homodimer or heterodimer formation to inhibit activity.

In one embodiment, the Raf kinase inhibitor includes, but is not limited to, encorafenib, sorafenib, lifirafenib, vemurafenib, dabrafenib, PLX-8394 (N-(3-(5-(2-cyclopropylpyrimidin-5-yl)-3a,7a-dihydro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl)-3-fluoropyrrolidine-1-sulfonamide), Raf-709 (N-(2-methyl-5-morpholino-6'-((tetrahydro-2H-pyran-4-yl)oxy)-[3,3'-bipyridin]-5-yl)-3-(trifluoromethyl)benzamide), LXH254 (N-(3-(2-(2-hydroxyethoxy)-6-morpholinopyridin-4-yl)-4-methylphenyl)-2-(trifluoromethyl)isonicotinamide), LY3009120 (1-(3,3-dimethylbutyl)-3-(2-fluoro-4-methyl-5-(7-methyl-2-(methylamino)pyrido[2,3-d]pyrimidin-6-yl)phenyl)urea), Tak-632 (N-(7-cyano-6-(4-fluoro-3-(2-(3-(trifluoromethyl)phenyl)acetamido)phenoxy)benzo[d]thiazol-2-yl)cyclopropanecarboxamide), CEP-32496 (1-(3-((6,7-dimethoxyquinazolin-4-yl)oxy)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea), CCT196969 (1-(3-(tert-butyl)-1-phenyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-((3-oxo-3,4-dihydropyrido[2,3-b]pyrazin-8-yl)oxy)phenyl)urea), and RO5126766 (N-[3-fluoro-4-[[4-methyl-2-oxo-7-(2-pyrimidin-5-yl)-2H-1-benzopyran-3-yl]methyl]-2-pyridinyl]-N'-methyl-sulfamide).
25

In one embodiment, the Raf kinase inhibitor is encorafenib. In one embodiment, the Raf kinase inhibitor is sorafenib. In one embodiment, the Raf kinase inhibitor is lifirafenib.

SHP2 Inhibitors

Provided herein is the method according to anyone of Embodiments 331-338, which further comprises simultaneous, separate, or sequential administration of an effective amount of a second compound, wherein the second compound is a SHP2 inhibitor.

Exemplary SHP2 inhibitors for use in the methods provided herein include, but are not limited to, SHP-099 (6-(4-amino-4-methylpiperidin-1-yl)-3-(2,3-dichlorophenyl)pyrazin-2-amine dihydrochloride), RMC-4550 ([3-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-6-(2,3-dichlorophenyl)-5-methylpyrazin-2-yl]methanol), TNO155, (3S,4S)-8-[6-amino-5-(2-amino-3-chloropyridin-4-yl)sulfanylpiazin-2-yl]-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine), and RMC-4630 (Revolution Medicine). In one embodiment, the SHP inhibitor for use in the methods provided herein is RMC-4630 (Revolution Medicine).

In another embodiment, exemplary SHP2 inhibitors for use in the methods provided herein include, but are not limited to, 3-[(1R,3R)-1-amino-3-methoxy-8-azaspiro[4.5]dec-8-yl]-6-(2,3-dichlorophenyl)-5-methyl-2-pyrazinemethanol (CAS 2172651-08-8), 3-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]dec-8-yl]-6-[(2,3-dichlorophenyl)thio]-5-methyl-2-pyrazinemethanol (CAS 2172652-13-8), 3-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]dec-8-yl]-6-[[3-chloro-2-(3-hydroxy-1-azetidynyl)-4-pyridinyl]thio]-5-methyl-2-pyrazinemethanol (CAS 2172652-38-7), and 6-[(2-amino-3-chloro-4-pyridinyl)thio]-3-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]dec-8-yl]-5-methyl-2-pyrazinemethanol (CAS 2172652-48-9).

In another embodiment, exemplary SHP2 inhibitors for use in the methods provided herein include, but are not limited to, 1-[5-(2,3-dichlorophenyl)-6-methylimidazo[1,5-a]pyrazin-8-yl]-4-methyl-4-piperidinamine (CAS 2240981-75-1), (1R)-8-[5-(2,3-dichlorophenyl)-6-methylimidazo[1,5-a]pyrazin-8-yl]-8-azaspiro[4.5]decan-1-amine (CAS 2240981-78-4), (3S,4S)-8-[7-(2,3-dichlorophenyl)-6-methylpyrazolo[1,5-a]pyrazin-4-yl]-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine (CAS 2240982-45-8), (3S,4S)-8-[7-[(2-amino-3-chloro-4-pyridinyl)thio]pyrazolo[1,5-a]pyrazin-4-yl]-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine (CAS 2240982-57-2), 4-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]dec-8-yl]-7-(2,3-dichlorophenyl)-6-methyl-pyrazolo[1,5-a]pyrazine-2-methanol (CAS 2240982-69-6), 7-[(2-amino-3-chloro-4-pyridinyl)thio]-4-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]dec-8-yl]-6-methyl-pyrazolo[1,5-a]pyrazine-2-methanol (CAS 2240982-73-2),

and (3S,4S)-8-[7-[(2-amino-3-chloro-4-pyridinyl)thio]-6-methylpyrazolo[1,5-a]pyrazin-4-yl]-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine (CAS 2240982-77-6).

In one embodiment, the SHP inhibitor for use in the methods provided herein is (1R)-8-[5-(2,3-dichlorophenyl)-6-methylimidazo[1,5-a]pyrazin-8-yl]-8-azaspiro[4.5]decan-1-amine (CAS 2240981-78-4).

In another embodiment, exemplary SHP2 inhibitors for use in the methods provided herein include, but are not limited to 3-[(1R)-1-amino-8-azaspiro[4.5]dec-8-yl]-6-(2,3-dichlorophenyl)-5-hydroxy-2-pyridinemethanol (CAS 2238840-54-3), 3-[(1R)-1-amino-8-azaspiro[4.5]dec-8-yl]-6-[(2,3-dichlorophenyl)thio]-5-hydroxy-2-pyridinemethanol (CAS 2238840-56-5), 5-[(1R)-1-amino-8-azaspiro[4.5]dec-8-yl]-2-(2,3-dichlorophenyl)-3-pyridinol (CAS 2238840-58-7), 3-[(1R)-1-amino-8-azaspiro[4.5]dec-8-yl]-6-(2,3-dichlorophenyl)-5-methyl-2-pyridinemethanol (CAS 2238840-60-1), (1R)-8-[6-(2,3-dichlorophenyl)-5-methyl-3-pyridinyl]-8-azaspiro[4.5]decan-1-amine (CAS 2238840-62-3), 3-[(1R)-1-amino-8-azaspiro[4.5]dec-8-yl]-6-[(2,3-dichlorophenyl)thio]-5-methyl-2-pyridinemethanol (CAS 2238840-63-4), (1R)-8-[6-[(2,3-dichlorophenyl)thio]-5-methyl-3-pyridinyl]-8-azaspiro[4.5]decan-1-amine (CAS 2238840-64-5), 5-(4-amino-4-methyl-1-piperidinyl)-2-[(2,3-dichlorophenyl)thio]-3-pyridinol (CAS 2238840-65-6), 5-[(1R)-1-amino-8-azaspiro[4.5]dec-8-yl]-2-[(2,3-dichlorophenyl)thio]-3-pyridinol (CAS 2238840-66-7), 6-[(2-amino-3-chloro-4-pyridinyl)thio]-3-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]dec-8-yl]-5-hydroxy-2-pyridinemethanol (CAS 2238840-67-8), 3-(4-amino-4-methyl-1-piperidinyl)-6-(2,3-dichlorophenyl)-5-hydroxy-2-pyridinemethanol (CAS 2238840-68-9), 3-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]dec-8-yl]-6-(2,3-dichlorophenyl)-5-methyl-2-pyridinemethanol (CAS 2238840-69-0), 6-[(2-amino-3-chloro-4-pyridinyl)thio]-3-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]dec-8-yl]-5-methyl-2-pyridinemethanol (CAS 2238840-70-3), 3-(4-amino-4-methyl-1-piperidinyl)-6-(2,3-dichlorophenyl)-5-methyl-2-pyridinemethanol (CAS 2238840-71-4), 6-[(2-amino-3-chloro-4-pyridinyl)thio]-3-(4-amino-4-methyl-1-piperidinyl)-2-pyridinemethanol (CAS 2238840-72-5), 5-[(2-amino-3-chloro-4-pyridinyl)thio]-2-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]dec-8-yl]-6-methyl-3-pyridinemethanol (CAS 2238840-73-6), 2-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]dec-8-yl]-5-(2,3-dichlorophenyl)-6-methyl-3-pyridinemethanol (CAS 2238840-74-7), 3-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]dec-8-yl]-6-(2,3-dichlorophenyl)-

5-hydroxy-2-pyridinemethanol (CAS 2238840-75-8), and 2-[(2-amino-3-chloro-4-pyridyl)sulfanyl]-5-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-6-(hydroxymethyl)pyridin-3-ol.

In one embodiment, the SHP inhibitor for use in the methods provided herein is 3-[(1R)-1-amino-8-azaspiro[4.5]dec-8-yl]-6-[(2,3-dichlorophenyl)thio]-5-hydroxy-2-pyridinemethanol (CAS 2238840-56-5).

In one embodiment, the SHP2 inhibitor for use in the methods provided herein is an inhibitor disclosed in US 10,590,090 B2, US 2020/017517 A1, US 2020/017511 A1, or WO 2019/075265 A1, each of which is herewith incorporated by reference in its entirety.

10

SOS1 Inhibitors

Provided herein is the method according to anyone of Embodiments 331-338, which further comprises simultaneous, separate, or sequential administration of an effective amount of a second compound, wherein the second compound is an SOS1 inhibitor.

Exemplary SOS1 inhibitors for use in the methods provided herein include, but are not limited to, BI 3406 (N-[(1R)-1-[3-amino-5-(trifluoromethyl)phenyl]ethyl]-7-methoxy-2-methyl-6-[(3S)-oxolan-3-yl]oxyquinazolin-4-amine), and BI 1701963.

Src Kinase Inhibitors

Provided herein is the method according to anyone of Embodiments 331-338, which further comprises simultaneous, separate, or sequential administration of an effective amount of a second compound, wherein the second compound is a Src kinase inhibitor.

The term "Src kinase" as used herein refers to a member of a mammalian nonreceptor tyrosine kinase family including: Src, Yes, Fyn, and Fgr (SrcA subfamily); Lck, Hck, Blk, and Lyn (SrcB subfamily), and Frk subfamily.

The term "Src kinase inhibitor" as used herein refers to a compound that is capable of negatively modulating or inhibiting all or a portion of the enzymatic activity of one or more member of the Src kinases.

Exemplary Src kinase inhibitors for use in the methods provided herein include, but are not limited to, dasatinib, ponatinib, vandetanib, bosutinib, saracatinib, KX2-391 (N-benzyl-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetamide), SU6656 ((Z)-N,N-

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dimethyl-2-oxo-3-((4,5,6,7-tetrahydro-1H-indol-2-yl)methylene)indoline-5-sulfonamide), PP
1 (1-(tert-butyl)-3-(p-tolyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine), WH-4-023 (2,6-
dimethylphenyl(2,4-dimethoxyphenyl)(2-((4-(4-methylpiperazin-1-
yl)phenyl)amino)pyrimidin-4-yl)carbamate), and KX-01 (N-benzyl-2-(5-(4-(2-
5 morpholinoethoxy)phenyl)pyridin-2-yl)acetamide).

In one embodiment, the Src kinase inhibitor is dasatinib. In one embodiment, the Src
kinase inhibitor is saracatinib. In one embodiment, the Src kinase inhibitor is ponatinib. In
one embodiment, the Src kinase inhibitor is vandetanib. In one embodiment, the Src kinase
inhibitor is KX-01.

Chemotherapeutic Agents

Provided herein is the method according to anyone of Embodiments 331-338, which
further comprises simultaneous, separate, or sequential administration of an effective amount
of a second compound, wherein the second compound is one or more chemotherapeutic
15 agent.

Exemplary chemotherapeutic agents for use in the methods provided herein include,
but are not limited to, leucovorin calcium (calcium folinate), 5-fluorouracil, irinotecan,
oxaliplatin, cisplatin, carboplatin, pemetrexed, docetaxel, paclitaxel, gemcitabine,
vinorelbine, chlorambucil, cyclophosphamide, and methotrexate.

Definitions

The following definitions are provided to assist in understanding the scope of this
disclosure.

Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction
25 conditions, and so forth used in the specification and claims are to be understood as being
modified in all instances by the term “about.” Accordingly, unless indicated to the contrary,
the numerical parameters set forth in the following specification and attached claims are
approximations that may vary depending upon the standard deviation found in their
respective testing measurements.

30 As used herein, if any variable occurs more than one time in a chemical formula, its
definition on each occurrence is independent of its definition at every other occurrence. If

the chemical structure and chemical name conflict, the chemical structure is determinative of the identity of the compound.

Stereoisomers

The compounds of the present disclosure may contain, for example, double bonds,
5 one or more asymmetric carbon atoms, and bonds with a hindered rotation, and therefore, may exist as stereoisomers, such as double-bond isomers (*i.e.*, geometric isomers (E/Z)), enantiomers, diastereomers, and atropoisomers. Accordingly, the scope of the instant disclosure is to be understood to encompass all possible stereoisomers of the illustrated compounds, including the stereoisomerically pure form (for example, geometrically pure,
10 enantiomerically pure, diastereomerically pure, and atropoisomerically pure) and stereoisomeric mixtures (for example, mixtures of geometric isomers, enantiomers, diastereomers, and atropoisomers, or mixture of any of the foregoing) of any chemical structures disclosed herein (in whole or in part), unless the stereochemistry is specifically identified.

15 If the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it. If the stereochemistry of a structure or a portion of a structure is indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing only the stereoisomer indicated. A bond drawn
20 with a wavy line indicates that both stereoisomers are encompassed. This is not to be confused with a wavy line drawn perpendicular to a bond which indicates the point of attachment of a group to the rest of the molecule.

The term “stereoisomer” or “stereoisomerically pure” compound as used herein refers to one stereoisomer (for example, geometric isomer, enantiomer, diastereomer and
25 atropoisomer) of a compound that is substantially free of other stereoisomers of that compound. For example, a stereoisomerically pure compound having one chiral center will be substantially free of the mirror image enantiomer of the compound and a stereoisomerically pure compound having two chiral centers will be substantially free of other enantiomers or diastereomers of the compound. A typical stereoisomerically pure
30 compound comprises greater than about 80% by weight of one stereoisomer of the compound

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and equal or less than about 20% by weight of other stereoisomers of the compound, greater than about 90% by weight of one stereoisomer of the compound and equal or less than about 10% by weight of the other stereoisomers of the compound, greater than about 95% by weight of one stereoisomer of the compound and equal or less than about 5% by weight of the other stereoisomers of the compound, or greater than about 97% by weight of one stereoisomer of the compound and equal or less than about 3% by weight of the other stereoisomers of the compound.

This disclosure also encompasses the pharmaceutical compositions comprising stereoisomerically pure forms and the use of stereoisomerically pure forms of any compounds disclosed herein. Further, this disclosure also encompasses pharmaceutical compositions comprising mixtures of stereoisomers of any compounds disclosed herein and the use of said pharmaceutical compositions or mixtures of stereoisomers. These stereoisomers or mixtures thereof may be synthesized in accordance with methods well known in the art and methods disclosed herein. Mixtures of stereoisomers may be resolved using standard techniques, such as chiral columns or chiral resolving agents. Further, this disclosure encompasses pharmaceutical compositions comprising mixtures of any of the compounds disclosed herein and one or more other active agents disclosed herein. *See*, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley-Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725; Eliel, *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions*, page 268 (Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

Tautomers

As known by those skilled in the art, certain compounds disclosed herein may exist in one or more tautomeric forms. Because one chemical structure may only be used to represent one tautomeric form, it will be understood that for convenience, referral to a compound of a given structural formula includes other tautomers of said structural formula. Accordingly, the scope of the instant disclosure is to be understood to encompass all tautomeric forms of the compounds disclosed herein.

Isotopically-Labelled Compounds

Further, the scope of the present disclosure includes all pharmaceutically acceptable isotopically-labelled compounds of the compounds disclosed herein, such as the compounds of Formula I, wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds disclosed herein include isotopes of hydrogen, such as ^2H and ^3H , carbon, such as ^{11}C , ^{13}C and ^{14}C , chlorine, such as ^{36}Cl , fluorine, such as ^{18}F , iodine, such as ^{123}I and ^{125}I , nitrogen, such as ^{13}N and ^{15}N , oxygen, such as ^{15}O , ^{17}O and ^{18}O , phosphorus, such as ^{32}P , and sulphur, such as ^{35}S . Certain isotopically-labelled compounds of Formula I, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium (^3H) and carbon-14 (^{14}C) are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with isotopes such as deuterium (^2H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be advantageous in some circumstances. Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies, for example, for examining target occupancy. Isotopically-labelled compounds of the compounds disclosed herein can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying General Synthetic Schemes and Examples using an appropriate isotopically-labelled reagent in place of the non-labelled reagent previously employed.

Solvates

As discussed above, the compounds disclosed herein and the stereoisomers, tautomers, and isotopically-labelled forms thereof or a pharmaceutically acceptable salt of any of the foregoing may exist in solvated or unsolvated forms.

The term "solvate" as used herein refers to a molecular complex comprising a compound or a pharmaceutically acceptable salt thereof as described herein and a

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stoichiometric or non-stoichiometric amount of one or more pharmaceutically acceptable solvent molecules. If the solvent is water, the solvate is referred to as a "hydrate."

Accordingly, the scope of the instant disclosure is to be understood to encompass all solvents of the compounds disclosed herein and the stereoisomers, tautomers and
5 isotopically-labelled forms thereof or a pharmaceutically acceptable salt of any of the foregoing.

Miscellaneous Definitions

This section will define additional terms used to describe the scope of the
10 compounds, compositions and uses disclosed herein.

The term "aryl" refers to an aromatic hydrocarbon group having 6-20 carbon atoms in the ring portion. Typically, aryl is monocyclic, bicyclic or tricyclic aryl having 6-20 carbon atoms. Furthermore, the term "aryl" as used herein, refers to an aromatic substituent which can be a single aromatic ring, or multiple aromatic rings that are fused together. Non-limiting
15 examples include phenyl, naphthyl or tetrahydronaphthyl, each of which may optionally be substituted with 1-4 substituents, such as alkyl, trifluoromethyl, cycloalkyl, halogen, hydroxy, alkoxy, acyl, alkyl-C(O)-O-, aryl-O-, heteroaryl-O-, amino, thiol, alkyl-S-, aryl-S--nitro, cyano, carboxy, alkyl-O-C(O)--, carbamoyl, alkyl-S(O)-, sulfonyl, sulfonamido, phenyl, and heterocycloalkyl.

20 The terms "C₁₋₄alkyl," and "C₁₋₆alkyl" as used herein refer to a straight or branched chain hydrocarbon containing from 1 to 4, and 1 to 6 carbon atoms, respectively. Representative examples of C₁₋₄alkyl or C₁₋₆ alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, pentyl and hexyl.

The terms "C₁₋₄alkylene" and "C₁₋₆alkylene" refer to a straight or branched divalent
25 alkyl group as defined herein containing 1 to 4, and 1 to 6 carbon atoms, respectively. Representative examples of alkylene include, but are not limited to, methylene, ethylene, n-propylene, iso-propylene, n-butylene, sec-butylene, iso-butylene, tert-butylene, n-pentylene, isopentylene, neopentylene, n-hexylene and the like.

The term "C₂₋₄alkenyl" as used herein refers to a saturated hydrocarbon containing 2
30 to 4 carbon atoms having at least one carbon-carbon double bond. Alkenyl groups include

both straight and branched moieties. Representative examples of C₂₋₄alkenyl include, but are not limited to, 1-propenyl, 2-propenyl, 2-methyl-2-propenyl, and butenyl.

The term "C₂₋₄alkynyl" as used herein refers to a saturated hydrocarbon containing 2 to 4 carbon atoms having at least one carbon-carbon triple bond. The term includes both straight and branched moieties. Representative examples of C₃₋₄alkynyl include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 2-butyne and 3-butyne.

The term "C₁₋₄alkoxy" or "C₁₋₆alkoxy" as used herein refers to -OR[#], wherein R[#] represents a C₁₋₄alkyl group or C₁₋₆alkyl group, respectively, as defined herein. Representative examples of C₁₋₄alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, iso-propoxy, and butoxy. Representative examples of C₁₋₆alkoxy include, but are not limited to, ethoxy, propoxy, iso-propoxy, and butoxy.

The term "C₃₋₈cycloalkyl" as used herein refers to a saturated carbocyclic molecule wherein the cyclic framework has 3 to 8 carbons. Representative examples of C₃₋₈cycloalkyl include, but are not limited to, cyclopropyl and cyclobutyl.

The term "deutero" as used herein as a prefix to another term for a chemical group refers to a modification of the chemical group, wherein one or more hydrogen atoms are substituted with deuterium ("D" or "²H"). For example, the term "C₁₋₄deuteroalkyl" refers to a C₁₋₄alkyl as defined herein, wherein one or more hydrogen atoms are substituted with D. Representative examples of C₁₋₄deuteroalkyl include, but are not limited to, -CH₂D, -CHD₂, -CD₃, -CH₂CD₃, -CDHCD₃, -CD₂CD₃, -CH(CD₃)₂, -CD(CHD₂)₂, and -CH(CH₂D)(CD₃).

The term "halogen" as used herein refers to -F, -Cl, -Br, or -I.

The term "halo" as used herein as a prefix to another term for a chemical group refers to a modification of the chemical group, wherein one or more hydrogen atoms are substituted with a halogen as defined herein. The halogen is independently selected at each occurrence. For example, the term "C₁₋₄haloalkyl" refers to a C₁₋₄alkyl as defined herein, wherein one or more hydrogen atoms are substituted with a halogen. Representative examples of C₁₋₄haloalkyl include, but are not limited to, -CH₂F, -CHF₂, -CF₃, -CHFCI, -CH₂CF₃, -CFHCF₃, -CF₂CF₃, -CH(CF₃)₂, -CF(CHF₂)₂, and -CH(CH₂F)(CF₃).

As used herein, the term "heteroaryl" refers to a 5-20 membered monocyclic- or bicyclic- or tricyclic-aromatic ring system, having 1 to 8 heteroatoms selected from N, O and S. In certain preferred aspects, the heteroaryl is a 5-10 membered ring system (e.g., 5-7

membered monocycle, an 8-10 membered bicycle or a 11-14 membered tricycle) or a 5-7 membered ring system. Exemplary monocyclic heteroaryl groups include 2- or 3-thienyl, 2- or 3-furyl, 2- or 3-pyrrolyl, 2-, 4-, or 5-imidazolyl, 3-, 4-, or 5-pyrazolyl, 2-, 4-, or 5-thiazolyl, 3-, 4-, or 5-isothiazolyl, 2-, 4-, or 5-oxazolyl, 3-, 4-, or 5-isoxazolyl, 3- or 5-1,2,4-triazolyl, 4- or 5-1,2,3-triazolyl, tetrazolyl, 2-, 3-, or 4-pyridyl, 3- or 4-pyridazinyl, 3-, 4-, or 5-pyrazinyl, 2-pyrazinyl, and 2-, 4-, and 5-pyrimidinyl. Exemplary bicyclic heteroaryl groups include 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinoliny, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinoliny, 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinoliny, 1-, 2-, 4-, 5-, 6-, 7-, or 8-benzimidazolyl and 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 8-indolyl.

10 The term "heteroaryl" also refers to a group in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocycloalkyl rings.

 As used herein, the term "heterocycle," "heterocycloalkyl" or "heterocyclo" refers to a saturated or unsaturated non-aromatic ring or ring system, e.g., which is a 4-, 5-, 6-, or 7-membered monocyclic, 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic or 10-, 11-, 12-, 13-, 14- or 15-membered tricyclic ring system and contains at least one heteroatom selected from O, S and N, where the N and S can also optionally be oxidized to various oxidation states. The heterocyclic group can be attached at a heteroatom or a carbon atom. The heterocycloalkyl can include fused or bridged rings as well as spirocyclic rings. Examples of heterocycles include tetrahydrofuran, dihydrofuran, 1, 4-dioxane, morpholine, 1,4-dithiane, piperazine, 20 piperidine, 1,3-dioxolane, imidazolidine, imidazoline, pyrroline, pyrrolidine, tetrahydropyran, dihydropyran, oxathiolane, dithiolane, 1,3-dioxane, 1,3-dithiane, oxathiane, thiomorpholine, azetidine, thiazolidine, morpholine, and the like.

 The term "pharmaceutically acceptable" as used herein refers to generally recognized for use in subjects, particularly in humans.

25 The term "pharmaceutically acceptable salt" as used herein refers to a salt of a compound that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, 30 malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid,

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benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, for example, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine, dicyclohexylamine, and the like. Additional examples of such salts can be found in Berge *et al.*, *J. Pharm. Sci.* 66(1):1-19 (1977). See also Stahl *et al.*, *Pharmaceutical Salts: Properties, Selection, and Use*, 2nd Revised Edition (2011).

The term “pharmaceutically acceptable excipient” as used herein refers to a broad range of ingredients that may be combined with a compound or salt disclosed herein to prepare a pharmaceutical composition or formulation. Typically, excipients include, but are not limited to, diluents, colorants, vehicles, anti-adherants, glidants, disintegrants, flavoring agents, coatings, binders, sweeteners, lubricants, sorbents, preservatives, and the like.

The term “subject” as used herein refers to humans and mammals, including, but not limited to, primates, cows, sheep, goats, horses, dogs, cats, rabbits, rats, and mice. In one embodiment the subject is a human.

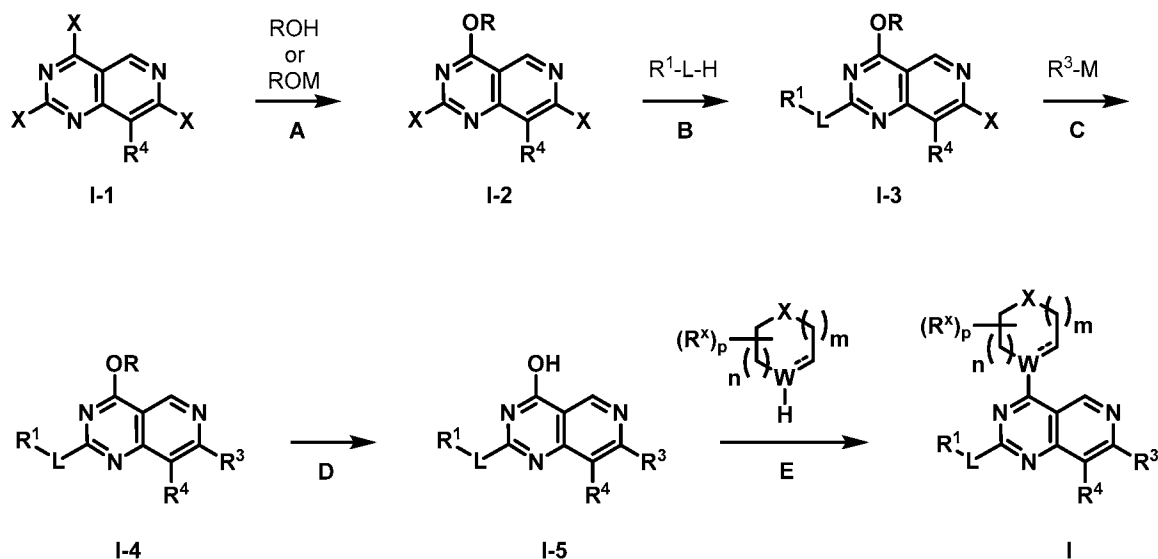
The term “therapeutically effective amount” as used herein refers to that amount of a compound disclosed herein that will elicit the biological or medical response of a tissue, a system, or subject that is being sought by a researcher, veterinarian, medical doctor or other clinician.

GENERAL SYNTHETIC PROCEDURES

The compounds provided herein can be synthesized according to the procedures described in this and the following sections. The synthetic methods described herein are merely exemplary, and the compounds disclosed herein may also be synthesized by alternate routes utilizing alternative synthetic strategies, as appreciated by persons of ordinary skill in the art. It should be appreciated that the general synthetic procedures and specific examples provided herein are illustrative only and should not be construed as limiting the scope of the present disclosure in any manner.

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Generally, the compounds of Formula I can be synthesized according to the following schemes. Any variables used in the following schemes are the variables as defined for Formula I, unless otherwise noted. All starting materials are either commercially available, for example, from Merck Sigma-Aldrich Inc., Fluorochem Ltd, and Enamine Ltd. or known in the art and may be synthesized by employing known procedures using ordinary skill. Starting material may also be synthesized via the procedures disclosed herein. Suitable reaction conditions, such as, solvent, reaction temperature, and reagents, for the Schemes discussed in this section, may be found in the examples provided herein.

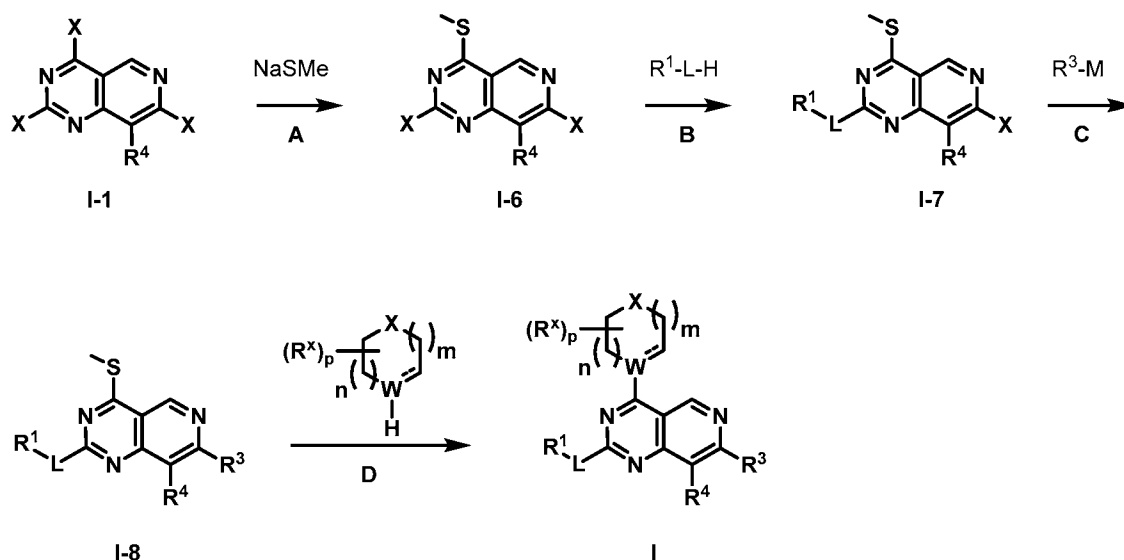


Scheme I

Compounds of Formula (I) can be prepared according to **Scheme I**. In step **A**, compound (**I-1**) is treated with an aliphatic alcohol, such as benzyl alcohol, and a base, such as Hunig's base, or metal alkoxide, such as potassium *tert*-butoxide, in a solvent such as 1,4-dioxane to give compound (**I-2**). In step **B**, compound (**I-2**) undergoes S_NAr reaction with a nucleophile having the formula R^1-L-H in a solvent such as acetonitrile, in the presence of a base such as Hunig's base, to give compound (**I-3**). In step **C**, compound (**I-3**) is coupled with an organometallic reagent or a boronic acid (ester) to provide compound (**I-4**). This coupling reaction proceeds in a solvent or mixture of solvents such as 1,4-dioxane and water, and a catalyst such as

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cataCXium A Pd G3, with or without a base such as potassium phosphate. In step **D**, compound (**I-4**) is treated with a suitable set of reagents, such as Pd/C with H₂ to remove the alkyl group R, giving compound (**I-5**). In Step **E**, compound (**I-5**) is treated with an optionally substituted cyclic amine in the presence of coupling reagent
 5 such as HATU, and a base such as Hunig's base, in a solvent such as DMA to give compounds of Formula (**I**). In some cases, the species R³ will contain protecting group(s), which can be removed in step **D** or after step **E** in the synthetic sequence.

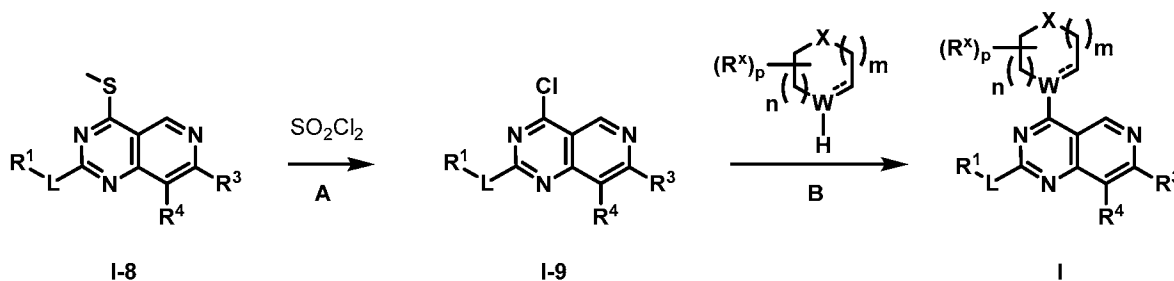


Scheme II

10 Compounds of Formula (**I**) can also be prepared according to Scheme **II**. In step **A**, compound (**I-1**) is treated with sodium thiomethoxide in a solvent such as tetrahydrofuran to give compound (**I-6**). In step **B**, compound (**I-6**) undergoes S_NAr
 reaction with a nucleophile having the formula R¹-L-H in a solvent such as acetonitrile in the presence of a base such as Hunig's base to give compound (**I-7**). In
 15 step **C**, compound (**I-7**) is coupled with an organometallic reagent or a boronic acid (ester) to provide compound (**I-8**). This coupling reaction proceeds in a solvent or mixture of solvents such as 1,4-dioxane and water, and a catalyst such as cataCXium A Pd G3, with or without a base such as potassium phosphate. In step **D**, compound (**I-8**) is coupled with an optionally substituted cyclic amine in the presence of a

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palladium catalyst, such as $\text{Pd}(\text{PPh}_3)_4$, a copper catalyst, such as CuTC , in a solvent such as 1,4-dioxane, to give compounds of formula (I). In some cases, the species R^3 will contain protecting group(s), which can be removed after step **D** in the synthetic sequence.

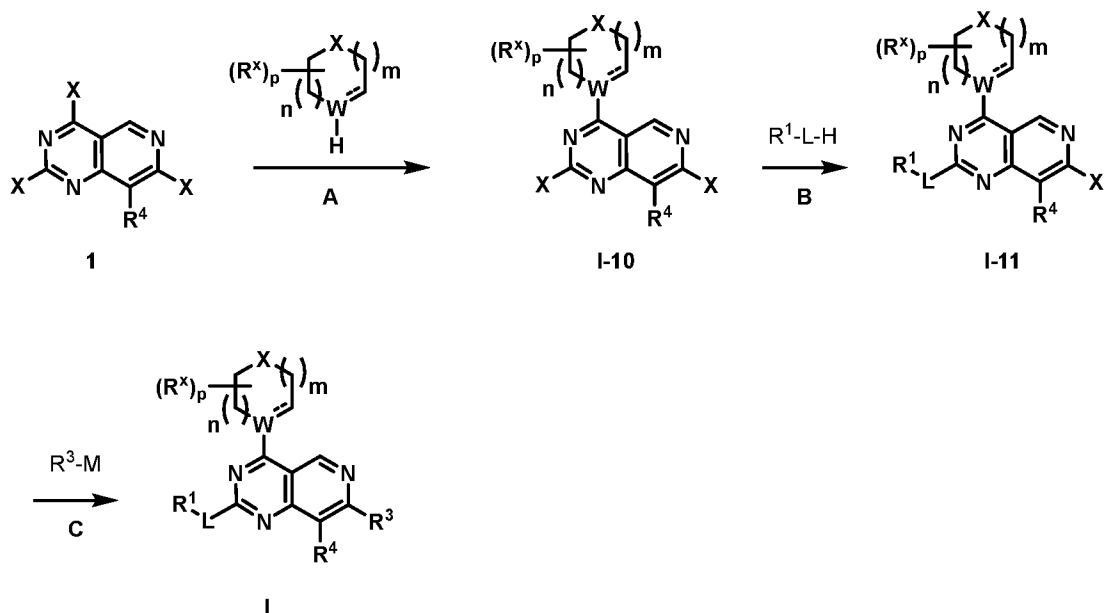


Scheme III

Compounds of Formula (I) can also be prepared according to Scheme III. In step **A**, compound (I-8) is treated with sulfonyl chloride in a solvent such as dichloromethane to give compound (I-9). In step **B**, compound (I-9) undergoes $\text{S}_{\text{N}}\text{Ar}$ reaction with an optionally substituted cyclic amine in a solvent such as acetonitrile in the presence of a base such as Hunig's base to give compounds of formula (I). In some cases, the species R^3 will contain protecting group(s), which can be removed after step **B** in the synthetic sequence.

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Scheme IV

Compounds of Formula (I) can also be prepared according to Scheme IV. In step A, compound (1) undergoes S_NAr reaction with an optionally substituted cyclic amine in a solvent such as dichloromethane and in the presence of a base such as Hunig's base to give compound (I-10). In step B, compound (I-10) undergoes S_NAr reaction with a nucleophile having the formula $R^1\text{-L-H}$ in a solvent such as acetonitrile, in the presence of a base such as Hunig's base to give compound (I-11). In step C, compound (I-11) is coupled with an organometallic reagent or a boronic acid (ester) to provide compounds of formula (I). This coupling reaction proceeds in a solvent or mixture of solvents such as 1,4-dioxane and water, and a catalyst such as cataCXium A Pd G3, with or without a base such as potassium phosphate. In some cases, the species R^3 will contain protecting group(s), which can be removed after step C in the synthetic sequence.

15

EXAMPLES

This section provides specific examples of compounds of Formula I and methods of making the same.

List of Abbreviations

Table 1

Ac	acetyl
AcCl	acetyl chloride
AcOH	acetic acid
aq or aq.	aqueous
Bn	benzyl
B ₂ pin ₂	bis(pinacolato)diboron
BOC or Boc	<i>tert</i> -butoxycarbonyl
cataCXium A Pd G3	mesylate[(di(1-adamantyl)- <i>n</i> -butylphosphine)-2-(2'-amino-1,1'-biphenyl)]palladium(II)
Cbz	benzyloxycarbonyl
CbzCl	benzyl chloroformate
CDI	carbonyldiimidazole
COD or cod	1,5-cyclooctadiene
CuTC	copper(I) thiophene-2-carboxylate
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DMA	<i>N,N</i> -dimethylacetamide
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
Dppf, DPPF or dppf	1,1'-bis(diphenylphosphino)ferrocene
Dtbbpy	4,4'-di- <i>tert</i> -butyl-2,2'-dipyridyl
eq or eq. or equiv.	equivalent
ESI or ES	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
G	gram(s)
H	hour(s)
HATU	1-[bis(dimethylamino)methylene]-1 <i>H</i> -1,2,3-triazolo[4,5- <i>b</i>]pyridinium 3-oxide hexafluorophosphate
HBpin	4,4,5,5-tetramethyl-1,3,2-dioxaborolane
HMPA	hexamethylphosphoramide
HOAc	acetic acid
HPLC	high pressure liquid chromatography
<i>i</i> Pr	<i>iso</i> -propyl
<i>i</i> Pr ₂ NEt or DIPEA	<i>N</i> -ethyl diisopropylamine (Hünig's base)
KOAc	potassium acetate
LC MS, LCMS, LC-MS or LC/MS	liquid chromatography mass spectroscopy
LHMDS or LiHMDS	lithium hexamethyldisilazide

m/z	mass divided by charge
Me	methyl
MeCN	acetonitrile
MeOH	methanol
Mg	milligrams
Min	minutes
mL	milliliters
MOM	methoxymethyl
MOMCl	methoxymethyl chloride
MS	mass spectra
NMR	nuclear magnetic resonance
PCy ₃ Pd G2	chloro[(tricyclohexylphosphine)-2-(2'-aminobiphenyl)]palladium(II)
Pd(dppf)Cl ₂ ·DCM, Pd(dppf)Cl ₂	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane
Pd(dtbpf)Cl ₂	[1,1'-bis(di- <i>tert</i> -butylphosphino)ferrocene]dichloropalladium(II)
Pd(PPh ₃) ₄	tetrakis(triphenylphosphine)palladium(0)
Ph	phenyl
PhMe	toluene
Pin	pinacolato
Piv	pivaloyl
PivCl	pivaloyl chloride
PMB	4-methoxybenzyl
Rbf	round-bottom flask
RP-HPLC	reverse phase high pressure liquid chromatography
RT or rt or r.t.	room temperature
sat. or satd.	saturated
SFC	supercritical fluid chromatography
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBDPSCl	<i>tert</i> -butyldiphenylsilyl chloride
TBS	<i>tert</i> -butyldimethylsilyl
TBSCl	<i>tert</i> -butyldimethylsilyl chloride
tBu	<i>tert</i> -butyl
TC	thiophene-2-carboxylate
TEA or Et ₃ N	triethylamine
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TIPSCl	triisopropylsilyl chloride
UV	ultraviolet

XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl
Xphos Pd G2	chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)

General Analytical and Purification Methods

Provided in this section are descriptions of the general analytical and purification methods used to prepare the specific examples provided herein.

5

Chromatography: Unless otherwise indicated, crude product-containing residues were purified by passing the crude material or concentrate through either a Biotage or ISCO brand silica gel column pre-packed with flash silica (SiO₂) and eluting the product off the column with a solvent gradient as indicated.

10

Preparative HPLC Method: Where indicated, the compounds described herein were purified via reverse phase HPLC using Waters FractionLynx or Gilson semi-preparative HPLC-MS system utilizing one of the following two HPLC columns: (a) Phenomenex Gemini column (5 micron, C18, 150 x 30 mm) or (b) Waters X-select CSH column (5
15 micron, C18, 100 x 30 mm). A typical run through the instrument included: eluting at 45 mL/min with a linear gradient of 10% (v/v) to 100% MeCN (0.1% v/v formic acid) in water (0.1% formic acid) over 10 minutes; conditions can be varied to achieve optimal separations.

Proton NMR Spectra: Unless otherwise indicated, all ¹H NMR spectra were collected on a
20 Bruker NMR instrument at 300, 400 or 500 MHz. All observed protons are reported as parts-per-million (ppm) downfield from tetramethylsilane (TMS) using the internal solvent peak as reference. Some ¹H signals may be missing due to exchange with D from MeOD, or due to signal suppression.

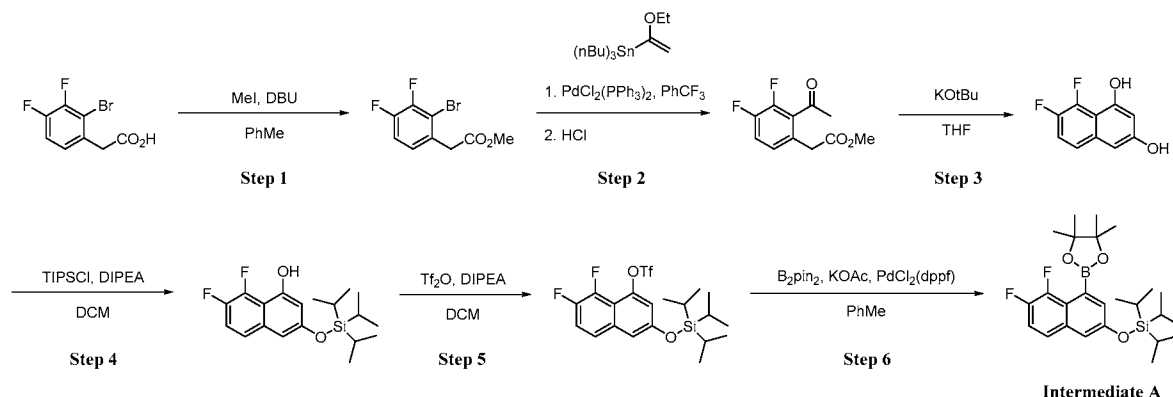
Mass Spectra (MS): Unless otherwise indicated, all mass spectral data for starting materials, intermediates and/or exemplary compounds are reported as mass/charge (m/z), having an
25 [M+H]⁺ molecular ion. The molecular ion reported was obtained by electrospray detection method (commonly referred to as an ESI MS) utilizing a Waters Acquity UPLC/MS system.

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Compounds having an isotopic atom, such as bromine and the like, are generally reported according to the detected isotopic pattern, as appreciated by those skilled in the art.

Preparation of Intermediates

5 ((5,6-Difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)oxy)triisopropylsilane (Intermediate A)



Step 1: Methyl 2-(2-bromo-3,4-difluorophenyl)acetate. To a 100-mL round-bottomed flask was added 2-(2-bromo-3,4-difluorophenyl)acetic acid (2.00 g, 7.97 mmol) and DBU (1.21 g, 1.20 mL, 7.97 mmol), and toluene (40 mL). To the mixture was added MeI (2.26 g, 1.0 mL, 15.93 mmol) and the mixture was stirred at rt for 4 h. Upon completion, the reaction was diluted with water and extracted with EtOAc. The organic layer was dried, concentrated, and chromatographed with 0-50% EtOAc in heptane to give methyl 2-(2-bromo-3,4-difluorophenyl)acetate (1.62 g, 6.11 mmol, 77 % yield) as a colorless oil.

10 m/z (ESI): 265.0 (M+H)⁺.

Step 2: Methyl 2-(2-acetyl-3,4-difluorophenyl)acetate. A microwave vial was charged with methyl 2-(2-bromo-3,4-difluorophenyl)acetate (1.62 g, 6.11 mmol), trifluorotoluene (15 mL), tributyl(1-ethoxyvinyl)stannane (4.41 g, 12.22 mmol), and *trans*-dichlorobis(triphenyl-phosphine)palladium (II) (0.86 g, 1.22 mmol). The vial was purged with nitrogen for 2 min, sealed, and placed in a microwave reactor for 12 h at 150 °C. Upon completion, the mixture was filtered through a celite / silica plug and concentrated. The resulting yellow oil was dissolved in THF (10 mL) and 5 mL of 5 N HCl were added. The reaction was stirred at rt for 30 min. Upon completion, the reaction was poured slowly into a separatory funnel containing saturated NaHCO₃. The mixture was extracted with EtOAc,

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dried, concentrated and chromatographed with 0-30% EtOAc in heptane to give methyl 2-(2-acetyl-3,4-difluorophenyl)acetate (1.21 g, 5.30 mmol, 87 % yield) as colorless oil. *m/z* (ESI): 229.1 (M+H)⁺.

Step 3: 7,8-Difluoronaphthalene-1,3-diol. To a 250 mL round-bottomed flask was added methyl 2-(2-acetyl-3,4-difluorophenyl)acetate (1.21 g, 5.30 mmol), KOtBu (1.79 g, 15.91 mmol) and THF (40 mL). The flask was capped and placed in a preheated aluminum block kept at 80 °C for 3 h. Upon completion, the reaction was diluted with 1 M HCl, extracted with DCM, and dried to give 7,8-difluoronaphthalene-1,3-diol (1.04 g, 5.30 mmol, 100 % yield) as red oil. *m/z* (ESI): 197.0 (M+H)⁺.

Step 4: 7,8-Difluoro-3-((triisopropylsilyl)oxy)naphthalen-1-ol. To a 100-mL round-bottomed flask was added 7,8-difluoronaphthalene-1,3-diol (0.75 g, 3.82 mmol), DIPEA (2.00 mL, 11.47 mmol) and DCM (38 mL). The solution was cooled to 0 °C and TIPS-Cl (0.66 g, 0.73 mL, 3.44 mmol) was added. The reaction was allowed to warm to rt. Upon completion, the reaction was concentrated and chromatographed with 0-30% EtOAc in heptanes. Isomers separated with silica gel column with 0-30% EtOAc in heptane to give 7,8-difluoro-3-((triisopropylsilyl)oxy)naphthalen-1-ol (0.88 g, 2.51 mmol, 66 % yield) (first eluting isomer) as the major product and 5,6-difluoro-4-((triisopropylsilyl)oxy)naphthalen-2-ol (0.18 g, 0.50 mmol, 13 % yield) (second eluting isomer) as the minor product. *m/z* (ESI): 353.2 (M+H)⁺.

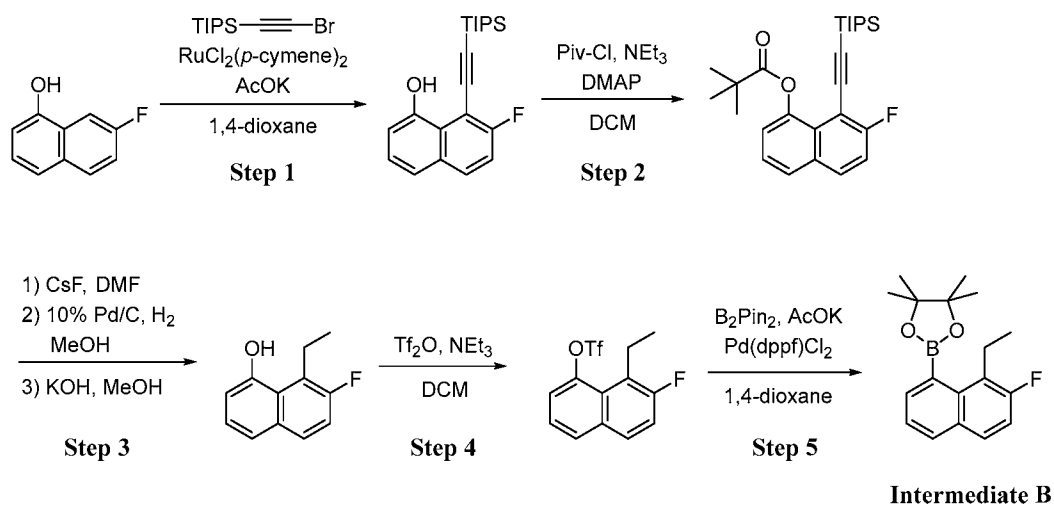
Step 5: 7,8-Difluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl trifluoromethanesulfonate. To a 100-mL round-bottomed flask was added 7,8-difluoro-3-((triisopropylsilyl)oxy)naphthalen-1-ol (0.88 g, 2.50 mmol), DIPEA (1.31 mL, 7.51 mmol) and DCM (25 mL). The solution was cooled to 0 °C and Tf₂O (1 M in DCM, 2.76 mL, 2.76 mmol) was added. The reaction was allowed to warm to rt and stir for 1 h. Upon completion, the reaction was poured into a separatory funnel containing saturated NaHCO₃ and extracted with DCM. The organic layer was dried and concentrated to give 7,8-difluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl trifluoromethanesulfonate (1.21 mg, 2.51 mmol, 100 % yield) as orange oil which was used in the following step without further purification. *m/z* (ESI): 485.1 (M+H)⁺.

Step 6: ((5,6-Difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)oxy)triisopropylsilane. A 100-mL round-bottomed flask was charged

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with 7,8-difluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl trifluoromethanesulfonate (1.21 g, 2.50 mmol), bis(pinacolato)diboron (1.27 g, 4.99 mmol), potassium acetate (0.86 g, 8.74 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium dichloride (0.37 g, 0.499 mmol) and toluene (25 mL). The reaction was purged with nitrogen for 5 minutes and then stirred at 80 °C for 12 h. Upon completion, the reaction was concentrated and chromatographed with a gradient of 0-40% EtOAc in hexanes to give ((5,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)oxy)triisopropylsilane (0.97 g, 2.09 mmol, 84 % yield). m/z (ESI): 463.3 (M+H)⁺.

10 **2-(8-Ethyl-7-fluoronaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Intermediate B)**



Step 1: 7-Fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-ol. A pressure relief vial was charged with potassium acetate (1.21 g, 12.3 mmol, Sigma Aldrich), 7-fluoro-1-naphthol (1.00 g, 6.17 mmol, Enamine), dichloro(*p*-cymene)ruthenium(II)dimer (0.38 g, 0.62 mmol, Alfa Aesar) and then purged with nitrogen for 5 min. The solids were then suspended in 1,4-dioxane (12 mL) and (bromoethynyl)triisopropylsilane (1.77 g, 1.63 mL, 6.78 mmol, Enamine) was added. The reaction was then stirred at 110 °C for 18 h and subsequently at room temperature for 2-d. Volatiles were removed in vacuo and the crude material was absorbed onto silica gel. The crude product was purified by column chromatography on silica gel, eluting with a gradient of 0-20% EtOAc in heptane to yield 7-fluoro-8-

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((triisopropylsilyl)ethynyl)naphthalen-1-ol (1.90 g, 5.55 mmol, 90 % yield) as a yellow oil.
 m/z (ESI, +ve ion): 343.0 (M+H)⁺.

Step 2: 7-Fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl pivalate. 7-Fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-ol (1.00 g, 2.92 mmol) was dissolved in
5 dichloromethane (11 mL) and cooled to 0 °C. DMAP (0.07 g, 0.58 mmol, Sigma-Aldrich Corporation) and TEA (0.89 g, 1.23 mL, 8.76 mmol, Sigma-Aldrich Corporation) were added, followed by dropwise addition of pivaloyl chloride (1.06 g, 1.08 mL, 8.76 mmol, Sigma-Aldrich Corporation). The mixture was warmed to room temperature and stirred for 45 minutes. Water (10 mL) was added and the aqueous layer extracted with DCM (2 × 10 mL).
10 The combined organic phase was dried over anhydrous Na₂SO₄. Volatiles were removed in vacuo and the crude material was purified by column chromatography on silica gel, eluting with a gradient of 0-10% EtOAc in heptane to yield 7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl pivalate (1.13 g, 2.65 mmol, 91 % yield) as yellow crystalline solid. m/z (ESI, +ve ion): 427.4 (M+H)⁺.

Step 3: 8-Ethyl-7-fluoronaphthalen-1-ol. A scintillation vial was charged with 7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl pivalate (1.13 g, 2.65 mmol) and dissolved in DMF (12 mL). Cesium fluoride (4.02 g, 26.5 mmol, Sigma-Aldrich Corporation) was added and the mixture stirred at rt for 30 minutes. Water (100 mL) was added and the aqueous phase extracted with EtOAc (2 × 20 mL). The combined organic layer
20 was dried over Na₂SO₄ and volatiles were then removed in vacuo to yield 8-ethynyl-7-fluoronaphthalen-1-yl pivalate (0.72 g, 2.65 mmol, quantitative yield) as a crude yellow oil that was used without further purification.

8-Ethynyl-7-fluoronaphthalen-1-yl pivalate (0.72 mg, 2.65 mmol) was dissolved in MeOH (9 mL) and palladium on activated carbon (85 mg, 0.795 mmol, Sigma-Aldrich Corporation) was added. The reaction vessel was purged with H₂ and then stirred under a H₂
25 atmosphere (15 psi) at room temperature for 2 h. The mixture was filtered over celite, washed with EtOAc until the filtrate ran clear and volatiles were removed in vacuo. The crude material was then dissolved in MeOH (10 mL) and potassium hydroxide (0.45 g, 7.95 mmol, VWR International, LLC) was added. After stirring at room temperature for 2 h, the pH of the solution was adjusted to pH = 3 using 1 M aq. HCl. Water (20 mL) was added and the
30 aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic layer was dried

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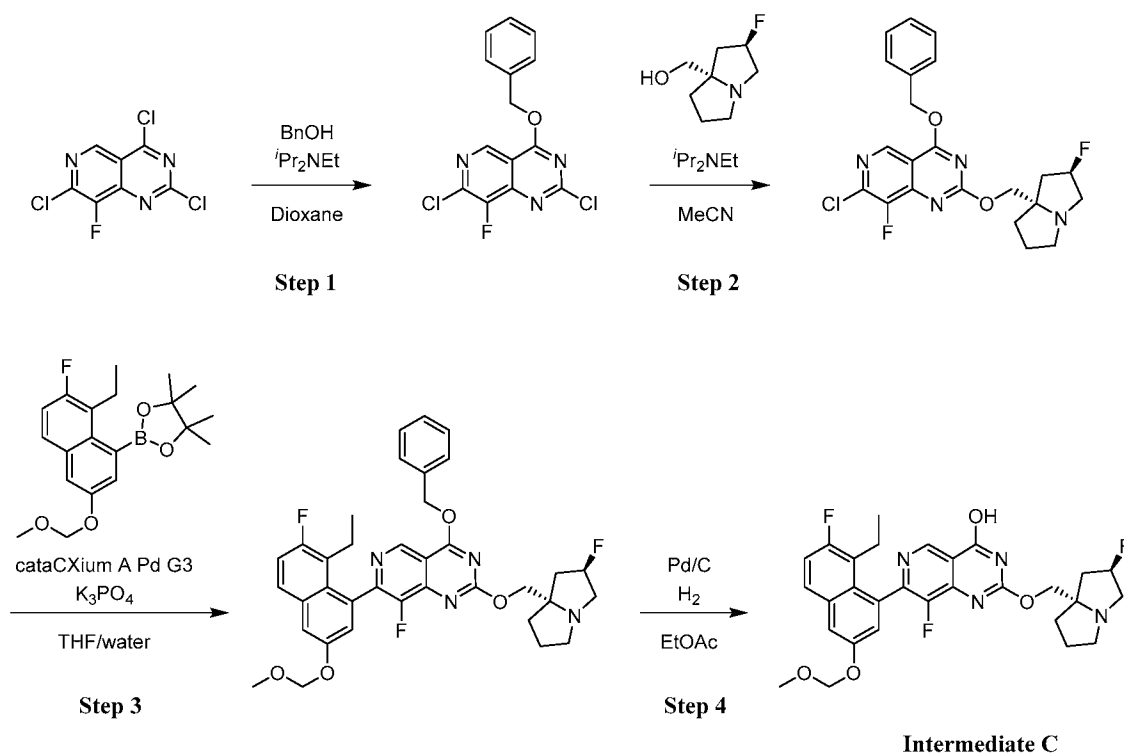
over Na₂SO₄ and volatiles were removed in vacuo. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0-20% EtOAc in heptane to yield 8-ethyl-7-fluoronaphthalen-1-ol (0.35 g, 1.84 mmol, 70% yield) over 3 steps as yellow oil. *m/z* (ESI, +ve ion): 191.2 (M+H)⁺.

5 **Step 4: 8-Ethyl-7-fluoronaphthalen-1-yl trifluoromethanesulfonate.** 8-Ethyl-7-fluoronaphthalen-1-ol (0.35 g, 1.84 mmol) was dissolved in DCM and cooled to 0 °C. TEA (0.28 g, 0.39 mL, 2.76 mmol, Sigma-Aldrich Corporation) was added, followed by dropwise addition of a 1 M Tf₂O solution (2.02 mL, 2.02 mmol, Sigma-Aldrich Corporation). The mixture was stirred at rt for 20 minutes and poured into ice water (20 mL). The aqueous
10 phase was extracted with DCM (2 x 10 mL), the combined organic layers were dried over Na₂SO₄ and volatiles were removed in vacuo. The crude mixture was purified by column chromatography on silica gel, eluting using a gradient of 0-5% EtOAc in heptane to yield 8-ethyl-7-fluoronaphthalen-1-yl trifluoromethanesulfonate (0.47 g, 1.47 mmol, 80 % yield) as colorless oil. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.86 (dd, J=8.3, 0.9 Hz, 1 H),
15 7.79 (dd, J=9.4, 6.5 Hz, 1 H), 7.59 (dt, J=7.7, 0.8 Hz, 1 H), 7.44 (t, J=8.2 Hz, 1 H), 7.36 (t, J=9.4 Hz, 1 H), 3.32 (qd, J=7.5, 2.9 Hz, 2 H), 1.29 (t, J=7.4 Hz, 3 H).

Step 5: 2-(8-Ethyl-7-fluoronaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Potassium acetate (0.43 g, 4.38 mmol, Sigma-Aldrich Corporation) was placed in a pressure relief vial and dried under vacuum. Then, 8-ethyl-7-fluoronaphthalen-1-yl trifluoromethanesulfonate (0.47 g, 1.46 mmol), bis(pinacolato)diboron (0.74 g, 2.92 mmol, Combi-Blocks Inc.) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (0.11 g, 0.15 mmol, Sigma-Aldrich Corporation) were added and the mixture stirred at 90 °C for 3 h and then at rt for 12 h. Volatiles were removed in vacuo and the crude mixture was purified
20 by column chromatography on silica gel, eluting with a gradient of 0-15% EtOAc in heptane to yield 2-(8-ethyl-7-fluoronaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.15 g, 0.50 mmol, 34% yield) as yellow wax. *m/z* (ESI, +ve ion): 301.0 (M+H)⁺.

7-(8-Ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol
30 **(Intermediate C)**

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Step 1: 4-(Benzyloxy)-2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidine. A 250-mL round-bottom flask charged with activated 3Å molecular sieves was added 1,4-dioxane (48 mL), DIPEA (9.22 g, 12.5 mL, 71.3 mmol), benzyl alcohol (3.86 g, 3.7 mL, 35.7 mmol) and 2,4,7-trichloro-8-fluoropyrido[4,3-*d*]pyrimidine (6.00 g, 23.8 mmol). The mixture was stirred at 85 °C for 2 h. Volatiles were removed in vacuo and the residue was purified by column chromatography on silica gel, eluting with 0 - 100% 3:1 EtOAc/EtOH blend in heptane to yield 4-(benzyloxy)-2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidine (3.30 g, 10.18 mmol, 43 % yield). *m/z* (ESI): 325.9 (M+H)⁺.

Step 2: 4-(Benzyloxy)-7-chloro-8-fluoro-2-(((2*S*,7*aR*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine. To a solution of 4-(benzyloxy)-2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidine (3.30 g, 10.18 mmol) in acetonitrile (20 mL) were added ((2*S*,7*aR*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methanol (1.78 g, 11.20 mmol) and DIPEA (5.26 g, 7.1 mL, 40.7 mmol). The reaction was stirred at 80 °C for 1 h. Volatiles were removed under reduced pressure and the mixture was purified by column chromatography on silica gel, eluting with 0-100% 3:1 EtOAc/EtOH blend in heptane with 2% triethylamine additive to yield 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2*S*,7*aR*)-2-

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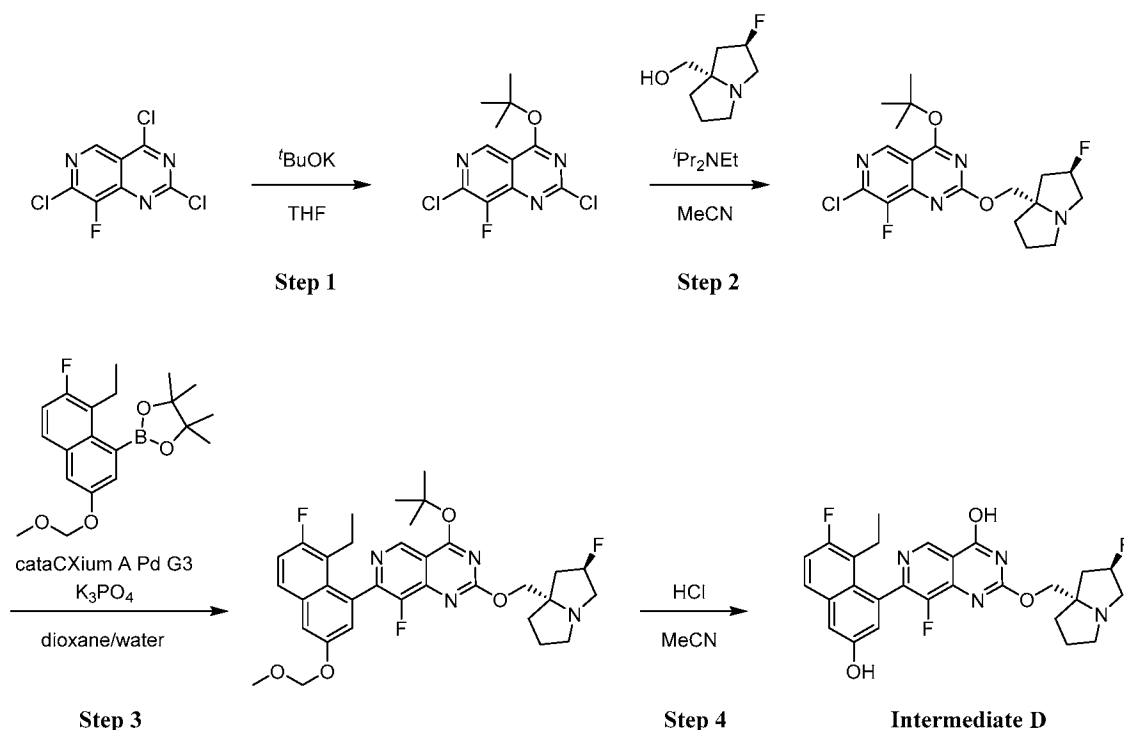
fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (2.60 g, 5.82 mmol, 57 % yield). *m/z* (ESI): 447.0 (M+H)⁺.

Step 3: 4-(Benzyloxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine. To a solution of 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2*S*,7*aR*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (2.60 g, 5.82 mmol) and 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.14 g, 8.73 mmol) in tetrahydrofuran (17 mL) and water (1.7 mL) were added potassium phosphate (3.70 g, 17.45 mmol) and cataCXium A Pd G3 (0.85 g, 1.16 mmol). The reaction mixture was stirred at 70 °C for 2 h. The reaction mixture was purified by column chromatography on silica gel, eluting with 0-50% 3:1 EtOAc/EtOH blend in heptane with 2% triethylamine additive to yield 4-(benzyloxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (2.42 g, 3.75 mmol, 65 % yield). *m/z* (ESI): 645.0 (M+H)⁺.

Step 4: 7-(8-Ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol. 4-(Benzyloxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (2.42 g, 3.75 mmol) was dissolved in ethyl acetate (75 mL). Palladium on activated carbon (0.80 g, 0.75 mmol) was added and the mixture stirred at rt under an atmosphere of H₂ overnight. The mixture was filtered over celite and the filtercake washed with DCM:MeOH (2:1) until the filtrate ran clear. Volatiles were removed in vacuo to yield 7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol as a brown foam which was used without further purification. *m/z* (ESI): 555.0 (M+H)⁺.

7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol (Intermediate D)

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Step 1: 4-(*tert*-Butoxy)-2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidine. To a stirring mixture of 2,4,7-trichloro-8-fluoropyrido[4,3-*d*]pyrimidine (2.50 g, 9.90 mmol) in THF (3.5 mL) at -40 °C was added slowly potassium *tert*-butoxide (1.0 M in THF, 14.9 mL, 14.85 mmol) over a period of 0.5 h. Additional potassium *tert*-butoxide (1.0 M in THF, 2.5 mL) was added after 1 h. The resulting mixture was stirred at -40 °C for 10 min before being poured onto ice and saturated aqueous ammonium hydroxide followed by extraction with EtOAc. The combined organics were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with a gradient of 0-20% EtOAc in heptane to give 4-(*tert*-butoxy)-2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidine (1.12 g, 3.86 mmol, 39 % yield). *m/z* (ESI): 234.0 (M-^tBu+H)⁺.

Step 2: 4-(*tert*-Butoxy)-7-chloro-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine. A mixture of 4-(*tert*-butoxy)-2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidine (0.58 g, 2.00 mmol), ((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methanol (0.45 g, 2.80 mmol) and 1,1'-dimethyltriethylamine (1.03 g, 1.4 mL, 8.00 mmol) in MeCN (6.0 mL) in a 10-mL microwave reaction vessel was

subjected to microwave irradiation (16 h at 75 °C). Volatiles were removed under reduced pressure and the crude mixture was purified by column chromatography on silica gel, eluting with a gradient of 0-50% (20% MeOH in DCM) in DCM to give 4-(*tert*-butoxy)-7-chloro-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (0.66 g, 1.60 mmol, 80 % yield) as off-white solid. *m/z* (ESI): 413.2 (M+H)⁺.

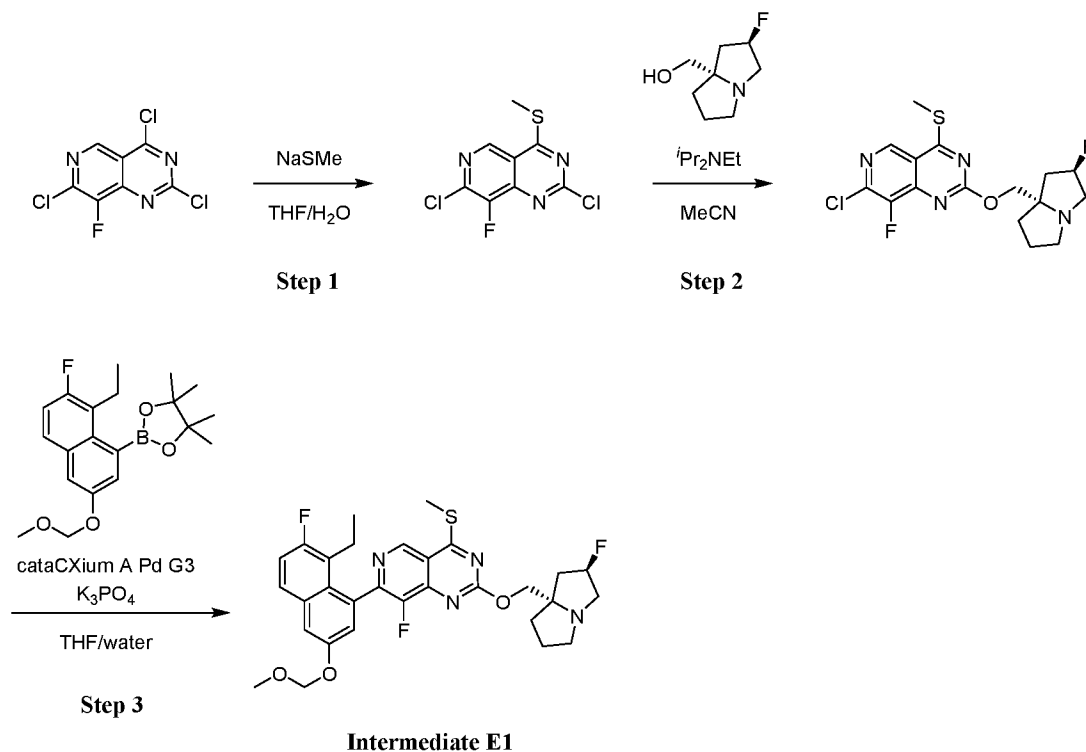
Step 3: 4-(*tert*-Butoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine. In a 5-mL microwave reaction vessel were placed 4-(*tert*-butoxy)-7-chloro-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (0.66 g, 1.60 mmol), 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.92 g, 2.56 mmol), cataCXium A Pd G3 (0.23 g, 0.32 mmol), and potassium phosphate tribasic (0.85 g, 4.00 mmol) followed by 1,4-dioxane (10 mL) and water (1.8 mL). The resulting mixture was purged with nitrogen for 10 min before being sealed and irradiated under microwave at 85 °C for 3 h. Volatiles were removed under reduced pressure, and the crude residue was purified by column chromatography on silica gel, eluting with a gradient of 0-50% (20% MeOH in DCM) in DCM to give 4-(*tert*-butoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (0.84 g, 1.38 mmol, 86 % yield) as colorless film. *m/z* (ESI): 611.2 (M+H)⁺.

Step 4: 7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol. To a stirred solution of 4-(*tert*-butoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (0.84 g, 1.38 mmol) in MeCN (2.0 mL) was added 4.0 M solution of HCl in dioxane (12 mL, 48.1 mmol) at rt. The resulting mixture was stirred at rt for 0.5 h. Volatiles were removed under reduced pressure. The crude residue was dissolved in MeOH/DCM, cooled in an ice bath, and neutralized with ammonium hydroxide before loading onto a silica gel precolumn and purified by column chromatography on silica gel, eluting with a gradient of 0-50% (20% MeOH in DCM) in DCM to give 7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-

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d]pyrimidin-4-ol (0.39 g, 0.76 mmol, 56 % yield) as off-white solid. *m/z* (ESI): 511.0 (M+H)⁺.

7-(8-Ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(methylthio)pyrido[4,3-*d*]pyrimidine (Intermediate E1)



Step 1: 2,7-Dichloro-8-fluoro-4-(methylthio)pyrido[4,3-*d*]pyrimidine. To a stirring solution of 2,4,7-trichloro-8-fluoropyrido[4,3-*d*]pyrimidine (3.50 g, 13.86 mmol) in tetrahydrofuran (40 mL) at 0 °C was added sodium methanethiolate (0.97 g, 13.9 mmol) in water (6 mL). The reaction was stirred at 0 °C for 0.5 h and a precipitate was formed. The precipitate was collected by filtration to afford 2,7-dichloro-8-fluoro-4-(methylthio)pyrido[4,3-*d*]pyrimidine (2.10 g, 7.95 mmol, 57 % yield) as white solid, which was used directly in the subsequent step. *m/z* (ESI): 264.0 (M+H)⁺.

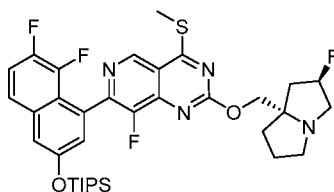
Step 2: 7-Chloro-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(methylthio)pyrido[4,3-*d*]pyrimidine. A mixture of 2,7-dichloro-8-fluoro-4-(methylthio)pyrido[4,3-*d*]pyrimidine (2.10 g, 7.95 mmol), ((2*R*,7*aS*)-2-

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fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methanol (1.90 g, 11.93 mmol), and Hunig's base (4.11 g, 5.6 mL, 31.8 mmol) in acetonitrile (25 mL) was stirred at 70 °C for 1.5 h. The reaction mixture was cooled to rt. The precipitate was collected by filtration and washed with heptane to afford a portion of the desired product. The filtrate was concentrated and purified by column chromatography on silica gel, eluting with a gradient of 0-50% (20% MeOH in DCM) in DCM to afford another portion of the desired product. Two portions were combined to give 7-chloro-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(methylthio)pyrido[4,3-*d*]pyrimidine (2.34 g, 6.05 mmol, 76 % yield) as orange solid. *m/z* (ESI): 387.0 (M+H)⁺.

Step 3: 7-(8-Ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(methylthio)pyrido[4,3-*d*]pyrimidine. A mixture of 7-chloro-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(methylthio)pyrido[4,3-*d*]pyrimidine (2.34 g, 6.05 mmol), 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.27 g, 9.07 mmol), cataCXium A Pd G3 (0.88 g, 1.21 mmol), and potassium phosphate tribasic (3.85 g, 18.15 mmol) was suspended in degassed water (4 mL) and 1,4-dioxane (30 mL). The reaction was stirred at 85 °C for 1.5 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography twice, eluting with first a gradient of 0-50% (20% MeOH in DCM) in DCM, then 0-50% 3:1 EtOAc/EtOH in heptane with 2% triethylamine additive to afford 7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(methylthio)pyrido[4,3-*d*]pyrimidine (1.50 g, 2.57 mmol, 42 % yield) as yellow solid. *m/z* (ESI): 585.0 (M+H)⁺.

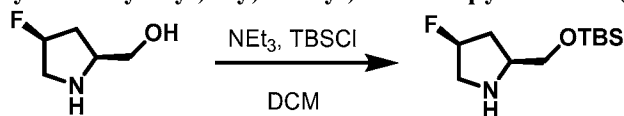
7-(7,8-Difluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(methylthio)pyrido[4,3-*d*]pyrimidine (Intermediate E2)



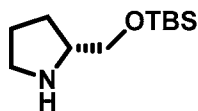
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Intermediate E2

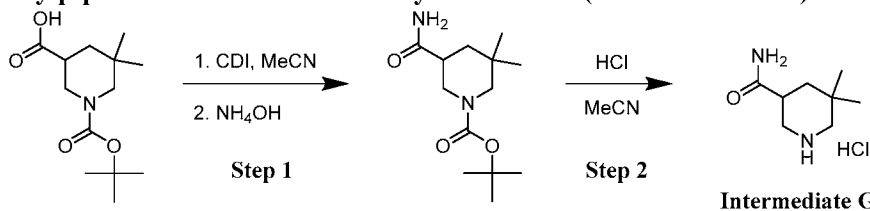
Synthesized in an analogous manner to **Intermediate E1**. m/z (ESI): 687.0 (M+H)⁺.

(2*S*,4*S*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-fluoropyrrolidine (Intermediate F1)**Intermediate F1**

5 ((2*S*,4*S*)-4-Fluoropyrrolidin-2-yl)methanol hydrochloride (0.50 g, 3.20 mmol) was dissolved in DCM (16 mL) before triethylamine (0.49 g, 0.67 mL, 4.80 mmol) was added. The solution cooled to 0 °C. *tert*-Butylchlorodimethylsilane (0.53 g, 3.50 mmol) was then added in one portion. The mixture warmed to rt and then stirred overnight. The crude mixture
10 was purified by column chromatography on silica gel, eluting with a gradient of 0-35% MeOH in DCM) to yield (2*S*,4*S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-fluoropyrrolidine (0.38 g, 1.60 mmol, 50 % yield). m/z (ESI): 234.2 (M+H)⁺.

(*R*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)pyrrolidine (Intermediate F2)**Intermediate F2**

Synthesized in an analogous manner to **Intermediate F1** from *D*-prolinol. m/z (ESI): 216.2 (M+H)⁺.

5,5-Dimethylpiperidine-3-carboxamide Hydrochloride (Intermediate G1)**Intermediate G1**

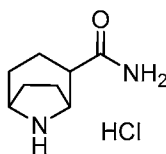
20 **Step 1: *tert*-Butyl 5-carbamoyl-3,3-dimethylpiperidine-1-carboxylate.** A solution of 1,1'-carbonyldiimidazole (0.14 g, 0.87 mmol, Acros Organics) in acetonitrile (2.3 mL) was added dropwise to a stirring solution of 1-[(*tert*-butoxy)carbonyl]-5,5-dimethylpiperidine-3-

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carboxylic acid (0.21 g, 0.83 mmol, Enamine) in acetonitrile (3.2 mL). The reaction mixture was then allowed to stir at rt. After 1 h, ammonium hydroxide (4.20 g, 4.6 mL, 0.12 mol, Fisher Scientific) was added and the reaction was stirred at the same temperature overnight. The organic solvent was removed under reduced pressure. The remaining solution was then diluted with EtOAc (10 mL) and the organic layer was washed with 10% aq. citric acid (10 mL), saturated aqueous sodium bicarbonate (10 mL), and brine (10 mL). The organic layer was then dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide *tert*-butyl 5-carbamoyl-3,3-dimethylpiperidine-1-carboxylate (0.20g, 0.77 mmol, 92 % yield), which was used directly in the next step without further purification. *m/z* (ESI): 201.2 (M+H-Bu)⁺.

Step 2: 5,5-Dimethylpiperidine-3-carboxamide hydrochloride. A vial was charged with *tert*-butyl 5-carbamoyl-3,3-dimethylpiperidine-1-carboxylate (0.20g, 0.77 mmol) and acetonitrile (20 mL). HCl (4 M in dioxane, 4.8 mL, 19 mmol, Sigma-Aldrich Corporation) was then added and the reaction was stirred at rt. After 1 h, the reaction was concentrated under reduced pressure to afford 5,5-dimethylpiperidine-3-carboxamide hydrochloride (0.14 g, 0.75 mmol, 97 % yield) as white solid. *m/z* (ESI): 157.2 (M+H)⁺.

***rel*-(1*S*,5*S*)-8-Azabicyclo[3.2.1]octane-2-carboxamide Hydrochloride (Intermediate G2)**

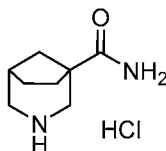


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Intermediate G2

Synthesized in an analogous manner to **Intermediate G1** using 8-[(*tert*-butoxy)carbonyl]-8-azabicyclo[3.2.1]octane-2-carboxylic acid (Pharmablock, Inc.). *m/z* (ESI): 155.2 (M+H)⁺.

***rel*-(1*R*,5*R*)-3-Azabicyclo[3.2.1]octane-1-carboxamide hydrochloride (Intermediate G3)**



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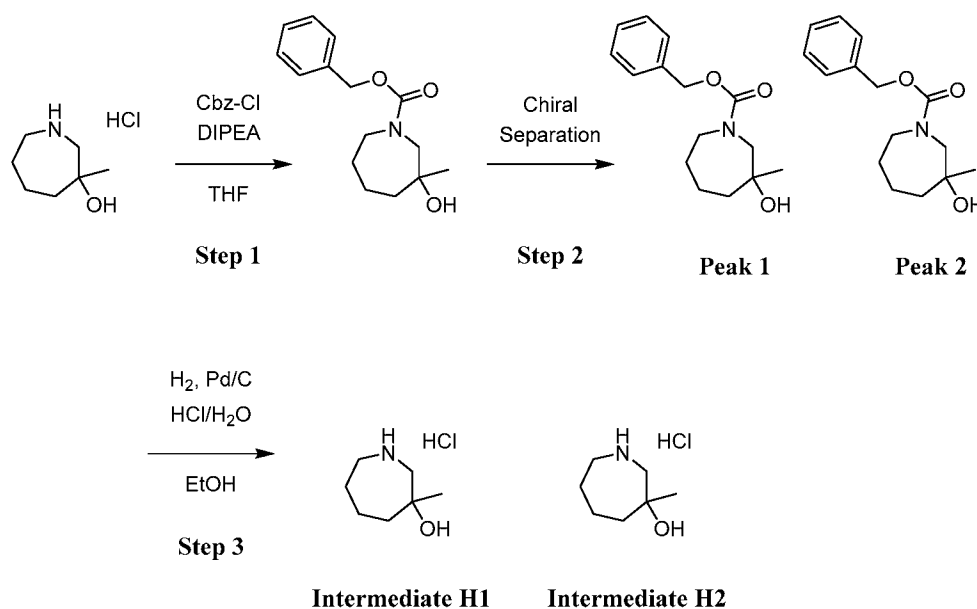
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Intermediate G3

Synthesized in an analogous manner to **Intermediate G1** using 3-[(*tert*-butoxy)carbonyl]-3-azabicyclo[3.2.1]octane-1-carboxylic acid (Enamine). m/z (ESI): 155.2 ($M+H$)⁺.

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3-Methylazepan-3-ol hydrochloride Isomer 1 (Intermediate H1) and Isomer 2 (Intermediate H2)



Step 1: Benzyl 3-hydroxy-3-methylazepane-1-carboxylate. To a 100-mL round-bottomed flask was added 3-methylazepan-3-ol hydrochloride (0.25 g, 1.51 mmol, Asta-tech), benzyl chloroformate (0.28 g, 0.24 mL, 1.66 mmol, Oakwood Products, Inc.), DIPEA (0.59 g, 0.8 mL, 4.53 mmol, Sigma-Aldrich Corporation) and THF (5.0 mL). The reaction was stirred at rt overnight. The solution was concentrated in vacuo. The crude material was purified by column chromatography on silica gel column, eluting with a gradient of 0 - 100% EtOAc in hexane to provide benzyl 3-hydroxy-3-methylazepane-1-carboxylate (0.33 g, 1.25 mmol, 83 % yield) as colorless oil. m/z (ESI): 264.2 ($M+H$)⁺.

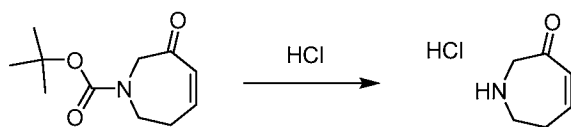
Step 2: Chiral separation. Benzyl 3-hydroxy-3-methylazepane-1-carboxylate (0.24 g) was purified via SFC using a Chiralpak IG, 21 × 250 mm 5 μm, column with a mobile

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phase of 20% methanol with 0.2% triethylamine using a flowrate of 80 mL/min to generate 89 mg of peak 1 with an ee of >99% and 91 mg of peak 2 with an ee of >99%.

Step 3: 3-Methylazepan-3-ol hydrochloride. Benzyl 3-hydroxy-3-methylazepan-1-carboxylate (89 mg, 0.34 mmol, Peak 1) was dissolved in ethanol (1.7 mL). Palladium on activated carbon (74 mg, 0.07 mmol, Sigma-Aldrich Corporation) and aqueous HCl solution (1 N, 0.2 mL, 0.42 mmol, Sigma-Aldrich Corporation) were added and the mixture stirred at rt under an atmosphere of H₂ for 10 h. The catalyst was removed and the solution was concentrated to provide 3-methylazepan-3-ol hydrochloride (isomer 1, **Intermediate H1**, 60 mg, 0.36 mmol). Isomer 2, **Intermediate H2** was obtained by the same method. *m/z* (ESI): 130.2 (M+H)⁺.

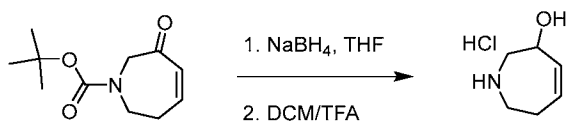
1,2,6,7-Tetrahydro-3H-azepin-3-one hydrochloride (**Intermediate I**)



Intermediate I

To a 25-mL round-bottomed flask was added *tert*-butyl 3-oxo-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate (0.10 g, 0.47 mmol, AstaTech, Inc) and HCl in 1,4-dioxane (4 M, 1.2 mL, 4.73 mmol, Sigma-Aldrich) in acetonitrile (2.4 mL). The reaction was stirred at rt overnight. The material was concentrated in vacuo to give a brown oil, which was used in the next step without further purification.

2,3,6,7-Tetrahydro-1H-azepin-3-ol hydrochloride (**Intermediate J**)



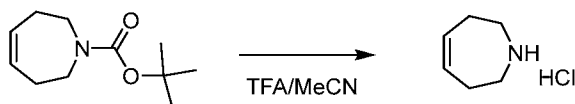
Intermediate J

To a 25-mL round-bottomed flask was added *tert*-butyl 3-oxo-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate (75 mg, 0.36 mmol, AstaTech, Inc) and sodium borohydride (40 mg, 1.07 mmol, Sigma-Aldrich Corporation) in THF (1.8 mL). A small amount of MeOH was added and the reaction was stirred at rt for 1 h. The reaction mixture was diluted with

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saturated NH_4Cl (10 mL) and extracted with EtOAc (2×10 mL). The organic extract was washed with saturated NaCl (10 mL) and dried over MgSO_4 . The solution was filtered and concentrated in vacuo to give a crude material, which was dissolved in 2 mL of DCM. At 0 °C, 2 mL of TFA was added. The reaction was stirred for 1 h. The mixture was concentrated in vacuo. To the residue was added 1 mL of 1 N HCl. The mixture was lyophilized to give 2,3,6,7-tetrahydro-1*H*-azepin-3-ol hydrochloride (60 mg, 0.40 mmol).

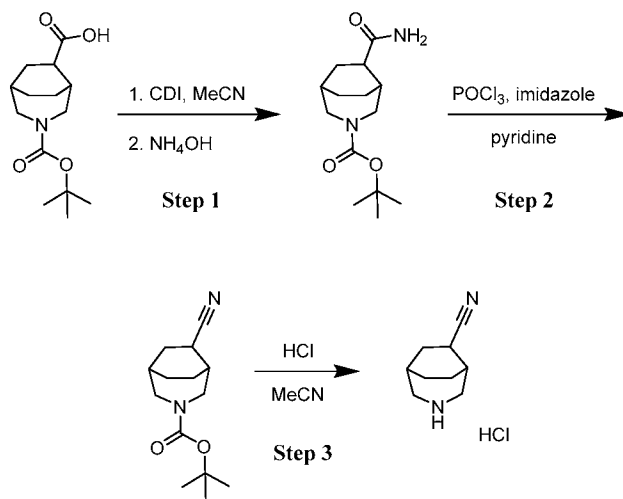
2,3,6,7-Tetrahydro-1*H*-azepine Hydrochloride (Intermediate K)



Intermediate K

To a 25-mL round-bottomed flask was added *tert*-butyl 2,3,6,7-tetrahydro-1*H*-azepine-1-carboxylate (0.25 g, 1.27 mmol, AstaTech, Inc) in acetonitrile (3.6 mL). TFA (0.74 g, 0.5 mL, 6.49 mmol, Sigma-Aldrich) was added at 0 °C. The reaction was then stirred at r.t. for 3 h then concentrated in vacuo. To the crude product was added HCl solution (1 N, 2.5 mL, 2.53 mmol, Sigma-Aldrich). The material was lyophilized to give 2,3,6,7-tetrahydro-1*H*-azepine hydrochloride as off-white solid, which was used in the next step without any further purification.

8-Oxa-3-azabicyclo[3.2.1]octane-6-carbonitrile Hydrochloride (Intermediate L1)



Intermediate L1

Step 1: *tert*-Butyl 6-carbamoyl-3-azabicyclo[3.2.2]nonane-3-carboxylate. A solution of 1,1'-carbonyldiimidazole (0.25 g, 1.56 mmol, Acros Organics) in acetonitrile (4.1 mL) was added dropwise to a stirring solution of 3-[(*tert*-butoxy)carbonyl]-3-azabicyclo[3.2.2]nonane-6-carboxylic acid (0.40 g, 1.49 mmol, Enamine) in acetonitrile (5.8 mL). The reaction mixture was then allowed to stir at rt. After 1 h, ammonium hydroxide (7.50 g, 0.22 mol, Fisher Scientific) was added and the reaction was stirred at the same temperature. After stirring overnight, the organic solvent was removed under reduced pressure and then the reaction mixture was diluted with EtOAc (10 mL) and the organic layer was washed with 10% aq. citric acid (10 mL), saturated aqueous sodium bicarbonate (10 mL), and brine (10 mL). The organic layer was then dried with sodium sulfate, filtered, and concentrated under reduced pressure to provide *tert*-butyl 6-carbamoyl-3-azabicyclo[3.2.2]nonane-3-carboxylate (0.34 g, 1.26 mmol, 85 % yield). *m/z* (ESI): 213.2 (M+H-Bu)⁺. The product was then carried forward without further purification.

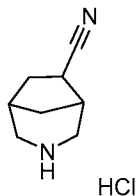
Step 2: *tert*-Butyl 6-cyano-3-azabicyclo[3.2.2]nonane-3-carboxylate. To a stirring solution of *tert*-butyl 6-carbamoyl-3-azabicyclo[3.2.2]nonane-3-carboxylate (0.13 g, 0.47 mmol) in pyridine (1.2 mL) was added 1*H*-imidazole (63 mg, 0.93 mmol, Sigma Aldrich). The resultant mixture was cooled to 0 °C, and phosphorous oxychloride (0.29 g, 0.17 mL, 1.86 mmol, Sigma-Aldrich Corporation) was added slowly dropwise and the mixture kept at the same temperature. After 1.2 h, the reaction was then quenched by the addition of saturated aqueous ammonium chloride (2 mL) and the aqueous layer extracted with EtOAc (3 × 3 mL). The combined organic layers were then washed with 10% copper sulfate (2 × 10 mL), dried with sodium sulfate, filtered, and concentrated under reduced pressure to provide *tert*-butyl 6-cyano-3-azabicyclo[3.2.2]nonane-3-carboxylate (94 mg, 0.38 mmol, 81 % yield). *m/z* (ESI): 151.2 (M+H-Boc)⁺. The product was then carried forward without further purification.

Step 3: 8-Oxa-3-azabicyclo[3.2.1]octane-6-carbonitrile hydrochloride. *tert*-Butyl 6-cyano-3-azabicyclo[3.2.2]nonane-3-carboxylate (94 mg, 0.38 mmol) was then dissolved in MeCN (3.5 mL) and HCl in 1,4-dioxane (4 M, 0.47 mL, 1.86 mmol, Sigma-Aldrich Corporation) was added. The reaction was then allowed to stir at rt for 15 min, and then the reaction was concentrated under reduced pressure to afford 3-azabicyclo[3.2.2]nonane-6-

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carbonitrile hydrochloride (71 mg, 0.38 mmol, 82 % yield) as off-white solid. The product was then carried forward without further purification. m/z (ESI): 151.2 (M+H)⁺.

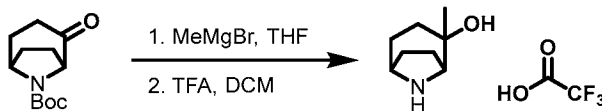
3-Azabicyclo[3.2.1]octane-6-carbonitrile Hydrochloride (Intermediate L2)



Intermediate L2

Synthesized in an analogous manner to **Intermediate L1**, using 3-[(*tert*-butoxy)carbonyl]-3-azabicyclo[3.2.1]octane-6-carboxylic acid (CAS#: 2287288-75-7, Enamine). m/z (ESI): 137.1 (M+H)⁺.

(1*S*,5*R*)-2-Methyl-8-azabicyclo[3.2.1]octan-2-ol 2,2,2-Trifluoroacetate (**Intermediate M1**)

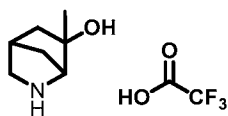


Intermediate M1

A round bottom flask was charged with *tert*-butyl (1*S*,5*R*)-2-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (0.50 g, 2.22 mmol, PharmaBlock) and THF (12 mL). The mixture was cooled to -78 °C and MeMgBr (1.5 mL, 4.44 mmol) was added. The mixture was allowed to warm to rt. Upon completion, the reaction was quenched with brine and extracted with EtOAc. The organic layer was dried and concentrated to give *tert*-butyl (1*S*,5*R*)-2-hydroxy-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate as colorless oil, which was dissolved in DCM (3 mL) and TFA (0.5 mL, 6.67 mmol). The mixture was stirred at rt. Upon completion, the reaction was concentrated in vacuo to give (1*S*,5*R*)-2-methyl-8-azabicyclo[3.2.1]octan-2-ol 2,2,2-trifluoroacetate (0.31 g, 2.22 mmol, 100 % yield), which was used in the following step without further manipulation. m/z (ESI): 142.1 (M+H)⁺.

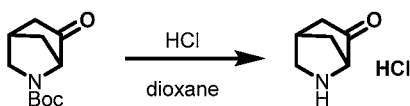
6-Methyl-2-azabicyclo[2.2.1]heptan-6-ol 2,2,2-Trifluoroacetate (**Intermediate M2**)

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**Intermediate M2**

Synthesized in an analogous manner to **Intermediate M1**, using *tert*-butyl 6-oxo-2-azabicyclo[2.2.1]heptane-2-carboxylate (Enamine). *m/z* (ESI): 128.1 (M+H)⁺.

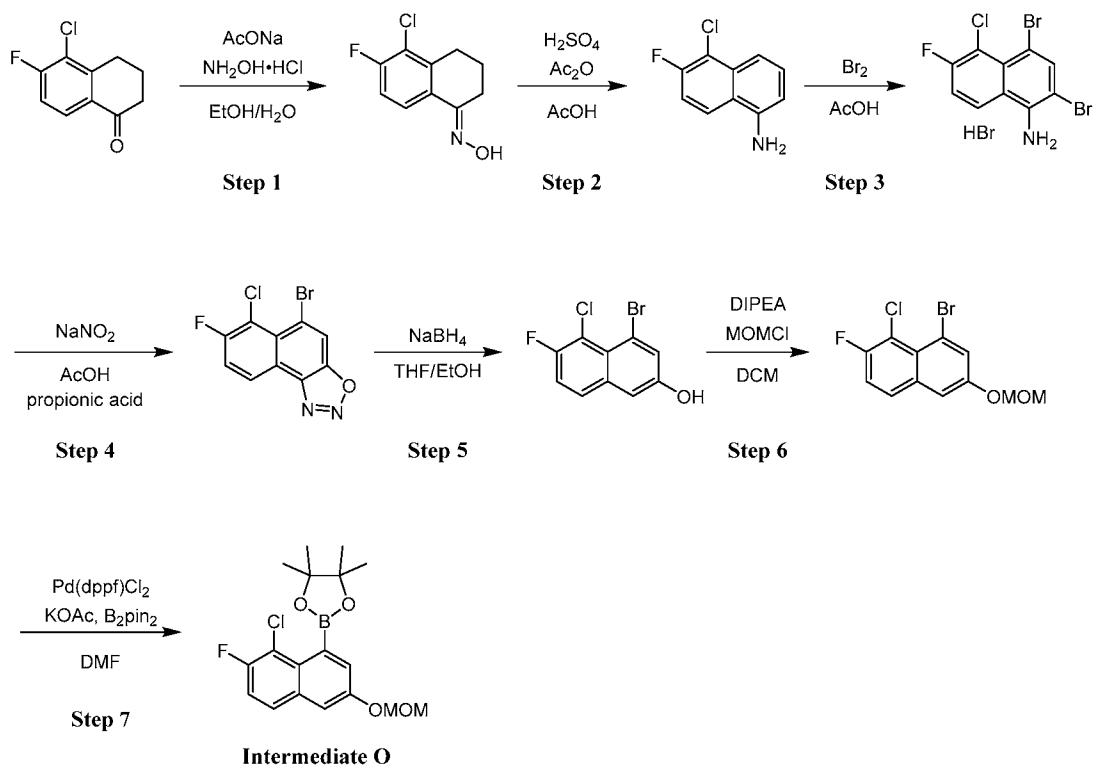
5 **2-Azabicyclo[2.2.1]heptan-6-one hydrochloride (Intermediate N)**

**Intermediate N**

A round bottom flask was charged with *tert*-butyl 6-oxo-2-azabicyclo[2.2.1]heptane-2-carboxylate (0.50 g, 2.37 mmol, Enamine) and 1,4-dioxane (11 mL). The mixture was cooled to -78 °C and HCl (4 M in dioxane, 1.78 mL, 7.10 mmol) was added. The mixture was
 10 allowed to stir at rt. Upon completion, the reaction was concentrated in vacuo to give 2-azabicyclo[2.2.1]heptan-6-one hydrochloride (0.26 g, 2.37 mmol, 100 % yield) as white solid, which was used in the following step without further purification. *m/z* (ESI): 112.1 (M+H)⁺

15 **2-(8-Chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Intermediate O)**

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Step 1: (*E*)-5-Chloro-6-fluoro-3,4-dihydronaphthalen-1(2*H*)-one oxime. To a solution of 5-chloro-6-fluoro-3,4-dihydronaphthalen-1(2*H*)-one (0.40 kg, 2.01 mol) in EtOH (2.4 L) and H₂O (0.8 L) was added NaOAc (0.25 kg, 3.02 mol) and NH₂OH·HCl (0.21 kg, 3.02 mol). The reaction was stirred at 25 °C for 12 h. Four reactions were carried out in parallel, and were combined for work up. The mixture was poured into ice, and then extracted with EtOAc (3 L × 3). The combined organic layers were combined, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give (*E*)-5-chloro-6-fluoro-3,4-dihydronaphthalen-1(2*H*)-one oxime (1.60 kg, 83% yield, 88.9% purity) as yellow solid. ¹H NMR: (400 MHz, CDCl₃) δ 7.81–7.78 (m, 1 H), 7.01 (t, *J* = 8.4 Hz, 1 H), 2.89–2.86 (m, 2 H), 2.82–2.79 (m, 2 H), 1.94–1.87 (m, 1 H).

Step 2: 5-Chloro-6-fluoronaphthalen-1-amine. To a solution of (*E*)-5-chloro-6-fluoro-3,4-dihydronaphthalen-1(2*H*)-one oxime (0.26 kg, 1.22 mol) in AcOH (1.6 L) was added H₂SO₄ (0.36 kg, 3.65 mol, 0.2 L) and Ac₂O (0.25 kg, 2.43 mol, 0.2 mL). The mixture was stirred at 90 °C for 2 h. Six reactions were carried out in parallel, and were combined for work up. Then the mixture was acidified with aqueous NaOH (15 L) till pH = 13 and

extracted with EtOAc (5 L $\times$ 2). The combined organic layers were dried with Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by reversed phase HPLC (0.1% HCl condition) to give 5-chloro-6-fluoronaphthalen-1-amine (0.35 kg, 24% yield, 99.5% purity) as red solid. ¹H NMR: (400 MHz, CDCl₃) δ 7.69–7.66 (m, 1 H), 7.61 (d, J = 8.4 Hz, 1 H), 7.37–7.33 (m, 1 H), 7.21–7.17 (m, 1 H), 6.72 (d, J = 7.6 Hz, 1 H), 4.11 (s, 2 H).

Step 3: 2,4-Dibromo-5-chloro-6-fluoronaphthalen-1-amine hydrobromide. A solution of 5-chloro-6-fluoronaphthalen-1-amine (93 g, 0.48 mol) in AcOH (0.65 L) was cooled to 0 °C, then Br₂ (0.30 kg, 1.90 mol, 98 mL) was added. The mixture was stirred at 25 °C for 12 h. Three reactions were carried out in parallel, and were combined for work up. The mixture was filtered, the filter cake was washed with MTBE/MeCN = 3/1 (800 mL) to give 2,4-dibromo-5-chloro-6-fluoronaphthalen-1-amine hydrobromide (0.27 kg, 54% yield) as brown solid.

Step 4: 5-Bromo-6-chloro-7-fluoronaphtho[1,2-*d*][1,2,3]oxadiazole. A solution of 2,4-dibromo-5-chloro-6-fluoronaphthalen-1-amine hydrobromide (0.15 kg, 0.34 mol) in AcOH (0.90 L) and propionic acid (0.37 L) was cooled to 0 °C, then NaNO₂ (27 g, 0.39 mol) was added. The mixture was stirred at 25 °C for 2 h. Two reactions were carried out in parallel, and were combined for work up. The reaction mixture was quenched by addition H₂O (2.0 L) at 20 °C, and then filtered, the filter cake was concentrated under reduced pressure to give a residue. The crude product was triturated with MTBE (500 mL $\times$ 2) at 25 °C for 30 min to give 5-bromo-6-chloro-7-fluoronaphtho[1,2-*d*][1,2,3]oxadiazole (0.16 kg, 65% yield, 84% purity) as brown solid. ¹H NMR: (400 MHz DMSO-*d*₆) δ 7.76 - 7.72 (m, 2 H), 7.34 (s, 1 H).

Step 5: 4-Bromo-5-chloro-6-fluoronaphthalen-2-ol. A solution of 5-bromo-6-chloro-7-fluoronaphtho[1,2-*d*][1,2,3]oxadiazole (80 g, 0.27 mol) in EtOH (0.40 L) and THF (0.16 L) was cooled to 0 °C, then NaBH₄ (20 g, 0.53 mol) was added. The mixture was stirred at 0 °C for 1.5 h. Two reactions were carried out in parallel, and were combined for work up. The reaction mixture was quenched by addition NH₄Cl (1.0 L) at 0 °C and then extracted with EtOAc (0.5 mL $\times$ 2). The combined organic layers were washed with brine (0.5 L), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography on silica gel, eluting with a gradient

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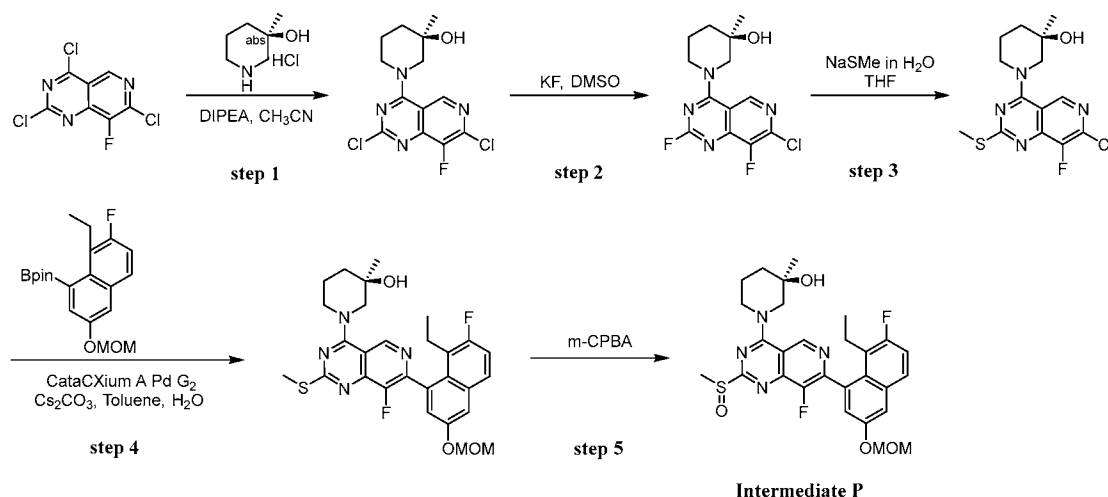
of 1:0 – 0:1 petroleum ether/EtOAc to give 4-bromo-5-chloro-6-fluoronaphthalen-2-ol (61 g, 42% yield) as brown solid. ¹H NMR: (400 MHz DMSO-*d*₆) δ 10.34 (s, 1 H), 7.88-7.84 (m, 1 H), 7.61 (s, 1 H), 7.57 (t, *J* = 9.2 Hz, 1 H), 7.31 (s, 1 H).

Step 6: 8-Bromo-1-chloro-2-fluoro-6-(methoxymethoxy)naphthalene. A solution of 4-bromo-5-chloro-6-fluoronaphthalen-2-ol (55 g, 0.20 mol) and DIPEA (77 g, 0.10 L, 0.60 mol) in DCM (0.33 L) was cooled to 0 °C, then MOMCl (32 g, 30 mL, 0.40 mol) was added to the mixture dropwise. The solution was warmed to 25 °C and stirred for 12 h. The reaction mixture was quenched by addition saturated NaHCO₃ (aq. 100 mL) at 25 °C, and then diluted with DCM (500 mL) and washed with H₂O (200 mL × 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel, eluting with a gradient of 20:1 – 1:1 petroleum ether/EtOAc to give 8-bromo-1-chloro-2-fluoro-6-(methoxymethoxy)naphthalene (50 g, 73% yield, 93% purity) as brown solid.

Step 7: 2-(8-Chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. A mixture of B₂pin₂ (62 g, 0.24 mol), 8-bromo-1-chloro-2-fluoro-6-(methoxymethoxy)naphthalene (26 g, 81 mmol), Pd(dppf)Cl₂ (6.0 g, 8.14 mmol), KOAc (20 g, 0.20 mol) in DMF (0.15 L) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 110 °C for 8 h under N₂ atmosphere. Two reactions were carried out in parallel, and were combined for work-up. The reaction mixture was diluted with EtOAc (500 mL) and washed with brine (500 mL). The organic phase was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with a gradient of 100:1 – 1:1 petroleum ether/EtOAc. The crude product was re-purified by reversed phase HPLC (neutral) to give 2-(8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (50.0 g) as white solid (38 g, 76% yield, 99% purity). ¹H NMR: (400 MHz CDCl₃) δ 7.57 - 7.54 (m, 1 H), 7.32 (s, 2 H), 7.28-7.22 (m, 1 H), 5.20 (s, 2 H), 3.42 (s, 3 H), 1.37 (s, 12 H).

(3R)-1-(7-(8-Ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(methylsulfinyl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (Intermediate P)

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Step 1. (R)-1-(2,7-Dichloro-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol. To a mixture of 2,4,7-trichloro-8-fluoropyrido[4,3-*d*]pyrimidine (25 g, 99 mmol, WuXi) in acetonitrile (500 mL) was added DIPEA (86 mL, 495 mmol) and (R)-3-methylpiperidin-3-ol hydrochloride (15 g, 99 mmol). The mixture was stirred at 0 °C for 0.5 h under N₂. The reaction mixture was diluted with water (1 L) and extracted with EtOAc (0.9 L × 3). The combined organic layers were dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 50/1 to 0/1) to give (R)-1-(2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol (28 g, 85 mmol, 85% yield) as yellow solid.

Step 2: (R)-1-(7-Chloro-2,8-difluoropyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol. To a solution of (R)-1-(2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol (20 g, 60.4 mmol) in dimethyl sulfoxide (300 mL) was added potassium fluoride (35 g, 604 mmol). The mixture was stirred at 80 °C for 12 h. The reaction mixture was partitioned between EtOAc (2000 mL) and water (500 mL). The mixture was extracted with EtOAc (500 mL × 3). The organic phase was separated, washed with brine (500 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was diluted with the mixture solution (Petroleum ether: EtOAc = 20:1, 150 mL). The suspension was stirred at 20 °C for 1 h. The mixture was then filtered through a fitted funnel. The filter cake was washed with MTBE (50 mL × 2) and concentrated under reduced pressure to give (R)-1-(7-chloro-2,8-difluoropyrido[4,3-*d*]pyrimidin-4-yl)-3-

methylpiperidin-3-ol (15 g, 47.8 mmol, 79% yield) as yellow solid. *m/z* (ESI): 315.1, 317.1 (M+H)⁺.

Step 3: (*R*)-1-(7-Chloro-8-fluoro-2-(methylthio)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol. To the mixture of (*R*)-1-(7-chloro-2,8-difluoropyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol (15 g, 47.7 mmol) in tetrahydrofuran (200 mL) was added sodium thiomethoxide (17 g, 47.7 mmol, 20% in H₂O) dropwise at 0 °C. The mixture was stirred at 20 °C for 2 h, diluted with H₂O (100 mL) and EtOAc (200 mL) and extracted with EtOAc (200 mL × 2). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was triturated with a mixed solvent (Petroleum ether: EtOAc=20:1, 500 mL) at 20 °C for 1 h. The suspension was filtered through a fitted funnel and the filter cake was washed with Petroleum ether:EtOAc=20:1, 15 mL × 2. The filtrate was concentrated under reduced pressure to give (*R*)-1-(7-chloro-8-fluoro-2-(methylthio)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol (15 g, 43 mmol, 90 % yield) as yellow solid.

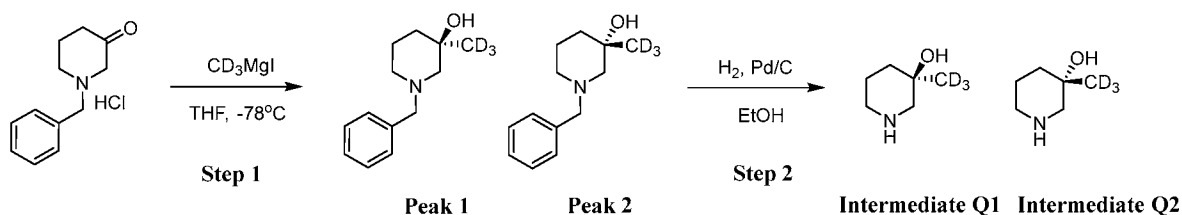
Step 4: (*R*)-1-(7-(8-Ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(methylthio)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol. A mixture of (*R*)-1-(7-chloro-8-fluoro-2-(methylthio)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol (9.0 g, 26.3 mmol), 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (11 g, 31.5 mmol, WuXi), cesium carbonate (17 g, 52.5 mmol) in 1,4-dioxane (170 mL) and water (15 mL) was degassed and purged with N₂ for 3 times. CataCXium A Pd G2 (1.8 g, 2.63 mmol) was then added to the mixture and the reaction was stirred at 100 °C for 8 h under N₂. The reaction mixture was diluted with EtOAc (200 mL) and water (200 mL), the layers were separated and the aqueous was extracted with EtOAc (400 mL × 2). The combined organic layers were washed with brine (500 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography with (SiO₂, Petroleum ether/Ethyl acetate = 5/1 to 1/1) to give (*R*)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(methylthio)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol (7.7 g, 14.3 mmol, 54% yield) as white solid. *m/z* (ESI): 541.3, 542.3 (M+H)⁺.

Step 5: (3*R*)-1-(7-(8-Ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(methylsulfinyl)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol. To the

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mixture of (*R*)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(methylthio)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol (7.0 g, 13.0 mmol) in dichloromethane (100 mL) was added *m*-CPBA (2.6 g, 13.0 mmol, 85% purity) in portions at 0 °C. Then the mixture was stirred at 0 °C for 1 h. The crude was purified by column chromatography directly (SiO₂, Petroleum ether/Ethyl acetate = 5/1 to 0/1) to give (*S*)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(methylsulfinyl)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol (5.0 g, 8.99 mmol, 69 % yield) as yellow solid. *m/z* (ESI): 557.1 (M+H)⁺.

10 **(*R*)-3-(Methyl-*d*3)piperidin-3-ol and (*S*)-3-(methyl-*d*3)piperidin-3-ol (Intermediate Q1 and Q2)**



Step 1. (*R*)-3-(Methyl-*d*3)piperidin-3-ol and (*S*)-3-(methyl-*d*3)piperidin-3-ol. A

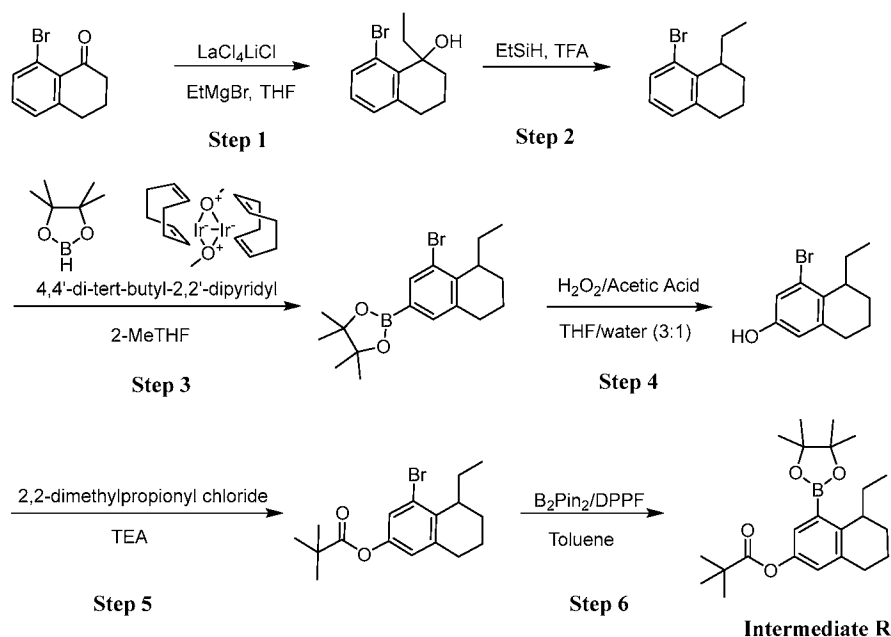
solution of 1-benzylpiperidin-3-one hydrochloride (3.0 g, 13.3 mmol, AA Blocks) in water (20 mL) was neutralized with potassium carbonate and extracted with ethyl acetate (50 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was redissolved in tetrahydrofuran (66 mL) and cooled to -78 °C. To the reaction was added methyl-*d*3-magnesium iodide solution (14.6 mL, 14.6 mmol, Sigma-Aldrich Corporation) dropwise. The reaction was stirred at -78 °C. After 30 minutes, the reaction was quenched with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate; the organic layer was concentrated. The crude product was purified by RP-MPLC chromatography, eluting with 0-50% (ACN/0.1% TFA) in (water/0.1% TFA). The product fractions were combined, frozen, and lyophilized; the residue was redissolved in ethyl acetate, washed with aqueous potassium carbonate, and concentrated to provide 1-benzyl-3-(methyl-*d*3)piperidin-3-ol (1.6 g, 7.44 mmol, 56 % yield) as colorless oil. The racemic mixture was purified via SFC using a Chiralpak AD (21 x 250 mm 5μm) column with a mobile phase of 10% methanol with 2% diethylamine using a flowrate of 120 mL/min,

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to provide two products. The first-eluting product (242 mg, 1.16 mmol, 8.7 % yield, ee: >99 %) was assigned the *R* stereochemistry. The second-eluting product (227 mg, 1.09 mmol, 8.2 % yield, ee: >90 %) was assigned the *S* stereochemistry.

Step 2. (*R*)-3-(Methyl-*d*3)piperidin-3-ol and (*S*)-3-(methyl-*d*3)piperidin-3-ol. A solution of either (*R*)-1-benzyl-3-(methyl-*d*3)piperidin-3-ol (0.24 g, 1.16 mmol) or (*S*)-1-benzyl-3-(methyl-*d*3)piperidin-3-ol (0.23 g, 1.09 mmol) in ethanol (6.0 mL) was stirred under hydrogen atmosphere (25 psi). After 2 hours, the reaction mixture was filtered through Celite and concentrated in vacuo to provide the title compounds as colorless oils. The isolated product were used in the next reactions without further purification; quantitative yield was assumed.

5-Ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6,7,8-tetrahydronaphthalen-2-yl pivalate (Intermediate R)



15

Step 1. 8-Bromo-1-ethyl-1,2,3,4-tetrahydronaphthalen-1-ol. To a 50-mL round-bottomed flask was added 8-bromo-3,4-dihydronaphthalen-1(2H)-one (0.72 g, 3.20 mmol, Ambeed, Inc.) and lanthanum(III) chloride bis(lithium chloride) complex solution, 0.6 M in THF (5.3 mL, 3.2 mmol, Sigma-Aldrich Corporation) in THF (13 mL). At 0 °C,

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ethylmagnesium bromide, 3.0 M in diethyl ether (1.3 mL, 3.84 mmol) was added and the reaction mixture was stirred for 1 h. The reaction mixture was then diluted with saturated NH₄Cl solution (10 mL) and extracted with EtOAc (2 × 10 mL). The organic extract was washed with saturated NaCl solution (20 mL) and dried over MgSO₄. The solution was filtered and concentrated in vacuo to give the crude material, which was absorbed onto a plug of silica gel and purified by column chromatography on silica gel, eluting with a gradient of 0 - 50% EtOAc in heptane, to provide 8-bromo-1-ethyl-1,2,3,4-tetrahydronaphthalen-1-ol (0.71 g, 2.78 mmol, 87 % yield) as yellow oil. *m/z* (ESI): 237.2 (M+H-H₂O)⁺.

Step 2. 8-Bromo-1-ethyl-1,2,3,4-tetrahydronaphthalene. To a 25-mL round-bottomed flask was added 8-bromo-1-ethyl-1,2,3,4-tetrahydronaphthalen-1-ol (0.48 g, 1.88 mmol) in DCM (7.5 mL). After cooling to -30 °C, triethylsilane (1.09 g, 9.41 mmol) was added, followed by dropwise addition of TFA (0.64 g, 0.44 mL, 5.6 mmol). The reaction mixture was stirred for 3 h while slowly warming to rt. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc (2 × 15 mL). The organic extract was washed with saturated NaCl solution (15 mL) and dried over MgSO₄. The solution was filtered and concentrated in vacuo to give the crude material, which was absorbed onto a plug of silica gel and purified by column chromatography on silica gel, eluting with a gradient of 0 - 20% EtOAc in heptane, to provide 8-bromo-1-ethyl-1,2,3,4-tetrahydronaphthalene (0.39 g, 1.63 mmol, 87 % yield) as colorless oil. *m/z* (ESI): 237.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.35 - 7.48 (m, 1 H), 7.29 - 7.58 (m, 2 H), 2.64 - 2.89 (m, 3 H), 1.84 - 2.04 (m, 1 H), 1.52 - 1.85 (m, 4 H), 1.30 - 1.45 (m, 1 H), 0.95 - 1.05 (m, 3 H).

Step 3. 2-(4-Bromo-5-ethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. A 20-mL vial was charged with 8-bromo-1-ethyl-1,2,3,4-tetrahydronaphthalene (0.21 g, 0.88 mmol), 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.28 g, 319 μL, 2.2 mmol, Sigma-Aldrich Corporation), 4,4'-di-*tert*-butyl-2,2'-dipyridyl (28 mg, 0.11 mmol), and di-μ-methoxybis(1,5-cyclooctadiene)diiridium(I) (58 mg, 0.088 mmol, Sigma-Aldrich Corporation). The reaction was purged with nitrogen for 5 min and then stirred at 65 °C for 3 h. The reaction mixture was concentrated and the crude material was absorbed onto a plug of silica gel and purified by column chromatography on silica gel, eluting with a gradient of 0 - 70% EtOAc in hexane, to provide 2-(4-bromo-5-ethyl-5,6,7,8-

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tetrahydronaphthalen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.20 g, 0.55 mmol, 62 % yield) as colorless oil.

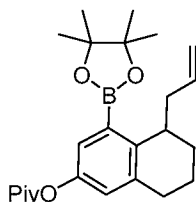
Step 4. 4-Bromo-5-ethyl-5,6,7,8-tetrahydronaphthalen-2-ol. To a 50-mL round-bottomed flask was added 2-(4-bromo-5-ethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.20 g, 0.55 mmol) in tetrahydrofuran (1.6 mL) and water (0.6 mL). After cooling to 0 °C, hydrogen peroxide (0.56 g, 0.5 mL, 4.93 mmol) was added slowly, followed by addition of acetic acid (1.65 g, 1.6 mL, 27.4 mmol) dropwise. The reaction mixture was stirred for 3 h, and then diluted with Saturated Na₂S₂O₃ solution (15 mL) and extracted with EtOAc (2 × 15 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The crude material was absorbed onto a plug of silica gel and purified by column chromatography on silica gel, eluting with a gradient of 0 - 50% EtOAc in hexane, to provide 4-bromo-5-ethyl-5,6,7,8-tetrahydronaphthalen-2-ol as oil (0.120 g, 0.47 mmol, 86 % yield). *m/z* (ESI): 255.0 (M+H)⁺.

Step 5. 4-Bromo-5-ethyl-5,6,7,8-tetrahydronaphthalen-2-yl pivalate. To a 50-mL round-bottomed flask was added 4-bromo-5-ethyl-5,6,7,8-tetrahydronaphthalen-2-ol (0.12 g, 0.47 mmol) and triethylamine (0.16 mL, 0.94 mmol) in tetrahydrofuran (2.4 mL). After cooling to 0 °C, 2,2-dimethylpropionyl chloride (87 µL, 0.71 mmol) was added slowly. The reaction mixture was stirred for 1 h, and the crude material was absorbed onto a plug of silica gel and purified by column chromatography on silica gel, eluting with a gradient of 0 - 25% EtOAc in hexane, to provide 4-bromo-5-ethyl-5,6,7,8-tetrahydronaphthalen-2-yl pivalate (0.12 g, 0.35 mmol, 75 % yield) as oil.

Step 6. 5-Ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6,7,8-tetrahydronaphthalen-2-yl pivalate. A 20-mL vial was charged with 4-bromo-5-ethyl-5,6,7,8-tetrahydronaphthalen-2-yl pivalate (0.12 g, 0.35 mmol), bis(pinacolato)diboron (54 mg, 0.21 mmol), potassium acetate (0.10 g, 1.06 mmol), and 1,1'-bis(diphenylphosphino)ferrocene-palladium dichloride (26 mg, 0.035 mmol) in toluene (2.4 mL). The reaction mixture was purged with nitrogen for 5 min and then stirred at 90 °C for 3 h. The crude material was absorbed onto a plug of silica gel and purified by column chromatography on silica gel, eluting with a gradient of 0 - 60% EtOAc in hexane, to provide 5-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6,7,8-tetrahydronaphthalen-2-yl pivalate as oil. *m/z* (ESI): 387.1 (M+H)⁺.

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5-Allyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6,7,8-tetrahydronaphthalen-2-yl pivalate (Intermediate S)



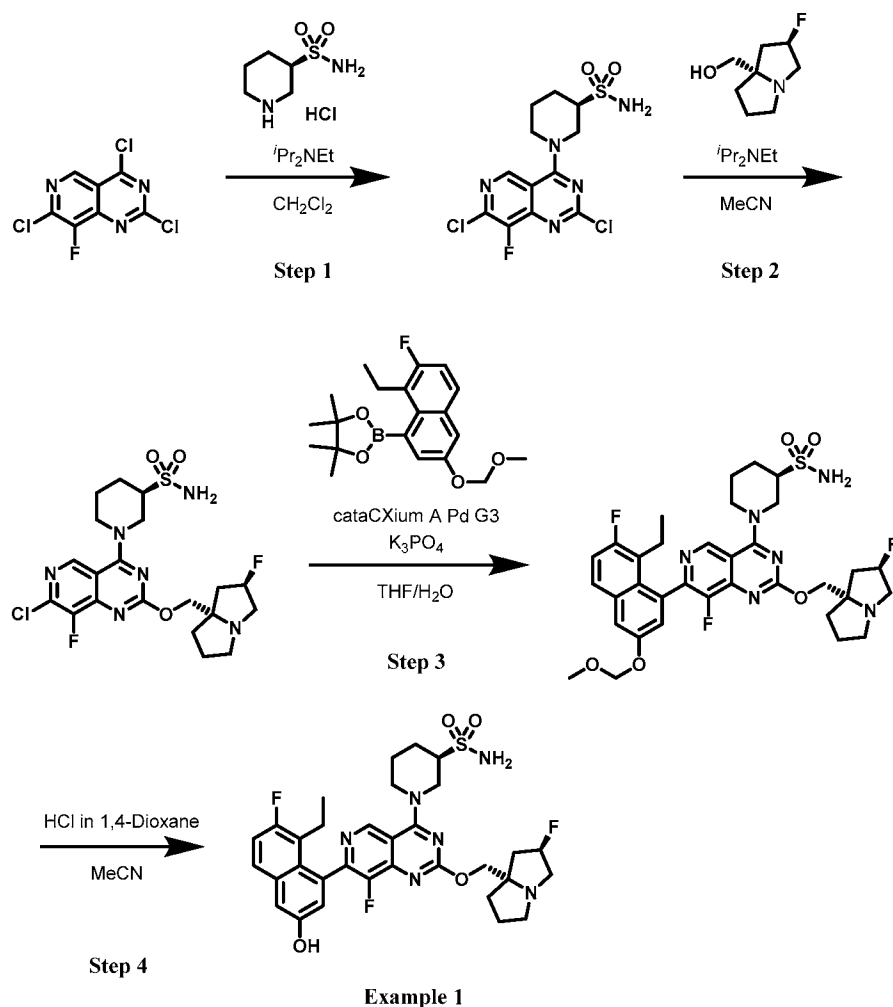
Intermediate S

5 The intermediate was synthesized in a similar way to **Intermediate R** using 8-bromo-3,4-dihydro-2h-naphthalen-1-one (CAS#: 651735-60-3, Aurum Pharmatech LLC) and conducted **Steps 3, 4, 5** before **Step 1** (using allylzinc bromide, 0.5 M in THF) and **Step 2**, to generate 5-allyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6,7,8-tetrahydronaphthalen-2-yl pivalate as oil. m/z (ESI): 399.2 (M+H)⁺.

10

(*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-sulfonamide (Example 1)

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Step 1: (3*R*)-1-(2,7-Dichloro-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-sulfonamide. To a 40-mL vial was added 2,4,7-trichloro-8-fluoropyrido[4,3-*d*]pyrimidine (0.10 g, 0.40 mmol, WuXi) and DCM (4.0 mL). The mixture was cooled to -40 °C, and then DIPEA (0.21 g, 0.28 mL, 1.58 mmol, Sigma-Aldrich) and (3*R*)-piperidine-3-sulfonamide hydrochloride (87 mg, 0.44 mmol, Enamine) was added. The reaction was then stirred at this temperature for 2 h. The reaction was then diluted with water (10 mL) and DCM (10 mL). The mixture was transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with DCM (3 × 10 mL). Then the organic layers were combined, dried with sodium sulfate, filtered, and concentrated under reduced pressure to provide a crude orange oil. The crude residue was purified by column chromatography using a gradient

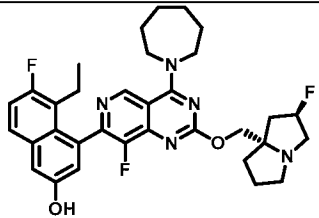
of 0-50% 3:1 EtOAc/EtOH (containing 2% triethylamine) in heptane to provide (*R*)-1-(2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-sulfonamide (95 mg, 0.25 mmol, 63 % yield) as white solid. *m/z* (ESI): 379.8 (M+H)⁺.

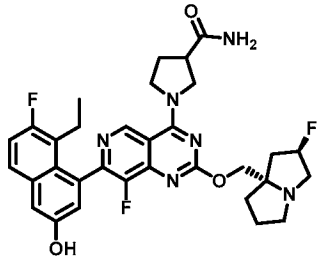
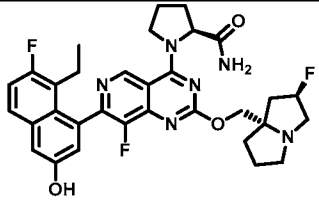
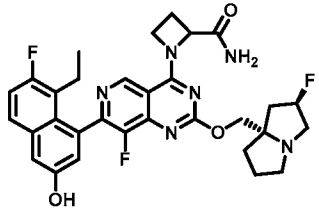
Step 2: (*R*)-1-(7-Chloro-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-sulfonamide. To a 20-mL vial was added ((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methanol (52 mg, 0.32 mmol, LabNetwork), DIPEA (0.13 g, 0.17 mL, 1.00 mmol, Sigma-Aldrich), 4 Å molecular sieves (100 mg), (*R*)-1-(2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-sulfonamide (95 mg, 0.25 mmol) and acetonitrile (0.8 mL). The reaction was stirred at 75 °C overnight. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0-75% 3:1 EtOAc/EtOH (with 2% triethylamine) in heptane to provide (*R*)-1-(7-chloro-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-sulfonamide (71 mg, 0.14 mmol, 57 % yield) as yellow solid. *m/z* (ESI): 503.0 (M+H)⁺.

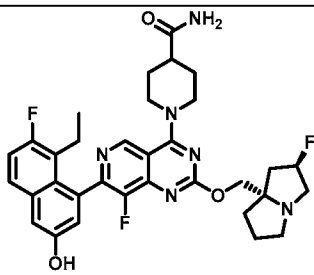
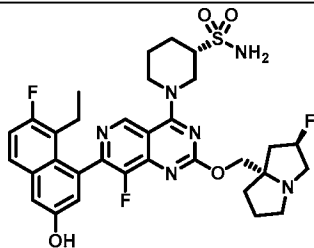
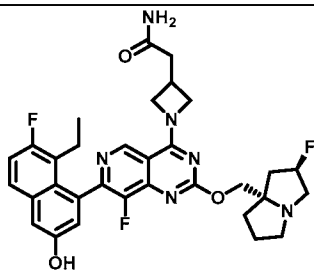
Step 3: (*R*)-1-(7-(8-Ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-sulfonamide. An 1 dram vial was charged with (*R*)-1-(7-chloro-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-sulfonamide (50 mg, 0.10 mmol), 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (54 mg, 0.15 mmol, WuXi), potassium phosphate (63 mg, 0.30 mmol, Sigma Aldrich Corporation), and cataCXium A Pd G3 (15 mg, 0.02 mmol, Sigma Aldrich Corporation). The vial was purged with nitrogen and the reactants were suspended in degassed tetrahydrofuran (0.9 mL) and water (90 µL). The reaction was then sealed and heated to 70 °C for 12 h. The reaction was concentrated under reduced pressure to provide a black oil. The black oil was then purified by column chromatography on silica gel, eluting with a gradient of 0-100% 3:1 EtOAc/EtOH (containing 2% triethylamine) in heptane to provide (*R*)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-sulfonamide (33 mg, 0.05 mmol, 48 % yield) as grey solid. *m/z* (ESI): 701.0 (M+H)⁺.

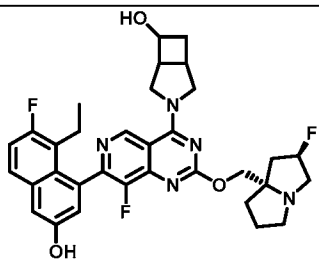
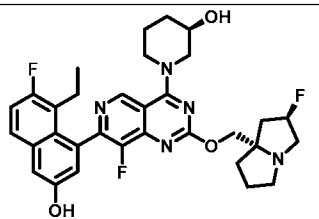
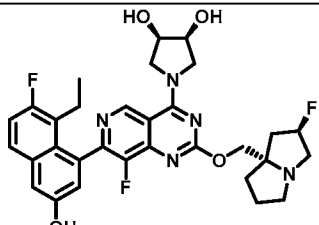
Step 4: (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-sulfonamide. A vial was charged with (*R*)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-sulfonamide (33 mg, 0.05 mmol) and acetonitrile (1.5 mL). HCl (4 M in 1,4-dioxane, 0.3 mL, 1.18 mmol, Sigma-Aldrich Corporation) was added and the reaction was stirred at room temperature for 15 min. The reaction was then concentrated under reduced pressure and then purified via reverse phase HPLC to provide (*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-sulfonamide as bis(2,2,2-trifluoroacetate) and as yellow solid (20 mg, 0.02 mmol, 47 % yield). *m/z* (ESI): 657.2 (M+H)⁺. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 9.20 (s, 1 H) 7.66 - 7.75 (m, 1 H) 7.34 (d, *J*=2.49 Hz, 1 H) 7.28 (s, 1 H) 7.07 (s, 1 H) 5.51 - 5.72 (m, 1 H) 5.01 (br s, 2 H) 4.67 - 4.82 (m, 1 H) 4.51 - 4.65 (m, 1 H) 3.75 - 4.16 (m, 5 H) 3.43 - 3.59 (m, 2 H) 2.55 - 2.86 (m, 2 H) 2.33 - 2.55 (m, 5 H) 2.01 - 2.27 (m, 4 H) 1.78 - 1.91 (m, 1 H) 0.82 (br d, *J*=10.16 Hz, 3 H).

Table 2: Examples 2 to 42 and 170 to 175. Prepared in an analogous manner to Example 1.

Ex. #	Structure	Name	Salt Form	Reagent	Method Change
2		4-(4-(Azepan-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol	Bis(2,2,2-trifluoroacetate)	Step 1: hexamethylenimine (CAS#: 111-49-9, Sigma-Aldrich Corporation)	

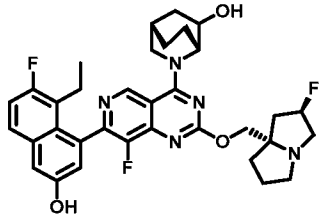
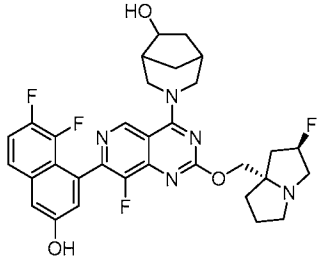
Ex. #	Structure	Name	Salt Form	Reagent	Method Change
3		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)pyrrolidine-3-carboxamide	2,2,2-trifluoroacetate	Step 1: pyrrolidine-3-carboxamide hydrochloride (CAS#: 644972-57-6, Enamine)	
4		(S)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)pyrrolidine-2-carboxamide	2,2,2-trifluoroacetate	Step 1: pyrrolidine-2-carboxylic acid amide (CAS#: 7531-52-4, Enamine)	
5		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azetidine-2-carboxamide	2,2,2-trifluoroacetate	Step 1: azetidine-2-carboxamide (CAS#: 130973-78-3, Combi-Blocks Inc.)	

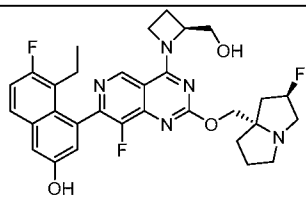
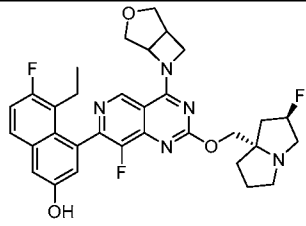
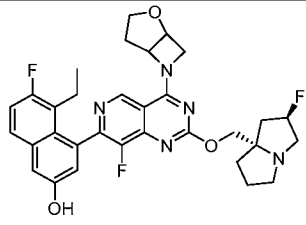
Ex. #	Structure	Name	Salt Form	Reagent	Method Change
6		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-4-carboxamide	2,2,2-trifluoroacetate	Step 1: isonipecotamide (CAS#: 39546-32-2, Combi-Blocks Inc.)	
7		(S)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3-sulfonamide	2,2,2-trifluoroacetate	Step 1: (3S)-piperidine-3-sulfonamide hydrochloride (CAS#: 2322932-58-9, Enamine)	
8		2-(1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azetidin-3-yl)acetamide	2,2,2-trifluoroacetate	Step 1: 2-(azetidin-3-yl)acetamide hydrochloride (CAS#: 1795493-56-9, Enamine)	

Ex. #	Structure	Name	Salt Form	Reagent	Method Change
9		3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.0]heptan-6-ol	hydrochloride	Step 1: 3-azabicyclo[3.2.0]heptan-6-ol (CAS#: 1375065-64-7, Enamine)	
10		(R)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol	Bis(2,2,2-trifluoroacetate)	Step 1: (3R)-piperidin-3-ol (CAS#: 62414-68-0, Combi-Blocks Inc.)	
11		(3S,4R)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)pyrrolidine-3,4-diol	2,2,2-trifluoroacetate	Step 1: cis-3,4-dihydroxypyrrolidine hydrochloride (CAS#: 186393-21-5, Synthonix Inc.)	

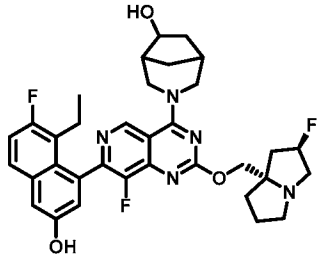
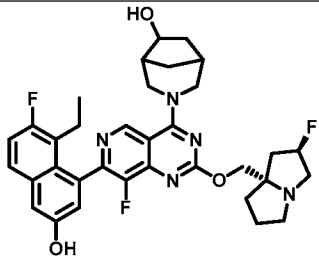
Ex. #	Structure	Name	Salt Form	Reagent	Method Change
12		(<i>R</i>)-1-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)piperidin-3-ol	2,2,2-trifluoroacetate	Step 1: (3 <i>R</i>)-piperidin-3-ol (CAS#: 62414-68-0, Combi-Blocks Inc.) Step 3: 2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (CAS#: 2621935-35-9, LabNetwork)	
13		(<i>R</i>)-1-(7-(8-Ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)piperidin-3-ol	2,2,2-trifluoroacetate	Step 1: (3 <i>R</i>)-piperidin-3-ol (CAS#: 62414-68-0, Combi-Blocks Inc.) Step 3: 2-(8-ethyl-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (CAS#: 2621932-60-1, LabNetwork)	

Ex. #	Structure	Name	Salt Form	Reagent	Method Change
14		(S)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol	2,2,2-trifluoroacetate	Step 1: (3S)-piperidin-3-ol (CAS 24211-55-0, Combi-Blocks Inc.)	
15		5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(3-methoxypiperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol	2,2,2-trifluoroacetate	Step 1: 3-hydroxypiperidine (CAS#: 6859-99-0, Combi-Blocks Inc.)	Additional step between Step 3 and Step 4 . Details included below.
16		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)pyrrolidin-3-ol	2,2,2-trifluoroacetate	Step 1: 3-pyrrolidinol (CAS#: 40499-83-0, Synthonix Inc.)	

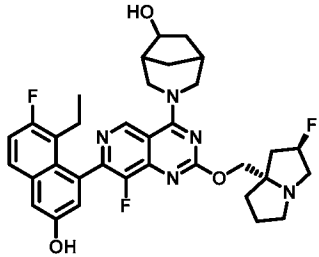
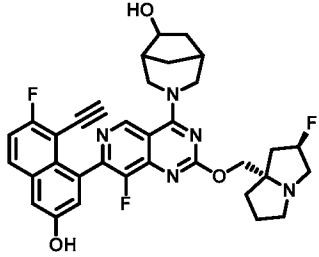
Ex. #	Structure	Name	Salt Form	Reagent	Method Change
17		(1 <i>R</i> ,4 <i>S</i>)-2-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-2-azabicyclo[2.2.2]octan-6-ol	2,2,2-trifluoroacetate	Step 1: 2-azabicyclo[2.2.2]octan-6-ol (CAS#: 738551-49-0, Enamine)	
18		3-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol	2,2,2-trifluoroacetate	Step 1: 3-azabicyclo[3.2.1]octan-6-ol hydrochloride (CAS#: 2305252-97-3, Enamine) Step 3: 2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (CAS#: 2621935-35-9, LabNetwork)	

Ex. #	Structure	Name	Salt Form	Reagent	Method Change
19		5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-((S)-2-(hydroxymethyl)azetidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol	bis(2,2,2-trifluoroacetate)	Step 1: (S)-2-azetidinemethanol hydrochloride (CAS#: 791807-66-4, Advanced ChemBlocks Inc.)	Step 2: NaH and THF were used.
20		4-(4-((1S,5R)-3-oxa-6-azabicyclo[3.2.0]heptan-6-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol	bis(2,2,2-trifluoroacetate)	Step 1: (1S,5R)-3-oxa-6-azabicyclo[3.2.0]heptane (CAS#: 2408936-87-6, Enamine)	Step 2: NaH and THF were used.
21		rel-4-(4-((1R,5R)-2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol	bis(2,2,2-trifluoroacetate)	Step 1: rel-(1R,5R)-2-oxa-6-azabicyclo[3.2.0]heptane hydrochloride (CAS#: 2137895-62-4, Enamine)	Step 2: NaH and THF were used.

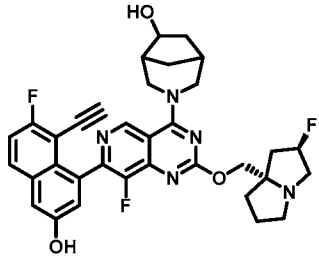
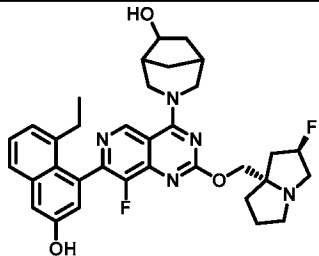
Ex. #	Structure	Name	Salt Form	Reagent	Method Change
22		4-(4-(3-(Chloromethyl)-3-(hydroxymethyl)pyrrolidin-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol	bis(2,2,2-trifluoroacetate)	Step 1: 2-oxa-6-azaspiro[3.5]nonane hydrochloride (CAS#: 1414885-19-0, Enamine)	Step 2: NaH and THF were used.
23		3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol Isomer 1	2,2,2-trifluoroacetate	Step 1: 3-azabicyclo[3.2.1]octan-6-ol hydrochloride (CAS#: 2305252-97-3, Enamine)	Chiral separation after Step 3 . Details included below.

Ex. #	Structure	Name	Salt Form	Reagent	Method Change
24		3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol Isomer 2	2,2,2-trifluoroacetate	Step 1: 3-azabicyclo[3.2.1]octan-6-ol hydrochloride (CAS#: 2305252-97-3, Enamine)	Chiral separation after Step 3 . Details included below.
25		3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol Isomer 3	2,2,2-trifluoroacetate	Step 1: 3-azabicyclo[3.2.1]octan-6-ol hydrochloride (CAS#: 2305252-97-3, Enamine)	Chiral separation after Step 3 . Details included below.

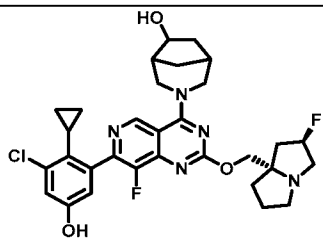
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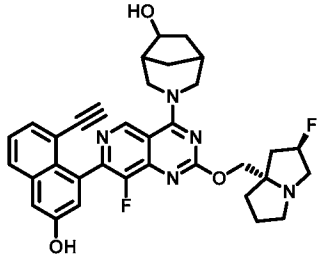
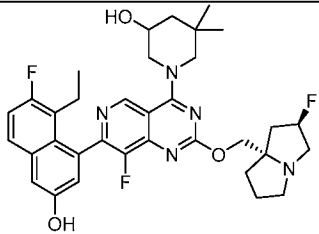
Ex. #	Structure	Name	Salt Form	Reagent	Method Change
26		3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol Isomer 4	2,2,2-trifluoroacetate	Step 1: 3-azabicyclo[3.2.1]octan-6-ol hydrochloride (CAS#: 2305252-97-3, Enamine)	Chiral separation after Step 3 . Details included below.
27		3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol Isomer 1	2,2,2-trifluoroacetate	Step 1: 3-azabicyclo[3.2.1]octan-6-ol hydrochloride (CAS#: 2305252-97-3, Enamine) Step 3: 2-[7-fluoro-3-(methoxymethoxy)-8-[2-[tris(1-methylethyl)silyl]ethynyl]-1-naphthalenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (CAS#: 2621932-37-2, LabNetwork)	Chiral separation after Step 1 . Details included below. Additional step after Step 4 . Procedure included below.

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Ex. #	Structure	Name	Salt Form	Reagent	Method Change
28		3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol Isomer 2	2,2,2-trifluoroacetate	Step 1: 3-azabicyclo[3.2.1]octan-6-ol hydrochloride (2305252-97-3, Enamine) Step 3: 2-[7-fluoro-3-(methoxymethoxy)-8-[2-[tris(1-methylethyl)silyl]ethynyl]-1-naphthalenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (CAS#: 2621932-37-2, LabNetwork)	Chiral separation after Step 1 . Detail included below. Additional step analogous to Example 27 after Step 4 .
29		(1 <i>R</i> ,5 <i>R</i> ,6 <i>R</i>)-3-(7-(8-ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol Isomer 1	2,2,2-trifluoroacetate	Step 1: 3-azabicyclo[3.2.1]octan-6-ol hydrochloride (CAS#: 2305252-97-3, Enamine) Step 3: 2-(8-ethyl-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (CAS#: 2621932-60-1, LabNetwork)	Chiral separation after Step 1 . Detail included below.

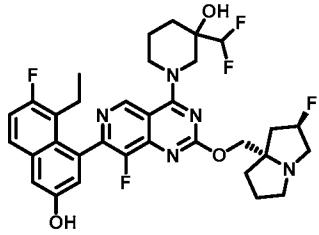
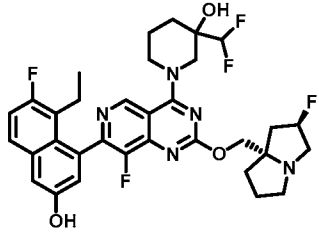
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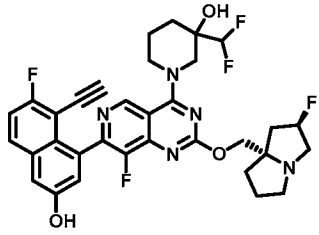
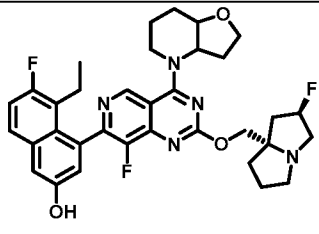
Ex. #	Structure	Name	Salt Form	Reagent	Method Change
30		(1<i>R</i>,5<i>R</i>,6<i>R</i>)-3-(7-(3-chloro-2-cyclopropyl-5-hydroxyphenyl)-8-fluoro-2-(((2<i>R</i>,7<i>aS</i>)-2-fluorotetrahydro-1<i>H</i>-pyrrolizin-7<i>a</i>(5<i>H</i>)-yl)methoxy)pyrido[4,3-<i>d</i>]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol Isomer 1	2,2,2-trifluoroacetate	Step 1: 3-azabicyclo[3.2.1]octan-6-ol hydrochloride (CAS#: 2305252-97-3, Enamine) Step 3: 2-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (CAS#: 2621936-26-1, LabNetwork)	Chiral separation after Step 1 . Detail included below.

Ex. #	Structure	Name	Salt Form	Reagent	Method Change
31		(1 <i>R</i> ,5 <i>R</i> ,6 <i>R</i>)-3-(7-(8-ethynyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol Isomer 1	2,2,2-trifluoroacetate	Step 1: 3-azabicyclo[3.2.1]octan-6-ol hydrochloride (CAS#: 2305252-97-3, Enamine) Step 3: triisopropyl((6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)silane (CAS#: 2621932-42-9, LabNetwork)	Chiral separation after Step 1 . Detail included below. Additional step analogous to Example 27 after Step 4 .
32		1-(7-(8-Ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-5,5-dimethylpiperidin-3-ol	2,2,2-trifluoroacetate	Step 1: 5,5-dimethylpiperidin-3-ol hydrochloride (CAS#: 100868-99-3, Enamine)	

Ex. #	Structure	Name	Salt Form	Reagent	Method Change
33		(3 <i>R</i> ,6 <i>S</i>)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-6-methylpiperidin-3-ol	bis(2,2,2-trifluoroacetate)	Step 1: (3 <i>R</i> ,6 <i>S</i>)-6-methylpiperidin-3-ol hydrochloride (CAS#: 2227198-81-2, Enamine)	
34		8-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octan-2-ol 2,2,2-trifluoroacetate	bis(2,2,2-trifluoroacetate)	Step 1: endo-8-azabicyclo[3.2.1]octan-2-ol (CAS#: 92283-30-2, Pharmablock, Inc.)	
35		(3 <i>R</i> ,4 <i>S</i>)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-4-methylpiperidin-3-ol	tris(2,2,2-trifluoroacetate)	Step 1: (3 <i>R</i> ,4 <i>S</i>)-4-methylpiperidin-3-ol hydrochloride (CAS#: 1932604-01-7, J&W Pharmlab)	

Ex. #	Structure	Name	Salt Form	Reagent	Method Change
36		(3 <i>R</i> ,6 <i>R</i>)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-6-methylpiperidin-3-ol	tetrakis(2,2,2-trifluoroacetate)	Step 1: (3 <i>R</i> ,6 <i>R</i>)-6-methylpiperidin-3-ol (CAS#: 285995-17-7, Enamine)	
37		5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)-4-(hexahydro-5 <i>H</i> -furo[2,3- <i>c</i>]pyrrol-5-yl)pyrido[4,3- <i>d</i>]pyrimidin-7-yl)naphthalen-2-ol	bis(2,2,2-trifluoroacetate)	Step 1: hexahydro-2 <i>H</i> -furo[2,3- <i>c</i>]pyrrole (CAS#: 1214875-23-6, Advanced ChemBlocks Inc.)	
38		(<i>R</i>)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-3-methylpiperidin-3-ol	bis(2,2,2-trifluoroacetate)	Step 1: (3 <i>R</i>)-3-methylpiperidin-3-ol hydrochloride (CAS#: 2305080-34-4, Pharmablock)	

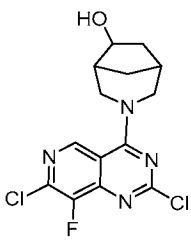
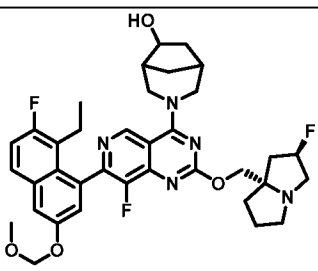
Ex. #	Structure	Name	Salt Form	Reagent	Method Change
39		3-(Difluoromethyl)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol Isomer 1	2,2,2-trifluoroacetate	Step 1: 3-(difluoromethyl)piperidin-3-ol hydrochloride (CAS#: 1909325-03-6, Enamine)	Chiral separation after Step 1 . Details included below.
40		3-(Difluoromethyl)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol Isomer 2	2,2,2-trifluoroacetate	Step 1: 3-(difluoromethyl)piperidin-3-ol hydrochloride (CAS#: 1909325-03-6, Enamine)	Chiral separation after Step 1 . Details included below.

Ex. #	Structure	Name	Salt Form	Reagent	Method Change
41		3-(Difluoromethyl)-1-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol Isomer 1	2,2,2-trifluoroacetate	Step 1: 3-(difluoromethyl)piperidin-3-ol hydrochloride (CAS#: 1909325-03-6, Enamine) Step 3: 2-[7-fluoro-3-(methoxymethoxy)-8-[2-[tris(1-methylethyl)silyl]ethynyl]-1-naphthalenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (CAS#: 2621932-37-2, LabNetwork)	Chiral separation after Step 1 . Details included below. Additional step analogous to Example 27 after Step 4 .
42		<i>rel</i> -5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-((3aR,7aR)-hexahydrofuro[3,2-b]pyridin-4(2H)-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol	2,2,2-trifluoroacetate	Step 1: <i>rac</i> -(3aR,7aR)-octahydrofuro[3,2-b]pyridine (CAS#: 1909293-80-6, Enamine)	

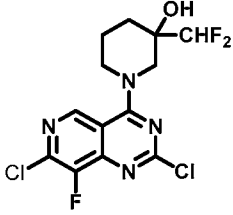
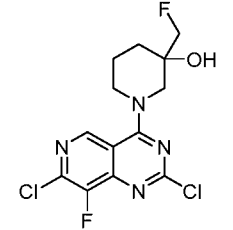
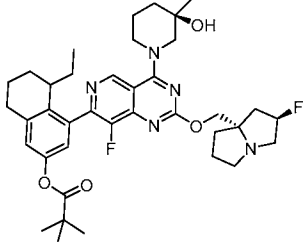
Ex. #	Structure	Name	Salt Form	Reagent	Method Change
170		(<i>R</i>)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-3-methylpiperidin-3-ol	bis(2,2,2-trifluoroacetate)	Step 1: 2,4,7-trichloropyridine[4,3- <i>d</i>]pyrimidine (CAS#: 2384434-96-0, eNovation Chemicals LLC)	
171		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-3-(fluoromethyl)piperidin-3-ol Isomer 1	2,2,2-trifluoroacetate	Step 1: 3-(fluoromethyl)piperidin-3-ol hydrochloride (CAS#: 2306262-40-6, AChem Block)	Chiral separation after Step 1 . Details included below.
172		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-3-(fluoromethyl)piperidin-3-ol Isomer 2	2,2,2-trifluoroacetate	Step 1: 3-(fluoromethyl)piperidin-3-ol hydrochloride (CAS#: 2306262-40-6, AChem Block)	Chiral separation after Step 1 . Details included below.

Ex. #	Structure	Name	Salt Form	Reagent	Method Change
173		(3R)-1-(7-(8-ethyl-3-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol Isomer 2	2,2,2-trifluoroacetate	Step 3: Intermediate R	Chiral separation after Step 3. Details included below. Step 4: 5 N NaOH in MeOH was used.
174		(3R)-1-(7-(8-ethyl-3-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol Isomer 1	2,2,2-trifluoroacetate	Step 3: Intermediate R	Chiral separation after Step 3. Details included below. Step 4: 5 N NaOH in MeOH was used.
175		(3R)-1-(7-(8-Allyl-3-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol	2,2,2-trifluoroacetate	Step 2: Intermediate S	Step 4: 5 N NaOH in MeOH was used.

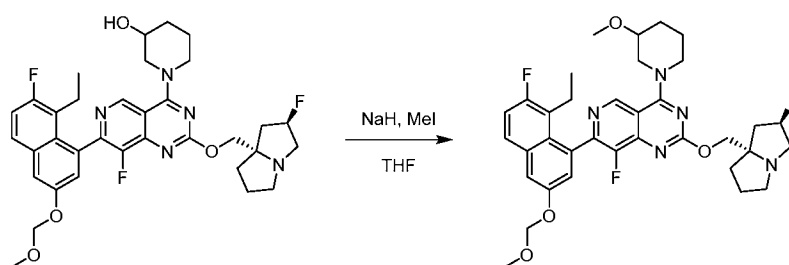
Table 3: SFC conditions for chiral separation.

Compound	SFC Conditions	Peaks to Ex. #
	Round 1 Column: Chiralcel OJ, 30 x 150 mm 5µm Mobile phase: 25% methanol Flowrate: 200 mL/min Yield: 3.3 g sample was submitted to generate 1.19g of peak 1 with an ee of <80%, 1.08 g of peak 2 with an ee of >99%, and 1.01 g of peak 3-4. Round 2 (peak 1) Reprocessed using under the same conditions to generate 1.01 g of peak 1 with an ee of >99%. Round 3 (peak 3-4) Column: Chiralcel OD, 21 x 150 mm 5µm Mobile phase: 35% methanol Flowrate: 80 mL/min Yield: 0.46 g of peak 3 with an ee of >99% and 0.48 g of peak 4 with an ee of >99%.	Peak 1: Example 27 Peak 2: Example 24 Example 28 Example 29 Example 30 Example 31
	Round 1 Column: (S,S) Whelk O-1 column, 21 x 250 mm Mobile phase: 55% CO₂ and 45% methanol w/ 0.2% diethylamine Flowrate: 80 mL/min Yield: 121 mg sample was submitted to generate 50 mg of peak 1 and 2 and 23 mg of peak 3 and 4. Round 2 (peak 1 and 2) Column: Chiralpak IE column, 21 x 150 mm Mobile phase: 40% CO₂ and 60% methanol w/ 0.2% diethylamine Flowrate: 80 mL Yield: 21.3 mg of peak 1 with ee> 99% and 22.7 mg of peak 2 with ee> 98%. Round 3 (peak 3 and 4) Column: Chiralpak IE column, 21 x 150 mm Mobile phase: 40% CO₂ and 60% methanol w/ 0.2% triethylamine Flowrate: 80 mL/min Yield: 7.6 mg of peak 1 with ee> 75% and 9.4 mg of peak 2 with ee> 89%.	Peak 1: Example 23 Peak 2: Example 24 Peak 3: Example 25 Peak 4: Example 26

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	Column: ChiralPak IG, 2 x 15 cm 5 μm Mobile phase: 25% MeOH Flowrate: 80 mL/min Yield: 739 mg of sample was submitted to generate 360 mg of peak 1 with an ee of 99% and 341 mg of peak 2 with an ee of 99%.	Peak 1: Example 39 Example 41 Peak 2: Example 40
	Column: ChiralPak IG, 2 x 25 cm 5 μm Mobile phase: 30% MeOH w/ 0.2% TEA Flowrate: 80 mL/min. Yield: 641 mg sample was submitted to generate 283 mg of peak 1 with an ee of 99% and 285 mg of peak 2 with an ee of 96%.	
	Column: (S,S) Whelk-O1, 21 x 250 mm 5 μm Mobile phase of 35% ethanol with 0.2% diethylamine using a Flowrate: 100 mL/min Yield: 33 mg sample was submitted to generate 14.7 mg of peak 1 with an ee of >99% and 18 mg of peak 2 with an ee of >99%.	

Additional Step for Example 15

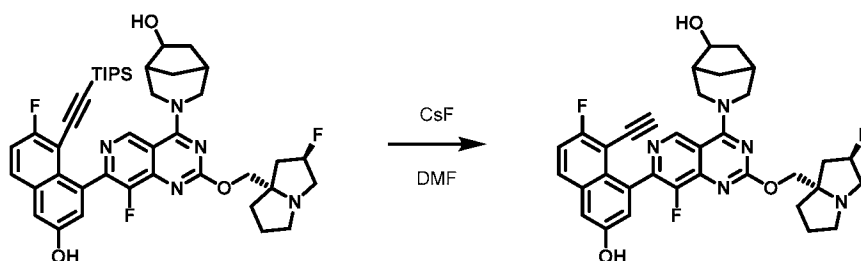


To a 20-mL vial was added 1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*S*,7*aR*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-
 5 *d*]pyrimidin-4-yl)piperidin-3-ol (0.10 g, 0.16 mmol, synthesized in an analogous manner to **Example 1**) and sodium hydride (19 mg, 0.47 mmol, TCI America) in tetrahydrofuran (1.6 mL) at 0 °C. The reaction was stirred at 0 °C for 20 min. Next, iodomethane (45 mg, 0.02 mL, 0.31 mmol, Sigma-Aldrich Corporation) was added and the reaction was warmed to rt
 10 for 2 h. The reaction mixture was diluted with water and extracted with CH₂Cl₂. The organic extract was dried over MgSO₄. The solution was filtered and concentrated in vacuo to give

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the crude material as light-yellow solid. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0-100% EtOAc in heptane to provide 7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*S*,7*aR*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(3-methoxypiperidin-1-yl)pyrido[4,3-*d*]pyrimidine as light-yellow solid. *m/z* (ESI): 652.3 (M+H)⁺.

Additional Step for Example 27



To a solution of 3-(8-fluoro-7-(7-fluoro-3-hydroxy-8-
 10 ((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-
 7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (0.15 g, 0.19
 mmol) in *N,N*-dimethylformamide (1.9 mL) was added cesium fluoride (0.25 g, 1.61 mmol,
 Sigma-Aldrich Corporation). The reaction mixture was stirred at rt for 2-d. The reaction
 mixture was partitioned between EtOAc and water. The aqueous layer was back extracted
 15 with EtOAc and the combined organics was dried over Na₂SO₄ and concentrated under
 reduced pressure. The crude material was purified by reverse phase HPLC to provide 3-(7-(8-
 ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-
 pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol as
 2,2,2-trifluoroacetate and as off-white solid (70 mg, 0.10 mmol, 50% yield).

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Table 4: Analytical Data of Examples 2 to 42 and 170 to 175.

Ex. #	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
2	592.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.23 (s, 1 H), 7.70 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.34 (d, <i>J</i> =2.5 Hz, 1 H), 7.28 (t, <i>J</i> =9.4 Hz, 1 H), 7.09 (d, <i>J</i> =2.5 Hz, 1 H), 5.46 - 5.74 (m, 1 H), 4.64 - 4.74 (m, 2 H), 4.14 - 4.27 (m, 4 H), 3.82 - 4.10 (m, 3 H), 3.45 - 3.53 (m, 1 H), 2.58 - 2.82 (m, 2 H), 2.33 - 2.57 (m, 4 H), 2.13 - 2.28 (m, 2 H), 2.04 - 2.13 (m, 4 H), 1.70 - 1.79 (m, 4 H), 0.83 (t, <i>J</i> =7.0 Hz, 3 H).
3	607.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.35 (s, 1 H) 7.65 - 7.75 (m, 1 H) 7.34 (d, <i>J</i> =2.72 Hz, 1 H) 7.27 (s, 1 H) 7.08 (d, <i>J</i> =2.09 Hz, 1 H) 5.47 - 5.67 (m, 1 H) 4.63 - 4.75 (m, 2 H) 3.80 - 4.39 (m, 7 H) 3.43 - 3.54 (m, 1 H) 3.35 - 3.40 (m, 1 H) 2.54 - 2.82 (m, 2 H) 2.29 - 2.54 (m, 6 H) 2.12 - 2.26 (m, 2 H) 0.77 - 0.85 (m, 3 H).
4	606.9	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.23 - 9.50 (m, 1 H) 7.71 (dd, <i>J</i> =8.99, 5.85 Hz, 1 H) 7.34 (d, <i>J</i> =2.72 Hz, 1 H) 7.28 (s, 1 H) 7.03 - 7.11 (m, 1 H) 5.50 - 5.71 (m, 1 H) 4.86 - 4.98 (m, 1 H) 4.65 (br d, <i>J</i> =2.09 Hz, 2 H) 4.22 - 4.45 (m, 2 H) 3.96 - 4.15 (m, 1 H) 3.83 - 3.96 (m, 2 H) 3.44 - 3.54 (m, 1 H) 2.57 - 2.80 (m, 2 H) 2.44 - 2.57 (m, 2 H) 2.38 (br d, <i>J</i> =4.60 Hz, 4 H) 2.12 - 2.29 (m, 4 H) 0.81 (t, <i>J</i> =7.42 Hz, 3 H).
5	592.9	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.00 - 9.10 (m, 1 H) 7.65 - 7.77 (m, 1 H) 7.34 (d, <i>J</i> =2.49 Hz, 1 H) 7.23 - 7.31 (m, 1 H) 7.06 (br d, <i>J</i> =2.70 Hz, 1 H) 5.48 - 5.69 (m, 1 H) 4.89 - 5.26 (m, 3 H) 4.58 - 4.77 (m, 2 H) 3.82 - 4.14 (m, 3 H) 3.42 - 3.54 (m, 1 H) 2.84 - 3.02 (m, 1 H) 2.37 (br d, <i>J</i> =2.70 Hz, 7 H) 2.10 - 2.25 (m, 2 H) 0.77 - 0.84 (m, 3 H).
6	621.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.14 (s, 1 H) 7.66 - 7.76 (m, 1 H) 7.33 - 7.39 (m, 1 H) 7.23 - 7.32 (m, 1 H) 7.08 (d, <i>J</i> =2.70 Hz, 1 H) 5.47 - 5.70 (m, 1 H) 4.62 - 4.83 (m, 4 H) 3.84 - 4.15 (m, 3 H) 3.54 - 3.68 (m, 2 H) 3.45 - 3.54 (m, 1 H) 2.66 (br s, 3 H) 2.37 (br s, 4 H) 2.14 - 2.28 (m, 2 H) 2.04 - 2.14 (m, 2 H) 1.89 - 2.04 (m, 2 H) 0.77 - 0.87 (m, 3 H).
7	657.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.20 (s, 1 H) 7.71 (dd, <i>J</i> =9.12, 5.80 Hz, 1 H) 7.34 (d, <i>J</i> =2.70 Hz, 1 H) 7.28 (s, 1 H) 7.03 - 7.11 (m, 1 H) 5.49 - 5.69 (m, 1 H) 4.94 - 5.06 (m, 1 H) 4.65 - 4.81 (m, 2 H) 4.49 - 4.64 (m, 1 H) 3.76 - 4.14 (m, 5 H) 3.42 - 3.58 (m, 2 H) 2.55 - 2.84 (m, 2 H) 2.34 - 2.52 (m, 5 H) 2.01 - 2.29 (m, 4 H) 1.76 - 1.92 (m, 1 H) 0.71 - 0.88 (m, 3 H).

Ex. #	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
8	606.9	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.00 (s, 1 H) 7.70 (dd, <i>J</i> =8.99, 5.85 Hz, 1 H) 7.33 (d, <i>J</i> =2.72 Hz, 1 H) 7.27 (t, <i>J</i> =9.30 Hz, 1 H) 7.05 (d, <i>J</i> =2.51 Hz, 1 H) 5.47 - 5.69 (m, 1 H) 4.97 - 5.17 (m, 1 H) 4.70 (br dd, <i>J</i> =16.30, 4.39 Hz, 4 H) 4.15 - 4.36 (m, 1 H) 3.80 - 4.13 (m, 3 H) 3.42 - 3.56 (m, 1 H) 3.35 (br s, 1 H) 2.76 (d, <i>J</i> =7.52 Hz, 4 H) 2.31 - 2.52 (m, 4 H) 2.10 - 2.25 (m, 2 H) 0.81 (s, 3 H).
9	606.3	¹ H NMR (METHANOL- <i>d</i> ₄ , 400 MHz) δ 9.44 (br d, 1H, <i>J</i> =9.0 Hz), 7.74 (dd, 1H, <i>J</i> =5.7, 8.9 Hz), 7.39 (d, 1H, <i>J</i> =2.3 Hz), 7.31 (t, 1H, <i>J</i> =9.4 Hz), 7.15 (d, 1H, <i>J</i> =2.3 Hz), 5.5-5.7 (m, 1H), 4.83 (br d, 3H, <i>J</i> =8.2 Hz), 4.42 (td, 2H, <i>J</i> =7.3, 14.3 Hz), 3.7-3.8 (m, 1H), 3.7-4.0 (m, 3H), 3.6-3.7 (m, 2H), 3.5-3.6 (m, 2H), 3.4-3.5 (m, 1H), 2.6-2.7 (m, 2H), 2.3-2.5 (m, 5H), 2.2-2.3 (m, 2H), 1.6-1.8 (m, 1H), 0.87 (br t, 3H, <i>J</i> =7.3 Hz).
10	594.3	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.25 (d, <i>J</i> =5.9 Hz, 1 H), 7.70 (dd, <i>J</i> =9.2, 5.9 Hz, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.27 (s, 1 H), 7.07 (t, <i>J</i> =3.1 Hz, 1 H), 5.50 - 5.69 (m, 1 H), 4.61 - 4.71 (m, 2 H), 3.81 - 4.28 (m, 8 H), 3.45 - 3.58 (m, 1 H), 2.71 - 2.80 (m, 1 H), 2.53 - 2.63 (m, 1 H), 2.33 - 2.51 (m, 4 H), 2.04 - 2.30 (m, 4 H), 1.70 - 1.86 (m, 2 H), 0.74 - 0.88 (m, 3 H).
11	596.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.34 (s, 1 H), 7.70 (dd, <i>J</i> =9.0, 5.6 Hz, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.23 - 7.31 (m, 1 H), 7.09 (d, <i>J</i> =2.5 Hz, 1 H), 5.44 - 5.78 (m, 1 H), 4.71 (br d, <i>J</i> =4.4 Hz, 2 H), 4.40 - 4.46 (m, 2 H), 4.04 - 4.12 (m, 2 H), 3.83 - 3.97 (m, 3 H), 3.45 - 3.57 (m, 1 H), 2.71 - 2.88 (m, 1 H), 2.30 - 2.62 (m, 6 H), 2.07 - 2.24 (m, 2 H), 1.63 - 1.64 (m, 1 H), 0.82 (br t, <i>J</i> =7.2 Hz, 3 H).
12	584.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.22 - 9.28 (m, 1 H), 7.64 (ddd, <i>J</i> =9.3, 4.8, 1.6 Hz, 1 H), 7.34 - 7.46 (m, 2 H), 7.28 (br d, <i>J</i> =4.0 Hz, 1 H), 5.49 - 5.70 (m, 1 H), 4.71 (br d, <i>J</i> =15.9 Hz, 2 H), 4.25 (br d, <i>J</i> =12.8 Hz, 1 H), 3.82 - 4.20 (m, 8 H), 3.46 - 3.57 (m, 1 H), 2.69 - 2.84 (m, 1 H), 2.55 - 2.66 (m, 1 H), 2.32 - 2.47 (m, 3 H), 2.11 - 2.22 (m, 2 H), 1.72 - 1.86 (m, 2 H).
13	576.3	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.21 - 9.26 (m, 1 H), 7.61 - 7.70 (m, 1 H), 7.38 (m, <i>J</i> =8.2 Hz, 1 H), 7.32 (d, <i>J</i> =2.7 Hz, 1 H), 7.19 (d, <i>J</i> =6.9 Hz, 1 H), 7.04 (t, <i>J</i> =3.0 Hz, 1 H), 5.47 - 5.73 (m, 1 H), 4.71 (br dd, <i>J</i> =16.5, 4.2 Hz, 2 H), 3.83 - 4.29 (m, 9 H), 3.56 (s, 1 H), 2.69 - 2.85 (m, 1 H), 2.66 (br s, 1 H), 2.24 - 2.50 (m, 5 H), 2.05 - 2.19 (m, 2 H), 1.72 - 1.88 (m, 2 H), 0.92 (td, <i>J</i> =7.4, 3.8 Hz, 3 H).

Ex. #	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
14	594.1	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.22 - 9.29 (m, 1 H), 7.70 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.34 (d, <i>J</i> =2.5 Hz, 1 H), 7.27 (t, <i>J</i> =9.4 Hz, 1 H), 7.08 (t, <i>J</i> =2.7 Hz, 1 H), 5.51 - 5.68 (m, 1 H), 4.62 - 4.74 (m, 2 H), 4.10 - 4.27 (m, 2 H), 3.83 - 4.08 (m, 6 H), 3.44 - 3.55 (m, 1 H), 2.73 - 2.81 (m, 1 H), 2.55 - 2.63 (m, 1 H), 2.43 - 2.52 (m, 2 H), 2.33 - 2.42 (m, 2 H), 2.04 - 2.30 (m, 4 H), 1.71 - 1.89 (m, 2 H), 0.82 (t, <i>J</i> =7.4 Hz, 3 H).
15	608.4	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.24 (d, <i>J</i> =1.0 Hz, 1 H), 7.70 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.34 (d, <i>J</i> =2.5 Hz, 1 H), 7.27 (t, <i>J</i> =1.0 Hz, 1 H), 7.08 (dd, <i>J</i> =6.0, 2.6 Hz, 1 H), 5.59 (dt, <i>J</i> =1.0 Hz, 1 H), 4.62 - 4.70 (m, 1 H), 4.26 - 4.46 (m, 2 H), 4.03 - 4.13 (m, 2 H), 3.87 - 3.98 (m, 2 H), 3.72 - 3.86 (m, 2 H), 3.62 - 3.70 (m, 1 H), 3.46 - 3.54 (m, 1 H), 3.34 - 3.36 (m, 3 H), 2.68 - 2.81 (m, 1 H), 2.63 - 2.66 (m, 1 H), 2.54 - 2.63 (m, 1 H), 2.31 - 2.53 (m, 4 H), 2.20 (br s, 2 H), 1.97 - 2.04 (m, 2 H), 1.78 (br s, 1 H), 0.82 (t, <i>J</i> =7.4 Hz, 3 H).
16	580.3	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.36 (s, 1 H), 7.70 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.27 (t, <i>J</i> =1.0 Hz, 1 H), 7.07 (dd, <i>J</i> =1.0 Hz, 1 H), 5.57 (dt, <i>J</i> =1.0 Hz, 1 H), 4.60 - 4.70 (m, 3 H), 3.83 - 4.13 (m, 5 H), 3.44 - 3.55 (m, 2 H), 2.69 - 2.81 (m, 1 H), 2.32 - 2.67 (m, 6 H), 2.09 - 2.32 (m, 4 H), 0.76 - 0.89 (m, 3 H).
17	620.4	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.25 - 9.44 (m, 1 H), 7.65 - 7.74 (m, 1 H), 7.34 (d, <i>J</i> =2.5 Hz, 1 H), 7.28 (t, <i>J</i> =9.4 Hz, 1 H), 7.07 (t, <i>J</i> =2.4 Hz, 1 H), 5.39 - 5.75 (m, 1 H), 4.60 - 4.73 (m, 2 H), 4.22 - 4.35 (m, 1 H), 3.91 (m, <i>J</i> =15.5 Hz, 5 H), 3.44 - 3.55 (m, 1 H), 2.11 - 2.81 (m, 12 H), 1.93 - 2.08 (m, 1 H), 1.73 - 1.92 (m, 2 H), 1.63 (br d, <i>J</i> =13.0 Hz, 1 H), 0.76 - 0.87 (m, 3 H).
18	610.2	¹ H NMR (METHANOL- <i>d</i> ₄ , 400 MHz) δ ppm 9.32 (s, 1H), 9.17 (s, 1H), 7.64 (ddd, 1H, <i>J</i> =1.4, 4.8, 9.3 Hz), 7.4-7.5 (m, 1H), 7.2-7.4 (m, 2H), 5.5-5.7 (m, 1H), 4.8-5.0 (m, 2H), 4.6-4.7 (m, 1H), 4.6-4.7 (m, 1H), 4.3-4.4 (m, 1H), 3.8-4.1 (m, 4H), 3.4-3.6 (m, 2H), 2.67 (s, 1H), 2.6-2.7 (m, 1H), 2.5-2.8 (m, 1H), 2.2-2.3 (m, 1H), 2.1-2.5 (m, 6H), 1.8-1.9 (m, 1H), 1.3-1.4 (m, 1H).
19	580.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 8.98 - 9.05 (m, 1 H), 7.64 - 7.74 (m, 1 H), 7.30 - 7.33 (m, 1 H), 7.22 - 7.29 (m, 1 H), 7.00 - 7.07 (m, 1 H), 5.46 - 5.67 (m, 1 H), 4.97 - 5.11 (m, 1 H), 4.56 - 4.73 (m, 4 H), 4.19 - 4.32 (m, 1 H), 3.81 - 4.08 (m, 4 H), 3.41 - 3.53 (m, 1 H), 2.29 - 2.78 (m, 9 H), 2.09 - 2.23 (m, 2 H), 0.74 - 0.84 (m, 3 H).

Ex. #	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
20	592.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 8.92 - 9.02 (m, 1 H), 7.63 - 7.73 (m, 1 H), 7.30 - 7.33 (m, 1 H), 7.22 - 7.29 (m, 1 H), 7.01 - 7.07 (m, 1 H), 5.47 - 5.67 (m, 1 H), 5.33 - 5.44 (m, 1 H), 4.89 - 5.02 (m, 1 H), 4.44 - 4.72 (m, 5 H), 3.80 - 4.28 (m, 4 H), 3.42 - 3.72 (m, 4 H), 2.27 - 2.78 (m, 6 H), 2.09 - 2.22 (m, 2 H), 0.74 - 0.86 (m, 3 H).
21	592.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 8.94 - 9.20 (m, 1 H), 7.63 - 7.72 (m, 1 H), 7.30 - 7.35 (m, 1 H), 7.21 - 7.29 (m, 1 H), 6.99 - 7.07 (m, 1 H), 5.49 - 5.68 (m, 1 H), 5.02 - 5.15 (m, 1 H), 4.61 - 4.73 (m, 4 H), 3.79 - 4.39 (m, 6 H), 3.42 - 3.56 (m, 1 H), 2.29 - 2.78 (m, 8 H), 2.09 - 2.24 (m, 2 H), 0.74 - 0.84 (m, 3 H).
22	656.1	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.17 - 9.26 (m, 1 H), 7.64 - 7.74 (m, 1 H), 7.31 - 7.34 (m, 1 H), 7.23 - 7.29 (m, 1 H), 7.02 - 7.09 (m, 1 H), 5.49 - 5.68 (m, 1 H), 4.64 - 4.79 (m, 2 H), 4.14 - 4.30 (m, 2 H), 3.84 - 4.10 (m, 5 H), 3.62 - 3.77 (m, 2 H), 3.53 - 3.60 (m, 2 H), 3.42 - 3.53 (m, 1 H), 2.53 - 2.83 (m, 2 H), 2.28 - 2.50 (m, 4 H), 2.10 - 2.27 (m, 2 H), 1.72 - 1.97 (m, 4 H), 0.74 - 0.85 (m, 3 H).
23	620.3	¹ H NMR (METHANOL- <i>d</i> ₄ , 400 MHz) δ 9.31 (d, 1H, <i>J</i> =18.4 Hz), 7.70 (dd, 1H, <i>J</i> =6.0, 8.9 Hz), 7.34 (d, 1H, <i>J</i> =2.7 Hz), 7.27 (t, 1H, <i>J</i> =9.3 Hz), 7.08 (dd, 1H, <i>J</i> =2.5, 15.0 Hz), 5.5-5.7 (m, 1H), 4.6-4.7 (m, 3H), 4.37 (qd, 1H, <i>J</i> =5.0, 10.2 Hz), 3.8-4.1 (m, 4H), 3.4-3.6 (m, 2H), 2.6-2.8 (m, 2H), 2.1-2.5 (m, 9H), 1.9-2.0 (m, 1H), 1.84 (br d, 1H, <i>J</i> =9.6 Hz), 1.37 (br dd, 1H, <i>J</i> =2.6, 13.7 Hz), 0.8-0.9 (m, 3H).
24	620.3	¹ H NMR (METHANOL- <i>d</i> ₄ , 400 MHz) δ 9.31 (d, 1H, <i>J</i> =18.4 Hz), 7.70 (dd, 1H, <i>J</i> =6.0, 8.9 Hz), 7.34 (d, 1H, <i>J</i> =2.7 Hz), 7.27 (t, 1H, <i>J</i> =9.3 Hz), 7.08 (dd, 1H, <i>J</i> =2.5, 15.0 Hz), 5.5-5.7 (m, 1H), 4.6-4.7 (m, 3H), 4.37 (qd, 1H, <i>J</i> =5.0, 10.2 Hz), 3.8-4.1 (m, 4H), 3.4-3.6 (m, 2H), 2.6-2.8 (m, 2H), 2.1-2.5 (m, 9H), 1.9-2.0 (m, 1H), 1.84 (br d, 1H, <i>J</i> =9.6 Hz), 1.37 (br dd, 1H, <i>J</i> =2.6, 13.7 Hz), 0.8-0.9 (m, 3H).
25	620.3	¹ H NMR (METHANOL- <i>d</i> ₄ , 400 MHz) δ 9.31 (d, 1H, <i>J</i> =18.4 Hz), 7.70 (dd, 1H, <i>J</i> =6.0, 8.9 Hz), 7.34 (d, 1H, <i>J</i> =2.7 Hz), 7.27 (t, 1H, <i>J</i> =9.3 Hz), 7.08 (dd, 1H, <i>J</i> =2.5, 15.0 Hz), 5.5-5.7 (m, 1H), 4.6-4.7 (m, 3H), 4.37 (qd, 1H, <i>J</i> =5.0, 10.2 Hz), 3.8-4.1 (m, 4H), 3.4-3.6 (m, 2H), 2.6-2.8 (m, 2H), 2.1-2.5 (m, 9H), 1.9-2.0 (m, 1H), 1.84 (br d, 1H, <i>J</i> =9.6 Hz), 1.37 (br dd, 1H, <i>J</i> =2.6, 13.7 Hz), 0.8-0.9 (m, 3H).

Ex. #	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
26	620.3	¹ H NMR (METHANOL-d ₄ , 400 MHz) δ 9.31 (d, 1H, <i>J</i> =18.4 Hz), 7.70 (dd, 1H, <i>J</i> =6.0, 8.9 Hz), 7.34 (d, 1H, <i>J</i> =2.7 Hz), 7.27 (t, 1H, <i>J</i> =9.3 Hz), 7.08 (dd, 1H, <i>J</i> =2.5, 15.0 Hz), 5.5-5.7 (m, 1H), 4.6-4.7 (m, 3H), 4.37 (qd, 1H, <i>J</i> =5.0, 10.2 Hz), 3.8-4.1 (m, 4H), 3.4-3.6 (m, 2H), 2.6-2.8 (m, 2H), 2.1-2.5 (m, 9H), 1.9-2.0 (m, 1H), 1.84 (br d, 1H, <i>J</i> =9.6 Hz), 1.37 (br dd, 1H, <i>J</i> =2.6, 13.7 Hz), 0.8-0.9 (m, 3H).
27	616.3	¹ H NMR (METHANOL-d ₄ , 400 MHz) δ 9.31-9.16 (m, 1H), 7.8-7.9 (m, 1H), 7.2-7.4 (m, 3H), 5.5-5.7 (m, 1H), 5.1-5.3 (m, 1H), 4.6-4.7 (m, 2H), 4.2-4.4 (m, 1H), 3.8-4.1 (m, 4H), 3.4-3.5 (m, 3H), 2.6-2.7 (m, 2H), 2.1-2.5 (m, 7H), 1.9-2.0 (m, 1H), 1.8-1.9 (m, 1H), 1.3-1.4 (m, 2H).
28	616.3	¹ H NMR (METHANOL-d ₄ , 400 MHz) δ 9.31-9.16 (m, 1H), 7.8-7.9 (m, 1H), 7.2-7.4 (m, 3H), 5.5-5.7 (m, 1H), 5.1-5.3 (m, 1H), 4.6-4.7 (m, 2H), 4.2-4.4 (m, 1H), 3.8-4.1 (m, 4H), 3.4-3.5 (m, 3H), 2.6-2.7 (m, 2H), 2.1-2.5 (m, 7H), 1.9-2.0 (m, 1H), 1.8-1.9 (m, 1H), 1.3-1.4 (m, 2H).
29	602.2	¹ H NMR (METHANOL-d ₄ , 400 MHz) δ 9.29 (d, 1H, <i>J</i> =9.8 Hz), 7.65 (d, 1H, <i>J</i> =8.2 Hz), 7.3-7.4 (m, 2H), 7.18 (d, 1H, <i>J</i> =7.3 Hz), 7.03 (dd, 1H, <i>J</i> =2.6, 13.9 Hz), 5.5-5.7 (m, 1H), 4.6-4.7 (m, 3H), 4.36 (br dd, 1H, <i>J</i> =5.1, 9.7 Hz), 3.8-4.1 (m, 4H), 3.4-3.6 (m, 2H), 2.5-2.8 (m, 2H), 2.1-2.5 (m, 10H), 1.8-2.0 (m, 2H), 1.3-1.4 (m, 1H), 0.91 (q, 3H, <i>J</i> =7.1 Hz).
30	598.2	¹ H NMR (METHANOL-d ₄ , 400 MHz) δ 9.30 (s, 1H), 7.00 (d, 1H, <i>J</i> =2.7 Hz), 6.82 (d, 1H, <i>J</i> =2.5 Hz), 5.5-5.7 (m, 1H), 4.35 (td, 1H, <i>J</i> =5.3, 10.2 Hz), 3.7-4.1 (m, 5H), 3.4-3.6 (m, 2H), 2.5-2.8 (m, 3H), 2.1-2.5 (m, 8H), 1.9-2.0 (m, 1H), 1.8-1.9 (m, 2H), 1.3-1.4 (m, 2H), 0.5-0.7 (m, 2H), 0.0-0.2 (m, 2H).
31	598.2	¹ H NMR (METHANOL-d ₄ , 400 MHz) δ 9.1-9.3 (m, 1H), 7.85 (br d, 1H, <i>J</i> =7.1 Hz), 7.5-7.6 (m, 1H), 7.3-7.5 (m, 2H), 7.2-7.3 (m, 1H), 5.6-5.7 (m, 1H), 5.21 (br d, 1H, <i>J</i> =12.3 Hz), 4.6-4.7 (m, 2H), 4.35 (dt, 1H, <i>J</i> =5.6, 10.7 Hz), 3.8-4.1 (m, 5H), 3.4-3.6 (m, 2H), 2.5-2.8 (m, 3H), 2.1-2.5 (m, 8H), 1.8-2.0 (m, 2H).
32	622.3	¹ H NMR (METHANOL-d ₄ , 400 MHz) δ 9.28 (br d, 1H, <i>J</i> =14.2 Hz), 7.71 (dd, 1H, <i>J</i> =5.9, 8.8 Hz), 7.2-7.4 (m, 2H), 7.10 (dd, 1H, <i>J</i> =2.2, 7.8 Hz), 5.5-5.7 (m, 1H), 4.69 (br s, 1H), 4.5-4.7 (m, 2H), 3.8-4.3 (m, 5H), 3.4-3.6 (m, 3H), 2.6-2.9 (m, 2H), 2.3-2.5 (m, 4H), 2.21 (br d, 2H, <i>J</i> =6.1 Hz), 1.9-2.0 (m, 1H), 1.5-1.7 (m, 1H), 1.15 (br d, 3H, <i>J</i> =4.6 Hz), 0.9-1.1 (m, 3H), 0.82 (br t, 3H, <i>J</i> =7.2 Hz).

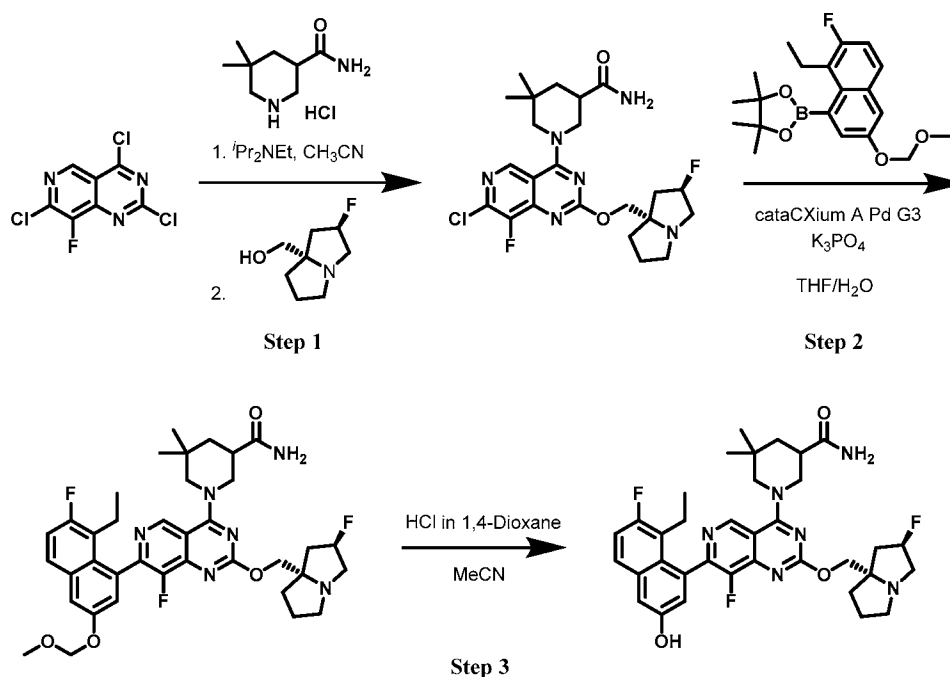
Ex. #	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
33	608.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.09 (s, 1 H), 7.70 (dd, <i>J</i> =9.1, 5.7 Hz, 1 H), 7.34 (d, <i>J</i> =2.5 Hz, 1 H), 7.28 (t, <i>J</i> =9.4 Hz, 1 H), 7.08 (dd, <i>J</i> =9.0, 2.7 Hz, 1 H), 5.52 - 5.71 (m, 1 H), 4.99 - 5.11 (m, 1 H), 4.58 - 4.67 (m, 2 H), 3.83 - 4.11 (m, 4 H), 3.45 - 3.56 (m, 1 H), 2.67 (s, 2 H), 2.32 - 2.63 (m, 5 H), 1.78 - 2.29 (m, 7 H), 1.59 (dd, <i>J</i> =6.9, 1.9 Hz, 3 H), 0.82 (dt, <i>J</i> =10.9, 7.4 Hz, 3 H).
34	620.4	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.19 (s, 1 H), 7.70 (dd, <i>J</i> =9.1, 5.7 Hz, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.28 (t, <i>J</i> =9.4 Hz, 1 H), 7.07 (d, <i>J</i> =2.5 Hz, 1 H), 5.51 - 5.68 (m, 1 H), 5.24 - 5.37 (m, 1 H), 5.09 - 5.20 (m, 1 H), 4.67 (br d, <i>J</i> =2.5 Hz, 2 H), 3.82 - 4.13 (m, 4 H), 3.46 - 3.55 (m, 1 H), 2.72 - 2.81 (m, 1 H), 2.60 (s, 1 H), 2.43 - 2.54 (m, 2 H), 2.34 - 2.42 (m, 2 H), 2.15 - 2.31 (m, 4 H), 1.91 - 2.11 (m, 4 H), 1.70 - 1.90 (m, 2 H), 0.83 (t, <i>J</i> =7.2 Hz, 3 H).
35	608.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.17 (s, 1 H), 7.70 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.27 (t, <i>J</i> =9.4 Hz, 1 H), 7.08 (t, <i>J</i> =2.4 Hz, 1 H), 5.53 - 5.74 (m, 1 H), 4.66 (br d, <i>J</i> =1.5 Hz, 2 H), 3.86 - 4.13 (m, 3 H), 3.43 - 3.64 (m, 4 H), 2.67 - 2.82 (m, 2 H), 2.56 - 2.66 (m, 1 H), 2.31 - 2.53 (m, 5 H), 2.13 - 2.26 (m, 2 H), 2.00 - 2.10 (m, 1 H), 1.78 (dt, <i>J</i> =8.7, 6.5, 6.5, 4.5, 4.5 Hz, 1 H), 1.42 - 1.59 (m, 1 H), 1.15 - 1.22 (m, 3 H), 0.82 (td, <i>J</i> =7.3, 4.2 Hz, 3 H).
36	608.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.40 - 9.50 (m, 1 H), 7.68 - 7.72 (m, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.25 - 7.30 (m, 1 H), 7.05 - 7.09 (m, 1 H), 5.49 - 5.71 (m, 2 H), 4.61 - 4.72 (m, 2 H), 3.91 (br d, <i>J</i> =17.3 Hz, 4 H), 3.50 (br dd, <i>J</i> =9.4, 5.4 Hz, 1 H), 2.69 - 2.81 (m, 1 H), 2.61 (br d, <i>J</i> =4.4 Hz, 1 H), 2.45 - 2.52 (m, 3 H), 2.31 - 2.42 (m, 4 H), 2.16 - 2.28 (m, 4 H), 1.49 - 1.54 (m, 3 H), 0.82 (t, <i>J</i> =7.3 Hz, 4 H).
37	606.3	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.35 (d, <i>J</i> =3.3 Hz, 1 H), 7.71 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.34 (d, <i>J</i> =2.5 Hz, 1 H), 7.28 (t, <i>J</i> =9.4 Hz, 1 H), 7.07 (t, <i>J</i> =3.1 Hz, 1 H), 5.48 - 5.70 (m, 1 H), 4.64 - 4.75 (m, 4 H), 4.23 - 4.49 (m, 3 H), 3.83 - 4.04 (m, 5 H), 3.45 - 3.58 (m, 1 H), 3.20 - 3.29 (m, 1 H), 2.71 - 2.81 (m, 1 H), 2.04 - 2.67 (m, 11 H), 0.72 - 0.88 (m, 3 H).
38	608.4	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.31 (s, 1 H), 7.70 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.27 (t, <i>J</i> =9.4 Hz, 1 H), 7.07 (t, <i>J</i> =2.4 Hz, 1 H), 5.48 - 5.72 (m, 1 H), 4.69 (s, 3 H), 4.38 (br t, <i>J</i> =12.0 Hz, 1 H), 3.84 - 4.14 (m, 3 H), 3.60 - 3.72 (m, 1 H), 3.43 - 3.56 (m, 2 H), 2.70 - 2.82 (m, 1 H), 2.56 - 2.66 (m, 1 H), 2.34 - 2.51 (m, 4 H), 2.13 - 2.30 (m, 3 H), 1.77 - 1.94 (m, 3 H), 1.32 (d, <i>J</i> =7.9 Hz, 3 H), 0.78 - 0.89 (m, 3 H).

Ex. #	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
39	644.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.27 - 9.36 (m, 1 H), 7.66 - 7.75 (m, 1 H), 7.32 - 7.36 (m, 1 H), 7.23 - 7.31 (m, 1 H), 7.05 - 7.11 (m, 1 H), 5.50 - 5.98 (m, 2 H), 4.66 - 4.76 (m, 3 H), 4.52 - 4.63 (m, 1 H), 3.83 - 4.12 (m, 3 H), 3.68 - 3.81 (m, 1 H), 3.42 - 3.55 (m, 2 H), 2.54 - 2.83 (m, 2 H), 2.32 - 2.53 (m, 4 H), 2.13 - 2.30 (m, 3 H), 1.85 - 2.08 (m, 3 H), 0.82 (d, <i>J</i> =7.1 Hz, 3 H).
40	644.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.27 - 9.36 (m, 1 H), 7.66 - 7.75 (m, 1 H), 7.32 - 7.37 (m, 1 H), 7.23 - 7.31 (m, 1 H), 7.05 - 7.11 (m, 1 H), 5.50 - 5.97 (m, 2 H), 4.64 - 4.76 (m, 3 H), 4.52 - 4.63 (m, 1 H), 3.83 - 4.11 (m, 3 H), 3.68 - 3.81 (m, 1 H), 3.42 - 3.56 (m, 2 H), 2.54 - 2.81 (m, 2 H), 2.31 - 2.51 (m, 4 H), 2.12 - 2.29 (m, 3 H), 1.87 - 2.05 (m, 3 H), 0.82 (br d, <i>J</i> =3.8 Hz, 3 H).
41	640.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.19 (s, 1 H), 7.85 - 7.93 (m, 1 H), 7.40 (d, <i>J</i> =2.5 Hz, 1 H), 7.31 - 7.38 (m, 1 H), 7.25 - 7.31 (m, 1 H), 5.48 - 5.98 (m, 2 H), 4.66 - 4.77 (m, 3 H), 4.51 - 4.64 (m, 1 H), 3.86 - 4.10 (m, 3 H), 3.74 - 3.86 (m, 1 H), 3.50 (br d, <i>J</i> =0.8 Hz, 3 H), 2.55 - 2.82 (m, 2 H), 2.31 - 2.51 (m, 3 H), 2.10 - 2.30 (m, 2 H), 1.80 - 2.07 (m, 3 H).
42	620.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 8.95 - 9.25 (m, 1 H), 7.70 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.23 - 7.46 (m, 2 H), 7.07 (dd, <i>J</i> =10.7, 2.5 Hz, 1 H), 5.34 - 5.73 (m, 1 H), 5.12 - 5.29 (m, 1 H), 4.61 - 4.77 (m, 3 H), 4.18 - 4.45 (m, 2 H), 3.74 - 4.03 (m, 5 H), 3.40 - 3.64 (m, 1 H), 2.56 - 2.92 (m, 3 H), 2.41 - 2.55 (m, 2 H), 2.10 - 2.41 (m, 6 H), 1.98 - 2.15 (m, 3 H), 1.78 - 1.93 (m, 1 H), 0.73 - 0.92 (m, 3 H).
170	590.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.60 - 9.73 (m, 1 H), 7.71 (s, 2 H), 7.36 (d, <i>J</i> =2.5 Hz, 1 H), 7.28 - 7.34 (m, 1 H), 7.14 (d, <i>J</i> =2.5 Hz, 1 H), 5.51 - 5.76 (m, 1 H), 4.90 - 4.95 (m, 1 H), 4.72 - 4.84 (m, 2 H), 4.39 - 4.55 (m, 1 H), 3.81 - 4.07 (m, 3 H), 3.57 - 3.73 (m, 1 H), 3.39 - 3.55 (m, 2 H), 2.56 - 2.84 (m, 2 H), 2.32 - 2.55 (m, 4 H), 2.11 - 2.32 (m, 3 H), 1.77 - 1.98 (m, 3 H), 1.36 (s, 3 H), 0.90 (t, <i>J</i> =7.4 Hz, 3 H).
171	626.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.29 - 9.36 (m, 1 H), 7.66 - 7.76 (m, 1 H), 7.32 - 7.37 (m, 1 H), 7.23 - 7.31 (m, 1 H), 7.05 - 7.12 (m, 1 H), 5.49 - 5.72 (m, 1 H), 4.60 - 4.79 (m, 3 H), 4.39 - 4.53 (m, 2 H), 4.25 - 4.38 (m, 1 H), 3.78 - 4.15 (m, 4 H), 3.42 - 3.66 (m, 2 H), 2.55 - 2.83 (m, 2 H), 2.31 - 2.53 (m, 4 H), 2.09 - 2.29 (m, 3 H), 1.78 - 1.98 (m, 3 H), 0.75 - 0.89 (m, 3 H).

Ex. #	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
172	626.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.28 - 9.38 (m, 1 H), 7.65 - 7.77 (m, 1 H), 7.32 - 7.37 (m, 1 H), 7.25 - 7.31 (m, 1 H), 7.02 - 7.13 (m, 1 H), 5.48 - 5.71 (m, 1 H), 4.57 - 4.81 (m, 3 H), 4.39 - 4.52 (m, 2 H), 4.25 - 4.38 (m, 1 H), 3.77 - 4.14 (m, 4 H), 3.42 - 3.67 (m, 2 H), 2.54 - 2.84 (m, 2 H), 2.31 - 2.54 (m, 4 H), 2.12 - 2.30 (m, 3 H), 1.75 - 1.98 (m, 3 H), 0.75 - 0.89 (m, 3 H)
173	594.4	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.34 (s, 1 H), 6.44 - 6.75 (m, 2 H), 5.28 - 5.83 (m, 1 H), 4.53 - 4.76 (m, 3 H), 4.24 - 4.41 (m, 1 H), 3.83 - 4.17 (m, 3 H), 3.39 - 3.74 (m, 3 H), 2.53 - 2.93 (m, 5 H), 2.29 - 2.50 (m, 3 H), 2.06 - 2.26 (m, 2 H), 1.67 - 1.95 (m, 7 H), 1.32 (s, 5 H), 0.33 - 0.60 (m, 3 H)
174	594.4	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.06 - 9.26 (m, 1 H), 6.35 - 6.83 (m, 2 H), 5.10 - 5.55 (m, 1 H), 4.46 - 4.60 (m, 1 H), 4.10 - 4.38 (m, 3 H), 3.56 - 3.72 (m, 1 H), 3.39 - 3.53 (m, 1 H), 3.14 - 3.28 (m, 3 H), 2.99 - 3.10 (m, 1 H), 2.69 - 2.89 (m, 3 H), 2.07 - 2.41 (m, 5 H), 1.67 - 2.06 (m, 12 H), 1.02 - 1.50 (m, 2 H), 0.41 - 0.64 (m, 3 H)
175	606.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.14 - 9.38 (m, 1 H), 6.49 - 6.90 (m, 2 H), 5.44 - 5.78 (m, 1 H), 5.09 - 5.33 (m, 1 H), 5.04 - 5.29 (m, 1 H), 4.83 - 4.97 (m, 1 H), 4.55 - 4.76 (m, 4 H), 4.27 - 4.41 (m, 1 H), 3.80 - 4.13 (m, 3 H), 3.37 - 3.71 (m, 4 H), 2.53 - 2.98 (m, 4 H), 2.31 - 2.48 (m, 3 H), 2.09 - 2.29 (m, 2 H), 1.55 - 1.95 (m, 7 H), 1.28 - 1.35 (m, 6 H)

1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-dimethylpiperidine-3-carboxamide (Example 43)

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Example 43

Step 1: 1-(7-Chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5,5-dimethylpiperidine-3-carboxamide.

To a suspension of 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (0.10 g, 0.40 mmol, LabNetwork) in acetonitrile (2.0 mL) at 0 °C was added 5,5-dimethylpiperidine-3-carboxamide hydrochloride (80 mg, 0.42 mmol, **Intermediate G1**) and DIPEA (0.21 mg, 0.28 mL, 1.58 mmol, Aldrich). The reaction was stirred at 0 °C. Separately, a solution of ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (0.11 g, 0.71 mmol, Labnetwork) in acetonitrile (1.0 mL) was dried over anhydrous magnesium sulfate. The mixture was stirred for 5 minutes at rt temperature, and then filtered through celite to remove the magnesium sulfate. After 20 minutes, (1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-5,5-dimethylpiperidine-3-carboxamide) was observed. Two mixtures were combined and the reaction was stirred at 80 °C overnight. The reaction was cooled to rt and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0-100 % 3:1 EtOAc/EtOH (with 2% triethylamine) in heptane to provide 1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-

yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-dimethylpiperidine-3-carboxamide (0.12 g, 0.24 mmol, 61 % yield) as orange solid. *m/z* (ESI): 495.0 (M+H)⁺.

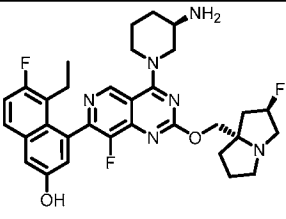
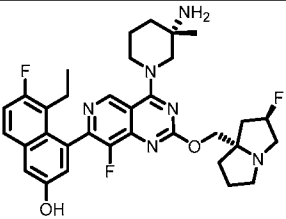
Step 2: 1-(7-(8-Ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-dimethylpiperidine-3-carboxamide. A 1 dram vial was charged with 1-(7-chloro-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-dimethylpiperidine-3-carboxamide (50 mg, 0.10 mmol), 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (55 mg, 0.15 mmol, PharmaBlock), potassium phosphate (64 mg, 0.30 mmol, Sigma Aldrich Corporation), and cataCXium A Pd G3 (15 mg, 0.02 mmol, Sigma Aldrich Corporation). The vial was purged with nitrogen and the reactants were suspended in degassed tetrahydrofuran (0.9 mL) and water (0.09 mL). The reaction was then sealed and stirred at 65 °C overnight. The reaction was then cooled to rt and concentrated under reduced pressure to afford a crude black oil. The oil was then purified via column chromatography on silica gel, eluting with a gradient of 0-100% 3:1 EtOAc/EtOH (with 2% triethylamine) in heptane to provide 1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-dimethylpiperidine-3-carboxamide (60 mg, 0.09 mmol, 85 % yield) as off-white solid. *m/z* (ESI): 693.2 (M+H)⁺.

Step 3: 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-dimethylpiperidine-3-carboxamide. 1-(7-(8-Ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-dimethylpiperidine-3-carboxamide (60 mg, 0.09 mmol) was dissolved in MeCN (3.1 mL) and HCl (4 M in 1,4-dioxane, 0.6 mL, 2.53 mmol, Sigma-Aldrich Corporation). The reaction was stirred at rt for 3 h then cooled to rt and concentrated under reduced pressure to provide a crude orange oil. The oil was then purified by reverse phase HPLC to provide 1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-dimethylpiperidine-3-carboxamide 2,2,2-trifluoroacetate (38 mg, 0.05 mmol, 49 % yield) as light-yellow solid. *m/z* (ESI): 649.2 (M+H)⁺. ¹H NMR (400 MHz,

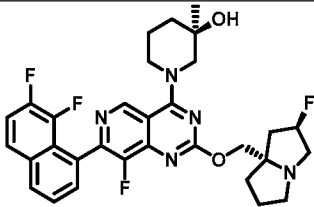
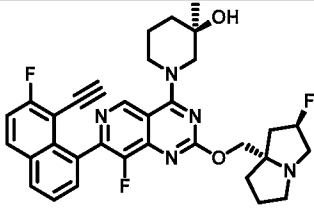
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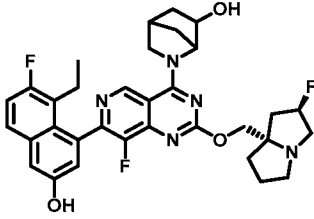
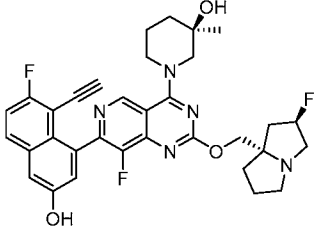
METHANOL-*d*₄) δ ppm 9.19 (s, 1 H), 7.65 - 7.75 (m, 1 H), 7.31 - 7.36 (m, 1 H), 7.23 - 7.30 (m, 1 H), 7.04 - 7.13 (m, 1 H), 5.49 - 5.71 (m, 1 H), 4.65 - 4.77 (m, 3 H), 4.36 - 4.49 (m, 1 H), 3.82 - 4.12 (m, 3 H), 3.35 - 3.54 (m, 3 H), 2.98 - 3.14 (m, 1 H), 2.54 - 2.86 (m, 2 H), 2.32 - 2.53 (m, 4 H), 2.14 - 2.30 (m, 2 H), 1.73 - 1.95 (m, 2 H), 1.12 (d, *J*=4.0 Hz, 3 H), 0.96 - 1.09 (m, 3 H), 0.73 - 0.87 (m, 3 H).

Table 5. Examples 44 to 72. Prepared in an analogous manner to Example 43.

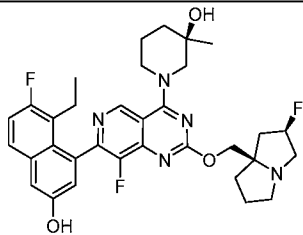
Ex. #	Structure	Name	Salt Form	Reagent	Method Change
44		4-(4-((<i>R</i>)-3-Aminopiperidin-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyridine-6-yl)-5-ethyl-6-fluoronaphthalen-2-ol	bis(2,2,2-trifluoroacetate)	Step 1: (<i>R</i>)- <i>tert</i> -butyl piperidin-3-ylcarbamate (CAS#: 309956-78-3, Ambeed, Inc.)	Addition of Step 1 and Step 2. Details included below.
45		4-(4-((<i>S</i>)-3-methylpiperidin-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyridine-6-yl)-5-ethyl-6-fluoronaphthalen-2-ol	bis(2,2,2-trifluoroacetate)	Step 1: <i>tert</i> -butyl <i>N</i> -[(3 <i>S</i>)-3-methylpiperidin-3-yl]carbamate (CAS#: 1363378-21-5, Pharmablock, Inc.)	Addition of Step 1 and Step 2. Details included below.

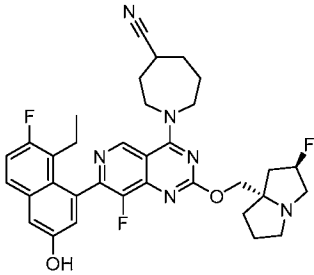
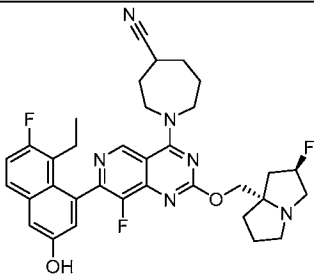
Ex. #	Structure	Name	Salt Form	Reagent	Method Change
46		4-(4-((<i>R</i>)-3-Amino-3-methylpiperidin-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyridino[4,3- <i>d</i>]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol	bis(2,2,2-trifluoroacetate)	Step 1: <i>tert</i> -butyl <i>N</i> -[(3 <i>R</i>)-3-methylpiperidin-3-yl]carbamate (CAS#: 1169762-18-8, Pharmablock, Inc.)	Addition of step analogous to Example 44 .
47		(3 <i>R</i> ,4 <i>S</i>)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyridino[4,3- <i>d</i>]pyrimidin-4-yl)-4-fluoropiperidin-3-ol	bis(2,2,2-trifluoroacetate)	Step 1: (3 <i>R</i> ,4 <i>S</i>)-4-fluoropiperidin-3-ol hydrochloride (CAS#: 1638765-12-4, Accelerate)	
48		(<i>R</i>)-1-(7-(8-Ethyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyridino[4,3- <i>d</i>]pyrimidin-4-yl)-3-methylpiperidin-3-ol	2,2,2-trifluoroacetate	Step 1: (3 <i>R</i>)-3-methylpiperidin-3-ol hydrochloride (CAS#: 2305080-34-4, Pharmablock) Step 2: 2-(8-ethyl-7-fluoronaphth	No Step 3

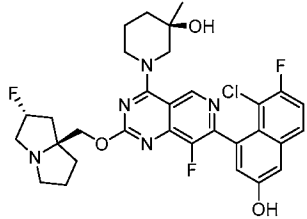
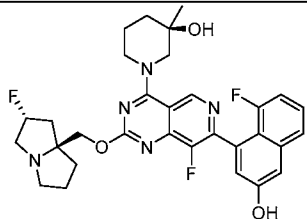
Ex. #	Structure	Name	Salt Form	Reagent	Method Change
				alen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Intermediate B)	
49		(R)-1-(7-(7,8-Difluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyridine-4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol	2,2,2-trifluoroacetate	Step 1: (3R)-3-methylpiperidin-3-ol hydrochloride (CAS#: 2305080-34-4, Pharmablock) Step 2: 2-(7,8-difluoronaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (CAS#: 2454490-85-6, LabNetwork)	No Step 3
50		(R)-1-(7-(8-Ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyridine-4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol	2,2,2-trifluoroacetate	Step 1: (3R)-3-methylpiperidin-3-ol hydrochloride (CAS#: 2305080-34-4, Pharmablock)	No Step 3. Additional step analogous to Example 27 after Step 2.

Ex. #	Structure	Name	Salt Form	Reagent	Method Change
		methylpiperidin-3-ol		Step 2: ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (CAS#: 2503307-87-5, LabNetwork)	
51		2-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyridine[4,3-d]pyrimidin-4-yl)-2-azabicyclo[2.2.1]heptan-6-ol	2,2,2-trifluoroacetate	Step 1: 2-azabicyclo[2.2.1]heptan-6-ol hydrochloride (CAS#: 2007916-89-2, AstaTech, Inc)	
52		(R)-1-(7-(8-Ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyridine[4,3-d]pyrimidin-4-yl)-2-azabicyclo[2.2.1]heptan-6-ol	bis(2,2,2-trifluoroacetate)	Step 1: (3R)-3-methylpiperidin-3-ol hydrochloride (CAS#: 2305080-34-4, Synnovator) Step 2: 2-[7-fluoro-3-(methoxymet	Addition of step analogous to Example 27 after Step 3 .

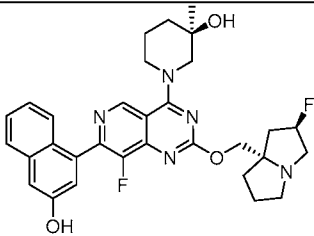
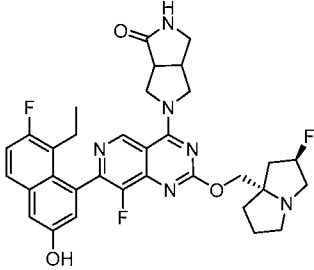
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Ex. #	Structure	Name	Salt Form	Reagent	Method Change
		yl)-3-methylpiperidin-3-ol		hoxy)-8-[2-[tris(1-methylethyl)silyl]ethynyl]-1-naphthalenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (CAS#: 2621932-37-2, LabNetwork)	
53		(R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aR)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyridine-4,3-d)pyrimidin-4-yl)-3-methylpiperidin-3-ol	2,2,2-trifluoroacetate	Step 1: (3R)-3-methylpiperidin-3-ol hydrochloride (CAS#: 2305080-34-4, Pharmablock); ((2R,7aR)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (CAS#: 2454490-66-3, LabNetwork)	

Ex. #	Structure	Name	Salt Form	Reagent	Method Change
54		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyridin-4-yl)azepane-4-carbonitrile Isomer 1	bis(2,2,2-trifluoroacetate)	Step 1: azepane-4-carbonitrile hydrochloride (CAS#: 1259062-50-4, AstaTech Inc.)	Chiral separation after Step 1 . Details included below.
55		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyridin-4-yl)azepane-4-carbonitrile Isomer 2	bis(2,2,2-trifluoroacetate)	Step 1: azepane-4-carbonitrile hydrochloride (CAS#: 1259062-50-4, AstaTech Inc.)	Chiral separation after Step 1 . Details included below.

Ex. #	Structure	Name	Salt Form	Reagent	Method Change
56		(R)-1-(7-(8-Chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyridin-4-yl)-3-methylpiperidin-3-ol	bis(2,2,2-trifluoroacetate)	Step 1: (3R)-3-methylpiperidin-3-ol hydrochloride (CAS#: 2305080-34-4), Synnovator) Step 2: 2-(8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Intermediate O)	
57		(R)-1-(8-Fluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyridin-4-yl)-3-methylpiperidin-3-ol	bis(2,2,2-trifluoroacetate)	Step 1: (3R)-3-methylpiperidin-3-ol hydrochloride (CAS#: 2305080-34-4), Synnovator) Step 2: 2-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (CAS#:	

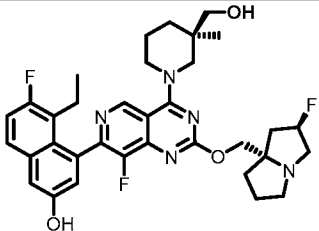
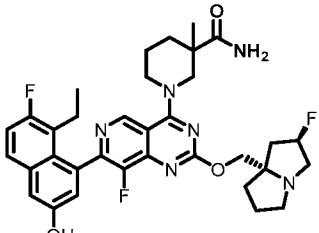
Ex. #	Structure	Name	Salt Form	Reagent	Method Change
				2621936-17-0, LabNetwork)	
58		(R)-1-(7-(8-Ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyridin-4-yl)-3-methylpiperidin-3-ol	2,2,2-trifluoroacetate	Step 1: (3R)-3-methylpiperidin-3-ol hydrochloride (CAS#: 2305080-34-4), Synnovator) Step 2: 2-(8-ethyl-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (CAS#: 2621932-60-1, LabNetwork)	
59		(R)-1-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyridin-4-yl)-3-methylpiperidin-3-ol	bis(2,2,2-trifluoroacetate)	Step 1: (3R)-3-methylpiperidin-3-ol hydrochloride (CAS#: 2305080-34-4), Synnovator) Step 2: 2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-	

Ex. #	Structure	Name	Salt Form	Reagent	Method Change
				tetramethyl-1,3,2-dioxaborolane (CAS#: 2621935-35-9, LabNetwork)	
60		(R)-1-(8-Fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(3-hydroxynaphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol	2,2,2-trifluoroacetate	Step 1: (3R)-3-methylpiperidin-3-ol hydrochloride (CAS#: 2305080-34-4, Synnovator) Step 2: 3-hydroxynaphthalene-1-boronic acid (CAS#: 1698028-43-1, Angel Pharmatech Ltd.)	No Step 3
61		rel-(3aR,6aS)-5-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-1(2H)-one	bis(2,2,2-trifluoroacetate)	Step 1: rac-(3aR,6aS)-octahydropyrrolo[3,4-c]pyrrol-1-one hydrochloride (CAS#: 2206134-91-8, Enamine)	

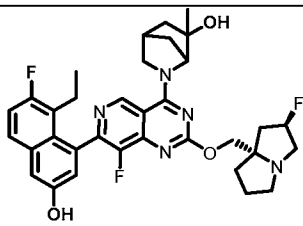
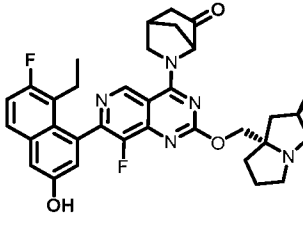
Ex. #	Structure	Name	Salt Form	Reagent	Method Change
62		5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-rel-((3aR,7aS)-hexahydrofuro[3,2-c]pyridin-5(4H)-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol	2,2,2-trifluoroacetate	Step 1: <i>rac</i> -(3aR,7aS)-octahydrofuro[3,2-c]pyridine hydrochloride (CAS#: 1629784-77-5, Enamine)	
63		<i>rel</i> -(3aR,7aR)-4-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyridino[4,3-d]pyrimidin-4-yl)octahydro-2H-pyrrolo[3,2-b]pyridin-2-one	2,2,2-trifluoroacetate	Step 1: <i>rac</i> -(3aR,7aR)-octahydro-1H-pyrrolo[3,2-b]pyridin-2-one hydrochloride (CAS#: 2241129-83-7, Enamine)	

Ex. #	Structure	Name	Salt Form	Reagent	Method Change
64		<i>rel</i> -(3 <i>S</i> ,6 <i>R</i>)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-6-methylpiperidine-3-carboxamide	2,2,2-trifluoroacetate	Step 1: <i>rac</i> -(3 <i>R</i> ,6 <i>S</i>)-6-methylpiperidine-3-carboxamide hydrochloride (CAS#: 2241141-04-6, Enamine)	
65		3-Ethyl-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)piperidin-3-ol	bis(2,2,2-trifluoroacetate)	Step 1: 3-ethylpiperidine-3-ol (CAS#: 1177299-74-9, Enamine)	
66		5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)-4-((<i>S</i>)-3-(hydroxymethyl)-3-methylpiperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-7-yl)-2-methylpiperidine-3-ol	2,2,2-trifluoroacetate	Step 1: [(3 <i>S</i>)-3-methylpiperidin-3-yl]methanol hydrochloride (CAS#: 1956435-41-8, Pharmablock, Inc.)	

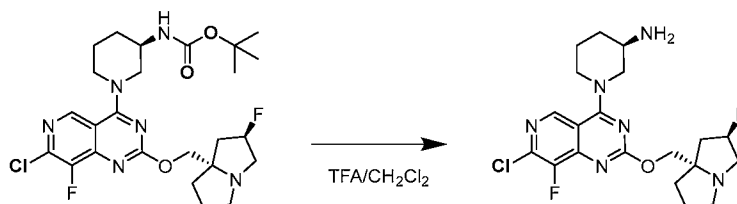
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Ex. #	Structure	Name	Salt Form	Reagent	Method Change
		yl)naphthalen-2-ol			
67		5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-((R)-3-(hydroxymethyl)-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol	2,2,2-trifluoroacetate	Step 1: [(3R)-3-methylpiperidin-3-yl]methanol hydrochloride (CAS#: 1956437-13-0, Pharmablock, Inc.)	
68		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidine-3-carboxamide	2,2,2-trifluoroacetate	Step 1: 3-methyl-3-piperidinecarboxamide hydrochloride (CAS#: 1315499-98-9, AA Blocks)	

Ex. #	Structure	Name	Salt Form	Reagent	Method Change
69		8-(7-(8-Ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyridino[4,3-d]pyrimidin-4-yl)-2-methyl-8-azabicyclo[3.2.1]octan-2-ol	bis(2, 2,2-trifluoroacetate)	Step 1: 2-methyl-8-azabicyclo[3.2.1]octan-2-ol 2,2,2-trifluoroacetate (Intermediate M1) Step 2: 2-(8-ethyl-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (CAS#: 2621932-60-1, LabNetwork)	
70		8-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyridino[4,3-d]pyrimidin-4-yl)-2-methyl-8-azabicyclo[3.2.1]octan-2-ol	bis(2, 2,2-trifluoroacetate)	Step 1: 2-methyl-8-azabicyclo[3.2.1]octan-2-ol 2,2,2-trifluoroacetate (Intermediate M1)	

Ex. #	Structure	Name	Salt Form	Reagent	Method Change
71		2-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-2-azabicyclo[2.2.1]heptan-6-ol	bis(2,2,2-trifluoroacetate)	Step 1: 6-methyl-2-azabicyclo[2.2.1]heptan-6-ol 2,2,2-trifluoroacetate (Intermediate M2)	
72		2-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-azabicyclo[2.2.1]heptan-6-one	bis(2,2,2-trifluoroacetate)	Step 1: 2-azabicyclo[2.2.1]heptan-6-one hydrochloride (Intermediate N)	

Additional Step for Example 44

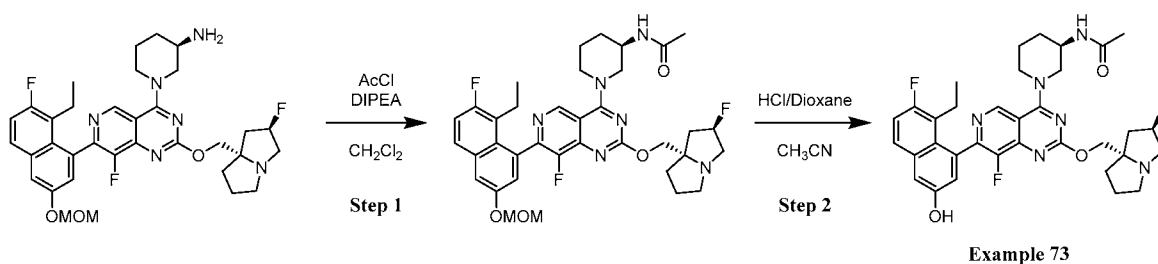


To a stirred solution of *tert*-butyl ((*R*)-1-(7-chloro-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-

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yl)carbamate (0.27 g, 0.50 mmol, synthesized in an analogous manner to **Example 1**) in DCM (2.0 mL) was added trifluoroacetic acid (1.50 g, 1.0 mL, 13.42 mmol, Sigma-Aldrich Corporation). The resulting mixture was stirred at rt for 1 h, and then was concentrated under reduced pressure. The residue was diluted with DCM and washed with aqueous saturated sodium bicarbonate. The organic layer was dried over Na₂SO₄ and evaporated to yield the product, which was used directly in the next step. *m/z* (ESI, +ve ion): 439.0 (M+H)⁺.

***N*-(((*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-yl)acetamide (Example 73)**



Step 1: ***N*-(((*R*)-1-(7-(8-Ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-yl)acetamide.** To a solution of (*R*)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-amine (35 mg, 0.06 mmol, prepared according to **Example 44**) in DCM (0.5 mL) was added DIPEA (21 mg, 0.03 mL, 0.17 mmol, Sigma-Aldrich Corporation), followed by acetyl chloride (5.2 mg, 4.7 μ L, 0.07 mmol, Sigma-Aldrich Corporation). The reaction mixture was stirred at rt for 15 min. The reaction mixture was concentrated under reduced pressure and purified by reverse phase HPLC to afford ***N*-(((*R*)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-yl)acetamide** (25 mg, 0.04 mmol, 67% yield) as yellow solid. *m/z* (ESI, +ve ion): 679.2 (M+H)⁺.

Step 2: ***N*-(((*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-**

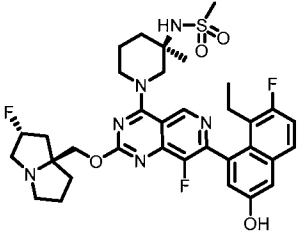
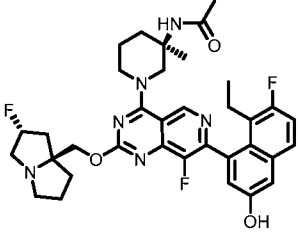
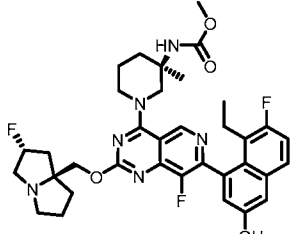
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d]pyrimidin-4-yl)piperidin-3-yl)acetamide. *N*-((*R*)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-yl)acetamide (25 mg, 0.04 mmol) was dissolved in acetonitrile (0.5 mL), HCl (4 M in dioxane, 13 mg, 0.01 mL, 0.37 mmol, Sigma-Aldrich Corporation) was added and the reaction mixture was stirred at rt for 0.5 h. The reaction mixture was purified by reverse phase HPLC to afford *N*-((*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-yl)acetamide bis(2,2,2-trifluoroacetate) (18 mg, 0.02 mmol, 38 % yield) as yellow solid. *m/z* (ESI, +ve ion): 635.2 (M+H)⁺. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 9.25 (d, *J*=2.7 Hz, 1 H), 7.70 (dd, *J*=9.0, 5.9 Hz, 1 H), 7.34 (d, *J*=2.7 Hz, 1 H), 7.28 (t, *J*=9.4 Hz, 1 H), 7.09 (dd, *J*=7.6, 2.6 Hz, 1 H), 5.46 - 5.72 (m, 1 H), 4.81 - 4.91 (m, 1 H), 4.69 - 4.77 (m, 2 H), 4.61 - 4.68 (m, 1 H), 4.55 (br d, *J*=13.0 Hz, 1 H), 3.85 - 4.12 (m, 4 H), 3.67 - 3.76 (m, 1 H), 3.35 - 3.53 (m, 2 H), 2.55 - 2.85 (m, 2 H), 2.32 - 2.53 (m, 4 H), 2.16 - 2.28 (m, 2 H), 1.95 - 2.13 (m, 4 H), 1.72 - 1.88 (m, 2 H), 0.78 - 0.86 (m, 3 H).

Table 6. Examples 74 to 78 synthesized in an analogous manner to Example 73.

Ex. #	Structure	Name	Salt Form	Reagent
74		1-((<i>R</i>)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)piperidin-3-yl)-3-(2-methoxyethyl)thiourea	2,2,2-trifluoroacetate	Step 1: 1-isothiocyanato-2-methoxyethane (CAS#: 38663-85-3, Enamine); triethylamine

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Ex. #	Structure	Name	Salt Form	Reagent
75		<i>N</i> -((<i>R</i>)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-3-methylpiperidin-3-yl)methanesulfonamide	bis(2,2,2-trifluoroacetate)	Step 1: methanesulfonyl chloride (CAS#: 124-63-0, Sigma-Aldrich Corporation)
76		<i>N</i> -((<i>R</i>)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-3-methylpiperidin-3-yl)acetamide	bis(2,2,2-trifluoroacetate)	
77		Methyl ((<i>R</i>)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-3-methylpiperidin-3-yl)carbamate	bis(2,2,2-trifluoroacetate)	Step 1: methyl chloroformate (CAS#: 79-22-1, Sigma-Aldrich Corporation)

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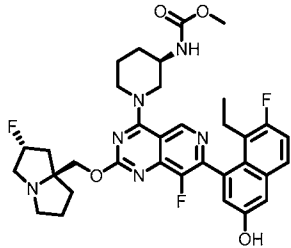
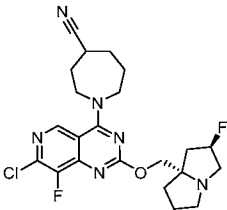
Ex. #	Structure	Name	Salt Form	Reagent
78		Methyl ((<i>R</i>)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)piperidin-3-yl)carbamate	2,2,2-trifluoroacetate	Step 1: methyl chloroformate (CAS#: 79-22-1, Sigma-Aldrich Corporation)

Table 7. SFC Conditions for Chiral Separation.

Separation	SFC Conditions	Peaks to Ex. #
	Column: Chiralcel OX, 2 x 25 cm 5 μ m column Mobile phase: 35% iPrOH with 0.2% DEA Flowrate: 80 mL/min. Yield: 160.9 mg was submitted to generate 60.4 mg of peak 1 with an ee of 99% and 53.9 mg of peak 2 with an ee of 95%.	Peak 1: Example 54 Peak 2: Example 55

5 Table 8: Analytical Data of Examples 44 to 78.

Ex. #	MS <i>m/z</i> (ESI): (<i>M</i> + <i>H</i>) ⁺	¹ H NMR
44	593.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.16 (s, 1 H), 7.71 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.35 (d, <i>J</i> =2.7 Hz, 1 H), 7.28 (t, <i>J</i> =9.4 Hz, 1 H), 7.07 (t, <i>J</i> =2.0 Hz, 1 H), 5.47 - 5.72 (m, 1 H), 4.73 - 4.76 (m, 2 H), 4.60 - 4.68 (m, 1 H), 4.44 (br dd, <i>J</i> =13.8, 4.6 Hz, 1 H), 3.74 - 4.14 (m, 5 H), 3.63 - 3.73 (m, 1 H), 3.46 - 3.54 (m, 1 H), 2.57 - 2.86 (m, 2 H), 2.28 - 2.53 (m, 5 H), 2.16 - 2.27 (m, 2 H), 2.04 - 2.15 (m, 1 H), 1.85 - 1.99 (m, 2 H), 0.81 (t, <i>J</i> =7.4 Hz, 3 H).

Ex. #	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
45	607.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.19 (s, 1 H), 7.71 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.35 (d, <i>J</i> =2.5 Hz, 1 H), 7.28 (t, <i>J</i> =9.3 Hz, 1 H), 7.07 (d, <i>J</i> =2.5 Hz, 1 H), 5.47 - 5.74 (m, 1 H), 4.73 - 4.76 (m, 2 H), 4.42 (t, <i>J</i> =13.6 Hz, 1 H), 4.22 - 4.30 (m, 1 H), 3.85 - 4.11 (m, 5 H), 3.46 - 3.54 (m, 1 H), 2.56 - 2.82 (m, 2 H), 2.33 - 2.54 (m, 4 H), 2.14 - 2.28 (m, 2 H), 2.01 - 2.14 (m, 4 H), 1.54 (d, <i>J</i> =5.0 Hz, 3 H), 0.81 (t, <i>J</i> =7.4 Hz, 3 H).
46	607.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.19 (s, 1 H), 7.71 (dd, <i>J</i> =9.2, 5.9 Hz, 1 H), 7.35 (d, <i>J</i> =2.5 Hz, 1 H), 7.28 (t, <i>J</i> =9.4 Hz, 1 H), 7.07 (d, <i>J</i> =2.5 Hz, 1 H), 5.46 - 5.74 (m, 1 H), 4.70 - 4.77 (m, 2 H), 4.40 (t, <i>J</i> =14.2 Hz, 1 H), 4.21 - 4.29 (m, 1 H), 3.84 - 4.12 (m, 5 H), 3.46 - 3.54 (m, 1 H), 2.58 - 2.86 (m, 2 H), 2.33 - 2.54 (m, 4 H), 2.15 - 2.29 (m, 2 H), 2.01 - 2.14 (m, 4 H), 1.54 (d, <i>J</i> =4.8 Hz, 3 H), 0.81 (td, <i>J</i> =7.3, 2.9 Hz, 3 H).
47	612.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ ppm 10.77 (br d, <i>J</i> =1.5 Hz, 1 H), 9.28 (d, <i>J</i> =4.2 Hz, 1 H), 7.78 (dd, <i>J</i> =9.1, 6.0 Hz, 1 H), 7.31 - 7.41 (m, 2 H), 7.03 (s, 1 H), 5.49 - 5.65 (m, 1 H), 4.88 - 5.02 (m, 1 H), 4.50 - 4.76 (m, 4 H), 4.05 (s, 6 H), 3.76 - 3.97 (m, 4 H), 3.25 - 3.39 (m, 1 H), 2.55 (br d, <i>J</i> =2.3 Hz, 1 H), 1.93 - 2.38 (m, 8 H), 0.74 (t, <i>J</i> =7.3 Hz, 3 H).
48	592.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.33 (s, 1 H), 8.05 - 8.12 (m, 1 H), 7.91 - 7.99 (m, 1 H), 7.55 - 7.62 (m, 1 H), 7.46 - 7.52 (m, 1 H), 7.34 - 7.43 (m, 1 H), 5.49 - 5.70 (m, 1 H), 4.61 - 4.75 (m, 3 H), 4.33 - 4.44 (m, 1 H), 3.83 - 4.13 (m, 3 H), 3.58 - 3.71 (m, 1 H), 3.41 - 3.54 (m, 2 H), 2.11 - 2.81 (m, 9 H), 1.76 - 1.94 (m, 3 H), 1.32 (s, 3 H), 0.79 - 0.91 (m, 3 H).
49	582.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.36 (s, 1 H), 8.09 - 8.22 (m, 1 H), 7.87 - 7.97 (m, 1 H), 7.67 - 7.77 (m, 2 H), 7.50 - 7.62 (m, 1 H), 5.49 - 5.70 (m, 1 H), 4.65 - 4.76 (m, 3 H), 4.35 - 4.45 (m, 1 H), 3.83 - 4.14 (m, 3 H), 3.62 - 3.71 (m, 1 H), 3.42 - 3.57 (m, 2 H), 2.55 - 2.83 (m, 2 H), 2.32 - 2.50 (m, 3 H), 2.12 - 2.28 (m, 2 H), 1.76 - 1.95 (m, 3 H), 1.28 - 1.37 (m, 3 H).
50	588.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.20 - 9.38 (m, 1 H), 8.10 - 8.21 (m, 2 H), 7.66 - 7.76 (m, 2 H), 7.43 - 7.54 (m, 1 H), 5.50 - 5.69 (m, 1 H), 4.65 - 4.77 (m, 3 H), 4.34 - 4.48 (m, 1 H), 3.82 - 4.11 (m, 3 H), 3.35 - 3.75 (m, 4 H), 2.54 - 2.81 (m, 2 H), 2.31 - 2.52 (m, 3 H), 2.11 - 2.28 (m, 2 H), 1.72 - 1.94 (m, 3 H), 1.29 (s, 3 H).
51	606.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.22 - 9.31 (m, 1 H), 7.64 - 7.76 (m, 1 H), 7.32 - 7.37 (m, 1 H), 7.23 - 7.31 (m, 1 H), 7.03 - 7.11 (m, 1 H), 5.48 - 5.70 (m, 1 H), 5.01 - 5.16 (m, 1 H), 4.62 - 4.75 (m, 2 H), 3.80 - 4.22 (m, 5 H), 3.58 - 3.76 (m, 1 H), 3.44 - 3.56 (m, 1

Ex. #	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
		H), 2.31 - 2.98 (m, 7 H), 1.98 - 2.29 (m, 4 H), 1.80 - 1.93 (m, 1 H), 1.54 - 1.77 (m, 1 H), 0.75 - 0.89 (m, 3 H).
52	604.1	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.10 - 9.35 (m, 1H), 7.82 - 7.96 (m, 1 H), 7.39 (d, <i>J</i> =2.5 Hz, 2 H), 7.22 - 7.29 (m, 1 H), 5.48 - 5.68 (m, 1 H), 4.60 - 4.80 (m, 3 H), 4.27 - 4.48 (m, 1 H), 3.85 - 4.15 (m, 3 H), 3.60 - 3.76 (m, 1 H), 3.36 - 3.59 (m, 3 H), 2.66 (s, 2 H), 2.37 (br s, 3 H), 2.10 - 2.27 (m, 2 H), 1.85 (br d, <i>J</i> =3.9 Hz, 3 H), 1.31 (d, <i>J</i> =19.5 Hz, 3 H).
53	608.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.31 (s, 1 H), 7.70 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.28 (t, <i>J</i> =9.4 Hz, 1 H), 7.08 (d, <i>J</i> =2.5 Hz, 1 H), 5.39 - 5.67 (m, 1 H), 4.79 - 4.83 (m, 2 H), 4.57 - 4.68 (m, 1 H), 4.29 - 4.43 (m, 1 H), 3.97 - 4.13 (m, 1 H), 3.42 - 3.79 (m, 5 H), 2.67 (s, 1 H), 2.50 (br d, <i>J</i> =4.0 Hz, 3 H), 2.10 - 2.34 (m, 5 H), 1.72 - 1.94 (m, 3 H), 1.32 (d, <i>J</i> =8.4 Hz, 3 H), 0.76 - 0.90 (m, 3 H).
54	617.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.25 (s, 1 H), 7.66 - 7.76 (m, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.23 - 7.32 (m, 1 H), 7.02 - 7.11 (m, 1 H), 5.49 - 5.72 (m, 1 H), 4.72 (br d, <i>J</i> =19.5 Hz, 2 H), 4.27 - 4.44 (m, 2 H), 4.13 - 4.25 (m, 1 H), 3.84 - 4.13 (m, 4 H), 3.44 - 3.57 (m, 1 H), 3.19 - 3.29 (m, 1 H), 2.68 (s, 2 H), 2.28 - 2.54 (m, 7 H), 2.11 - 2.26 (m, 3 H), 1.99 - 2.08 (m, 2 H), 0.81 (t, <i>J</i> =7.4 Hz, 3 H).
55	617.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.25 (s, 1 H), 7.67 - 7.74 (m, 1 H), 7.34 (d, <i>J</i> =2.5 Hz, 1 H), 7.23 - 7.31 (m, 1 H), 7.06 - 7.12 (m, 1 H), 5.47 - 5.70 (m, 1 H), 4.64 - 4.79 (m, 2 H), 4.28 - 4.45 (m, 2 H), 4.13 - 4.24 (m, 1 H), 3.85 - 4.13 (m, 4 H), 3.45 - 3.55 (m, 1 H), 3.21 - 3.28 (m, 1 H), 2.68 (s, 2 H), 2.40 (br d, <i>J</i> =6.0 Hz, 7 H), 2.13 - 2.27 (m, 3 H), 2.00 - 2.11 (m, 2 H), 1.79 - 1.94 (m, 1 H), 0.77 - 0.86 (m, 3 H).
56	614.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.31 (d, <i>J</i> =1.7 Hz, 1 H), 7.79 - 7.89 (m, 1 H), 7.38 - 7.48 (m, 2 H), 7.22 - 7.27 (m, 1 H), 5.49 - 5.69 (m, 1 H), 4.61 - 4.76 (m, 3 H), 4.33 - 4.44 (m, 1 H), 3.82 - 4.12 (m, 3 H), 3.59 - 3.70 (m, 1 H), 3.41 - 3.54 (m, 2 H), 2.54 - 2.82 (m, 2 H), 2.31 - 2.50 (m, 3 H), 2.12 - 2.27 (m, 2 H), 1.78 - 1.94 (m, 3 H), 1.33 (d, <i>J</i> =7.3 Hz, 3 H).

Ex. #	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
57	580.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.32 (d, <i>J</i> =2.1 Hz, 1 H), 7.63 (d, <i>J</i> =8.2 Hz, 1 H), 7.39 - 7.46 (m, 1 H), 7.37 (s, 1 H), 7.18 - 7.24 (m, 1 H), 6.90 - 6.99 (m, 1 H), 5.44 - 5.70 (m, 1 H), 4.62 - 4.77 (m, 3 H), 4.33 - 4.43 (m, 1 H), 3.82 - 4.12 (m, 3 H), 3.60 - 3.72 (m, 1 H), 3.39 - 3.57 (m, 2 H), 2.53 - 2.84 (m, 2 H), 2.29 - 2.51 (m, 3 H), 2.09 - 2.27 (m, 2 H), 1.74 - 1.94 (m, 3 H), 1.33 (d, <i>J</i> =3.8 Hz, 3 H).
58	590.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.31 (d, <i>J</i> =6.3 Hz, 1 H), 7.62 - 7.70 (m, 1 H), 7.35 - 7.43 (m, 1 H), 7.26 - 7.35 (m, 1 H), 7.14 - 7.22 (m, 1 H), 6.99 - 7.08 (m, 1 H), 5.42 - 5.73 (m, 1 H), 4.59 - 4.75 (m, 3 H), 4.32 - 4.43 (m, 1 H), 3.82 - 4.13 (m, 3 H), 3.56 - 3.73 (m, 1 H), 3.42 - 3.54 (m, 2 H), 2.49 - 2.85 (m, 2 H), 2.09 - 2.49 (m, 7 H), 1.76 - 1.94 (m, 3 H), 1.33 (d, <i>J</i> =9.0 Hz, 3 H), 0.86 - 0.97 (m, 3 H).
59	598.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.34 (s, 1 H), 7.59 - 7.69 (m, 1 H), 7.37 (s, 2 H), 7.24 - 7.32 (m, 1 H), 5.48 - 5.69 (m, 1 H), 4.64 - 4.75 (m, 3 H), 4.35 - 4.43 (m, 1 H), 3.82 - 4.13 (m, 3 H), 3.62 - 3.71 (m, 1 H), 3.41 - 3.56 (m, 2 H), 2.52 - 2.81 (m, 2 H), 2.30 - 2.51 (m, 3 H), 2.09 - 2.27 (m, 2 H), 1.75 - 1.94 (m, 3 H), 1.33 (d, <i>J</i> =2.3 Hz, 3 H).
60	562.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.37 (s, 1 H), 7.76 - 7.84 (m, 1 H), 7.51 - 7.60 (m, 1 H), 7.42 - 7.50 (m, 1 H), 7.30 - 7.35 (m, 1 H), 7.27 (s, 2 H), 5.49 - 5.73 (m, 1 H), 4.64 - 4.76 (m, 3 H), 4.36 - 4.44 (m, 1 H), 3.83 - 4.14 (m, 3 H), 3.64 - 3.73 (m, 1 H), 3.40 - 3.55 (m, 2 H), 2.55 - 2.83 (m, 2 H), 2.31 - 2.51 (m, 3 H), 2.12 - 2.27 (m, 2 H), 1.77 - 1.95 (m, 3 H), 1.33 (s, 3 H).
61	619.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.38 (d, <i>J</i> =3.3 Hz, 1 H), 7.66 - 7.75 (m, 1 H), 7.32 - 7.37 (m, 1 H), 7.23 - 7.31 (m, 1 H), 7.03 - 7.11 (m, 1 H), 5.47 - 5.72 (m, 1 H), 4.70 (s, 2 H), 4.47 - 4.64 (m, 2 H), 4.26 - 4.38 (m, 1 H), 3.81 - 4.14 (m, 4 H), 3.68 - 3.78 (m, 1 H), 3.35 - 3.55 (m, 4 H), 2.54 - 2.85 (m, 2 H), 2.32 - 2.54 (m, 4 H), 2.11 - 2.27 (m, 2 H), 0.82 (s, 3 H).
62	620.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.23 (s, 1 H), 7.66 - 7.76 (m, 1 H), 7.34 (d, <i>J</i> =2.5 Hz, 1 H), 7.24 - 7.31 (m, 1 H), 7.03 - 7.13 (m, 1 H), 5.49 - 5.70 (m, 1 H), 4.64 - 4.76 (m, 2 H), 4.29 - 4.40 (m, 1 H), 4.16 - 4.27 (m, 2 H), 3.84 - 4.13 (m, 5 H), 3.72 - 3.84 (m, 2 H), 3.43 - 3.54 (m, 1 H), 2.54 - 2.82 (m, 3 H), 2.32 - 2.54 (m, 4 H), 2.09 - 2.32 (m, 5 H), 1.72 - 1.84 (m, 1 H), 0.82 (t, <i>J</i> =7.4 Hz, 3 H).

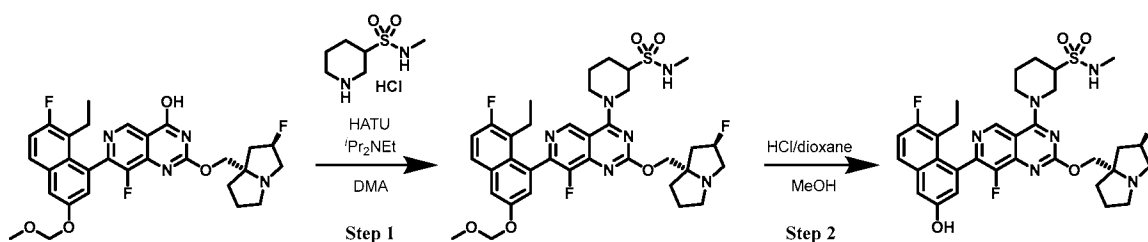
Ex. #	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
63	633.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.16 (d, <i>J</i> =1.7 Hz, 1 H), 7.68 - 7.75 (m, 1 H), 7.34 (d, <i>J</i> =2.5 Hz, 1 H), 7.22 - 7.31 (m, 1 H), 7.03 - 7.11 (m, 1 H), 5.50 - 5.70 (m, 2 H), 4.65 - 4.77 (m, 2 H), 4.39 - 4.49 (m, 1 H), 3.79 - 4.13 (m, 5 H), 3.42 - 3.57 (m, 1 H), 2.56 - 2.95 (m, 4 H), 2.42 - 2.55 (m, 2 H), 2.31 - 2.42 (m, 2 H), 2.15 - 2.29 (m, 2 H), 1.88 - 2.14 (m, 3 H), 1.76 - 1.88 (m, 1 H), 0.77 - 0.87 (m, 3 H).
64	635.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.18 - 9.30 (m, 1 H), 7.63 - 7.76 (m, 1 H), 7.34 (d, <i>J</i> =2.5 Hz, 1 H), 7.22 - 7.30 (m, 1 H), 7.05 - 7.11 (m, 1 H), 5.45 - 5.70 (m, 1 H), 5.12 - 5.27 (m, 1 H), 4.83 - 4.95 (m, 1 H), 4.64 - 4.75 (m, 2 H), 3.81 - 4.13 (m, 4 H), 3.43 - 3.56 (m, 1 H), 2.55 - 2.88 (m, 3 H), 2.10 - 2.54 (m, 8 H), 1.92 - 2.04 (m, 1 H), 1.66 - 1.78 (m, 1 H), 1.50 - 1.60 (m, 3 H), 0.74 - 0.88 (m, 3 H).
65	622.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.37 (d, <i>J</i> =8.5 Hz, 1 H), 7.70 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.28 (t, <i>J</i> =9.4 Hz, 1 H), 7.07 - 7.12 (m, 1 H), 5.46 - 5.70 (m, 1 H), 4.62 - 4.77 (m, 3 H), 4.44 (br dd, <i>J</i> =20.0, 13.5 Hz, 1 H), 3.81 - 4.15 (m, 3 H), 3.35 - 3.65 (m, 3 H), 2.56 - 2.87 (m, 2 H), 2.29 - 2.51 (m, 4 H), 2.13 - 2.29 (m, 3 H), 1.75 - 1.93 (m, 3 H), 1.56 - 1.69 (m, 2 H), 0.97 - 1.07 (m, 3 H), 0.83 (br t, <i>J</i> =7.3 Hz, 3 H).
66	622.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.22 (s, 1 H), 7.70 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.27 (t, <i>J</i> =9.4 Hz, 1 H), 7.08 (dd, <i>J</i> =4.4, 2.7 Hz, 1 H), 5.44 - 5.72 (m, 1 H), 4.61 - 4.77 (m, 3 H), 3.78 - 4.27 (m, 6 H), 3.45 - 3.61 (m, 2 H), 3.35 - 3.41 (m, 1 H), 2.56 - 2.84 (m, 2 H), 2.33 - 2.51 (m, 4 H), 2.22 (dtd, <i>J</i> =14.4, 7.0, 7.0, 3.1 Hz, 2 H), 1.87 - 2.01 (m, 2 H), 1.69 - 1.81 (m, 1 H), 1.54 - 1.64 (m, 1 H), 0.95 - 1.12 (m, 3 H), 0.78 - 0.87 (m, 3 H).
67	622.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.23 (s, 1 H), 7.70 (dd, <i>J</i> =9.1, 5.7 Hz, 1 H), 7.25 - 7.35 (m, 2 H), 7.07 - 7.12 (m, 1 H), 5.48 - 5.72 (m, 1 H), 4.61 - 4.77 (m, 3 H), 4.12 - 4.21 (m, 1 H), 3.84 - 4.09 (m, 5 H), 3.45 - 3.65 (m, 2 H), 3.35 - 3.40 (m, 1 H), 2.56 - 2.80 (m, 2 H), 2.33 - 2.51 (m, 4 H), 2.14 - 2.29 (m, 2 H), 1.86 - 2.01 (m, 2 H), 1.68 - 1.81 (m, 1 H), 1.55 - 1.64 (m, 1 H), 0.97 - 1.15 (m, 3 H), 0.78 - 0.88 (m, 3 H).
68	635.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.22 (dd, <i>J</i> =11.7, 2.3 Hz, 1 H), 7.70 (dd, <i>J</i> =8.0, 5.7 Hz, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.27 (t, <i>J</i> =9.6 Hz, 1 H), 7.09 (t, <i>J</i> =2.6 Hz, 1 H), 5.46 - 5.76 (m, 1 H), 4.81 - 4.90 (m, 1 H), 4.64 - 4.73 (m, 2 H), 4.48 - 4.61 (m, 1 H), 3.81 - 4.15 (m, 3 H), 3.46 - 3.65 (m, 3 H), 2.55 - 2.84 (m, 2 H), 2.16 - 2.51 (m, 7 H), 1.79 - 1.97 (m, 3 H), 1.28 (s, 3 H), 0.77 - 0.89 (m, 3 H).

Ex. #	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
69	616.3	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄): δ ppm 8.86 - 9.23 (m, 1 H), 7.66 (d, <i>J</i> =7.3 Hz, 1 H), 7.36 - 7.44 (m, 1 H), 7.32 (s, 1 H), 7.16 - 7.23 (m, 1 H), 6.98 - 7.10 (m, 1 H), 5.45 - 5.70 (m, 1 H), 5.06 - 5.23 (m, 1 H), 4.57 - 4.77 (m, 4 H), 3.79 - 4.19 (m, 3 H), 3.44 - 3.57 (m, 1 H), 1.62 - 3.21 (m, 16 H), 1.35 (s, 2 H), 0.84 - 1.00 (m, 3 H).
70	634.3	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄): δ ppm 8.91 - 9.22 (m, 1 H), 7.71 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.34 (d, <i>J</i> =2.1 Hz, 1 H), 7.28 (t, <i>J</i> =9.4 Hz, 1 H), 7.02 - 7.14 (m, 1 H), 5.48 - 5.70 (m, 1 H), 4.79 - 5.24 (m, 2 H), 4.60 - 4.77 (m, 3 H), 3.82 - 4.21 (m, 3 H), 3.46 - 3.57 (m, 1 H), 1.65 - 2.81 (m, 16 H), 1.26 - 1.36 (m, 2 H), 0.76 - 0.90 (m, 3 H).
71	620.3	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄): δ ppm 9.31 - 9.58 (m, 1 H), 7.70 (dd, <i>J</i> =9.1, 5.7 Hz, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.28 (t, <i>J</i> =9.4 Hz, 1 H), 7.03 - 7.12 (m, 1 H), 5.49 - 5.69 (m, 1 H), 5.34 (br d, <i>J</i> =1.9 Hz, 1 H), 4.68 - 4.78 (m, 4 H), 3.87 - 4.30 (m, 4 H), 3.44 - 3.54 (m, 1 H), 2.55 - 2.93 (m, 3 H), 2.32 - 2.49 (m, 3 H), 2.12 - 2.29 (m, 2 H), 1.79 - 2.07 (m, 3 H), 1.45 - 1.71 (m, 4 H), 0.77 - 0.91 (m, 3 H).
72	604.3	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄): δ ppm 9.46 - 9.56 (m, 1 H), 9.24 - 9.51 (m, 1 H), 7.70 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.27 (t, <i>J</i> =9.4 Hz, 1 H), 7.01 - 7.14 (m, 1 H), 5.49 - 5.75 (m, 1 H), 5.18 (br s, 1 H), 4.84 (br d, <i>J</i> =15.3 Hz, 1 H), 4.39 - 4.77 (m, 2 H), 3.76 - 4.13 (m, 4 H), 3.41 - 3.53 (m, 1 H), 3.23 (br s, 1 H), 2.10 - 2.77 (m, 11 H), 0.70 - 0.90 (m, 3 H).
74	710.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄): δ ppm 9.29 (d, <i>J</i> =15.5 Hz, 1 H), 7.70 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.27 (t, <i>J</i> =9.3 Hz, 1 H), 7.05 - 7.10 (m, 1 H), 5.48 - 5.75 (m, 1 H), 4.90 - 4.99 (m, 1 H), 4.62 - 4.75 (m, 2 H), 4.39 - 4.61 (m, 2 H), 3.60 - 4.14 (m, 7 H), 3.46 - 3.55 (m, 3 H), 3.35 - 3.40 (m, 3 H), 2.31 - 2.88 (m, 6 H), 2.12 - 2.29 (m, 3 H), 1.99 - 2.10 (m, 1 H), 1.75 - 1.91 (m, 2 H), 0.78 - 0.90 (m, 3 H).
75	685.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄): δ ppm 9.15 (d, <i>J</i> =6.2 Hz, 1 H), 7.67 - 7.73 (m, 1 H), 7.34 (d, <i>J</i> =2.5 Hz, 1 H), 7.27 (t, <i>J</i> =9.4 Hz, 1 H), 7.07 (t, <i>J</i> =2.4 Hz, 1 H), 5.45 - 5.74 (m, 1 H), 4.92 (br d, <i>J</i> =13.2 Hz, 1 H), 4.68 - 4.77 (m, 2 H), 4.34 - 4.57 (m, 1 H), 3.61 - 4.13 (m, 5 H), 3.45 - 3.54 (m, 1 H), 2.98 (d, <i>J</i> =15.5 Hz, 3 H), 2.31 - 2.84 (m, 6 H), 1.98 - 2.30 (m, 4 H), 1.79 - 1.92 (m, 2 H), 1.53 (s, 3 H), 0.78 - 0.89 (m, 3 H).

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Ex. #	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
76	649.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.16 (d, <i>J</i> =2.5 Hz, 1 H), 7.70 (dd, <i>J</i> =8.4, 6.1 Hz, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.28 (t, <i>J</i> =9.3 Hz, 1 H), 7.06 - 7.14 (m, 1 H), 5.48 - 5.71 (m, 1 H), 4.94 - 5.19 (m, 1 H), 4.65 - 4.75 (m, 2 H), 4.39 (br dd, <i>J</i> =13.2, 4.8 Hz, 1 H), 3.76 - 4.14 (m, 5 H), 3.45 - 3.55 (m, 1 H), 2.59 - 2.82 (m, 2 H), 2.33 - 2.53 (m, 4 H), 2.06 - 2.28 (m, 4 H), 1.75 - 1.96 (m, 5 H), 1.46 (d, <i>J</i> =12.1 Hz, 3 H), 0.77 - 0.89 (m, 3 H).
77	665.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.17 (d, <i>J</i> =5.0 Hz, 1 H), 7.68 - 7.73 (m, 1 H), 7.34 (d, <i>J</i> =2.5 Hz, 1 H), 7.28 (t, <i>J</i> =9.4 Hz, 1 H), 7.08 (dd, <i>J</i> =5.6, 2.5 Hz, 1 H), 5.50 - 5.71 (m, 1 H), 4.89 - 5.07 (m, 1 H), 4.62 - 4.76 (m, 2 H), 4.47 (br d, <i>J</i> =12.8 Hz, 1 H), 3.79 - 4.13 (m, 4 H), 3.68 - 3.76 (m, 1 H), 3.41 - 3.54 (m, 4 H), 2.55 - 2.86 (m, 2 H), 2.34 - 2.53 (m, 4 H), 2.18 - 2.32 (m, 2 H), 2.05 - 2.15 (m, 2 H), 1.76 - 1.87 (m, 2 H), 1.40 (d, <i>J</i> =12.8 Hz, 3 H), 0.78 - 0.91 (m, 3 H).
78	651.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.23 (d, <i>J</i> =2.9 Hz, 1 H), 7.70 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.27 (t, <i>J</i> =9.4 Hz, 1 H), 7.08 (dd, <i>J</i> =9.6, 2.7 Hz, 1 H), 5.45 - 5.73 (m, 1 H), 4.97 (br d, <i>J</i> =10.5 Hz, 1 H), 4.62 - 4.77 (m, 2 H), 4.48 - 4.58 (m, 1 H), 3.80 - 4.15 (m, 4 H), 3.62 - 3.75 (m, 4 H), 3.46 - 3.59 (m, 1 H), 3.34 - 3.42 (m, 1 H), 2.33 - 2.88 (m, 6 H), 2.16 - 2.29 (m, 2 H), 2.08 - 2.16 (m, 1 H), 1.98 - 2.07 (m, 1 H), 1.69 - 1.84 (m, 2 H), 0.82 (dt, <i>J</i> =11.6, 7.4 Hz, 3 H).

1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-*N*-methylpiperidine-3-sulfonamide (Example 79)



5

Example 79

Step 1: 1-(7-(8-Ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-*N*-methylpiperidine-3-sulfonamide. An 8-mL vial was charged with 7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-

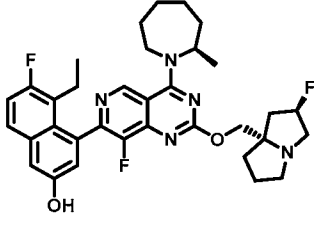
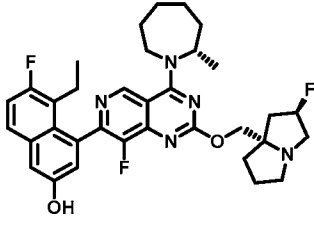
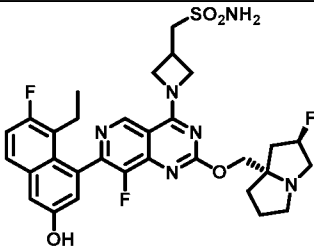
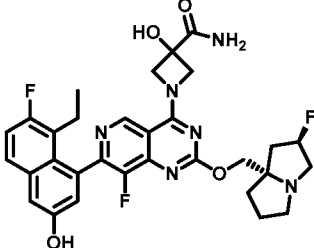
- 214 -

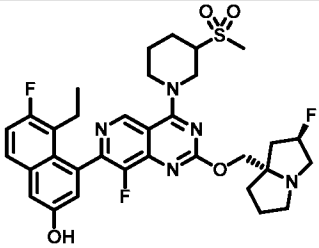
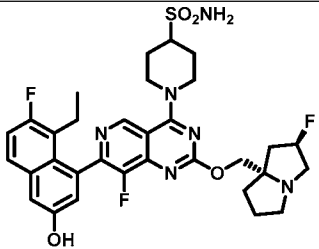
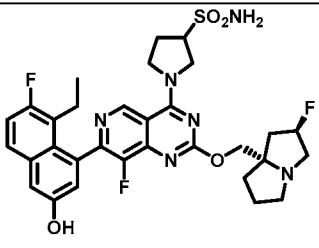
fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol (40 mg, 0.072 mmol), *N,N*-diisopropylethylamine (46 mg, 0.06 mL, 0.36 mmol) and *N,N*-dimethylacetamide (0.4 mL). The solution was stirred at rt for 10 min before HATU (0.11 g, 0.29 mmol) was added. After 10 min, a solution of *N*-methylpiperidine-3-sulfonamide (13 mg, 0.072 mmol, Enamine) in DMA was added to the vial and the reaction was stirred at rt for 30 min. The mixture was purified by column chromatography on silica gel, eluting with 0-50% 3:1 EtOAc/EtOH blend in heptane with 2% triethylamine additive to yield 1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-*N*-methylpiperidine-3-sulfonamide (47 mg, 0.066 mmol, 91 % yield). *m/z* (ESI): 715.2 (M+H)⁺.

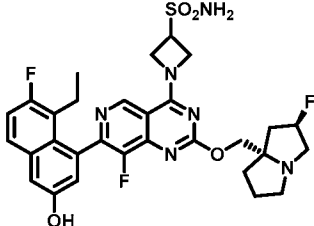
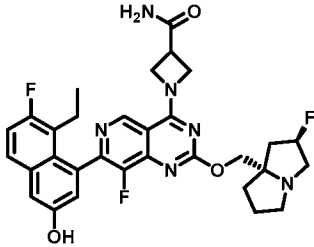
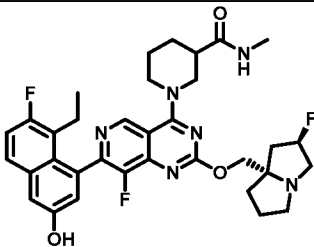
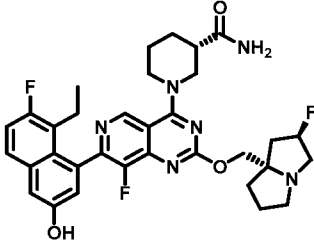
Step 2: 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-*N*-methylpiperidine-3-sulfonamide. 1-(7-(8-Ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-*N*-methylpiperidine-3-sulfonamide (47 mg, 0.066 mmol) was stirred in methanol (0.3 mL) and hydrogen chloride (4.0 M in dioxane, 0.3 mL, 1.32 mmol) at rt for 1 h. Volatiles were removed under reduced pressure. The crude product was purified by reverse phase HPLC to yield 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-*N*-methylpiperidine-3-sulfonamide as its TFA salt (16 mg, 0.020 mmol, 30 % yield). *m/z* (ESI): 671.0 (M+H)⁺. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 9.19 (s, 1 H), 7.66 - 7.75 (m, 1 H), 7.32 - 7.36 (m, 1 H), 7.23 - 7.31 (m, 1 H), 7.05 - 7.11 (m, 1 H), 5.50 - 5.70 (m, 1 H), 4.85 - 4.99 (m, 1 H), 4.78 - 4.83 (m, 1 H), 4.68 - 4.74 (m, 1 H), 4.44 - 4.60 (m, 1 H), 3.74 - 4.13 (m, 5 H), 3.55 - 3.65 (m, 1 H), 3.46 - 3.55 (m, 1 H), 2.80 (s, 3 H), 2.56 - 2.78 (m, 2 H), 2.31 - 2.53 (m, 5 H), 2.02 - 2.29 (m, 4 H), 1.76 - 1.96 (m, 1 H), 0.76 - 0.88 (m, 3 H).

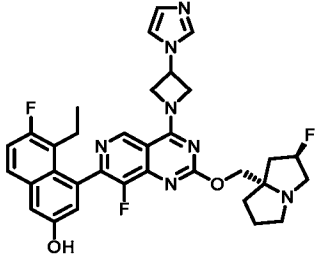
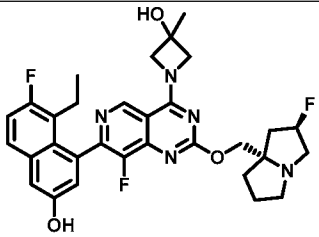
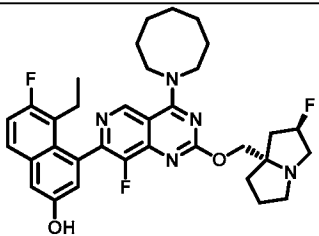
Table 9: Examples 80 to 147 and 176-177. prepared in an analogous manner to Example 79.

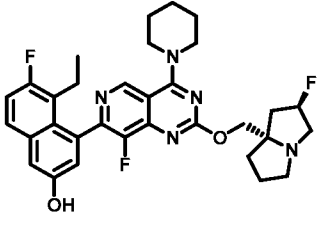
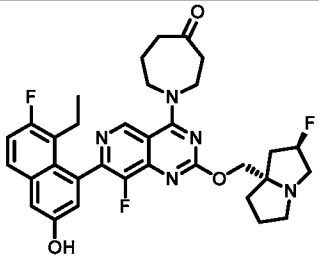
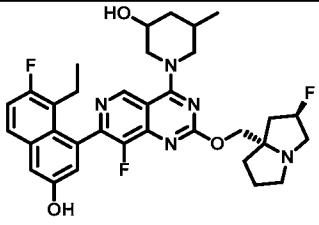
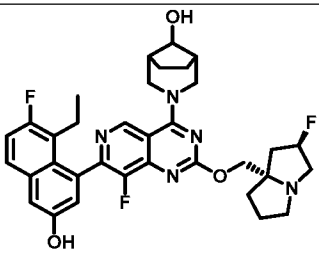
Ex.#	Structure	Name	Salt Form	Reagent	Method Change

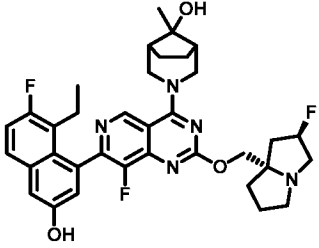
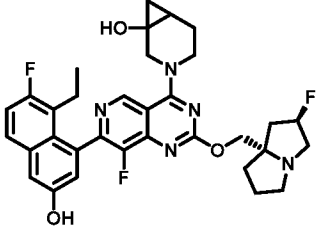
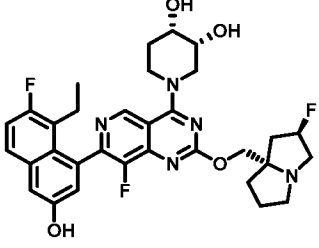
80		5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-((R)-2-methylazepan-1-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol	Bis(2,2,2-trifluoroacetate)	Step 1: (R)-2-methylazepan-1-yl hydrochloride (CAS#: 331994-00-4, Synnovator)	
81		5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-((S)-2-methylazepan-1-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol	Bis(2,2,2-trifluoroacetate)	Step 1: (S)-2-methylazepan-1-yl hydrochloride (CAS#: 2431997-40-7, Synnovator)	
82		(1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azetidin-3-yl)methanesulfonamide	2,2,2-trifluoroacetate	Step 1: (azetidin-3-yl)methanesulfonamide hydrochloride (CAS#: 2413904-31-9, Enamine)	
83		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido	2,2,2-trifluoroacetate	Step 1: 3-hydroxyazetidin-3-carboxamide trifluoroacetic acid (CAS#: 2044797-06-8, Enamine)	

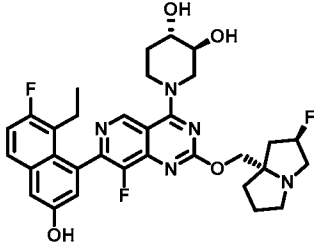
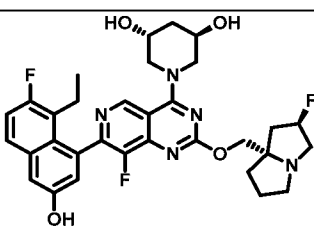
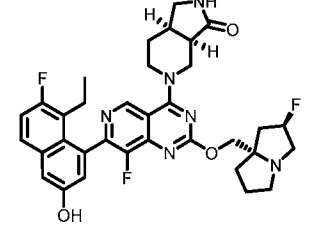
		[4,3- <i>d</i>]pyrimidin-4-yl)-3-hydroxyazetidine-3-carboxamide			
84		5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)-4-(3-(methylsulfonyl)piperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-7-yl)naphthalen-2-ol	2,2,2-trifluoroacetate	Step 1: 3-methanesulfonylpiperidine (CAS#: 290328-56-2, Enamine)	
85		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)piperidine-4-sulfonamide	2,2,2-trifluoroacetate	Step 1: piperidine-4-sulfonamide hydrochloride (CAS#: 1251923-46-2, Enamine)	
86		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)pyrrolidine-3-sulfonamide	2,2,2-trifluoroacetate	Step 1: 3-pyrrolidinesulfonamide (CAS#: 1208507-46-3, Enamine)	

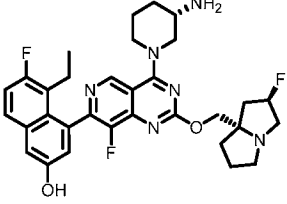
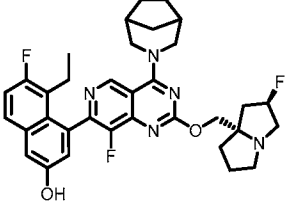
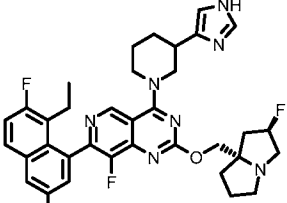
87		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azetidine-3-sulfonamide	2,2,2-trifluoroacetate	Step 1: 3-azetidinesulfonamide hydrochloride (CAS#: 1909318-76-8, Enamine)	
88		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azetidine-3-carboxamide	2,2,2-trifluoroacetate	Step 1: azetidine-3-carboxamide hydrochloride (CAS#: 124668-45-7, Combi-Blocks Inc.)	
89		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-N-methylpiperidine-3-carboxamide	2,2,2-trifluoroacetate	Step 1: N-methylpiperidine-3-carboxamide hydrochloride (CAS#: 475060-42-5, Enamine)	
90		(S)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido	2,2,2-trifluoroacetate	Step 1: (S)-piperidine-3-carboxylic acid amide (CAS#: 88495-55-0, Oakwood Products, Inc.)	

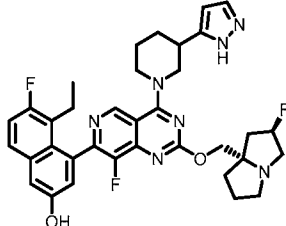
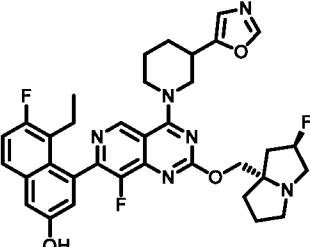
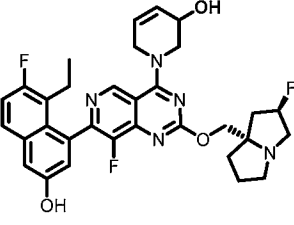
		[4,3- <i>d</i>]pyrimidin-4-yl)piperidine-3-carboxamide			
91		4-(4-(3-(1 <i>H</i> -Imidazol-1-yl)azetidin-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol	2,2,2-trifluoroacetate	Step 1: 1-(azetidin-3-yl)-1 <i>H</i> -imidazole dihydrochloride (CAS#: 153836-44-3, Enamine)	
92		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-3-methylazetidin-3-ol	2,2,2-trifluoroacetate	Step 1: 3-methylazetidin-3-ol hydrochloride (CAS#: 124668-46-8, Advanced ChemBlocks Inc.)	
93		4-(4-(Azocan-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol	Free base	Step 1: azocane (CAS#: 1121-92-2, Sigma-Aldrich Corporation)	The product was re-purified by column chromatography on silica gel, eluting with 0% to 100% (2 M NH ₃ in MeOH/DCM) in DCM

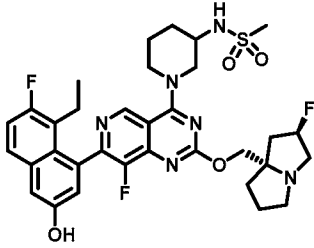
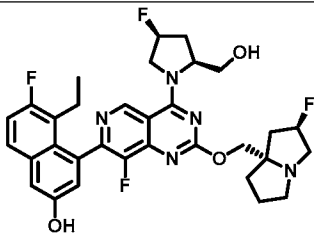
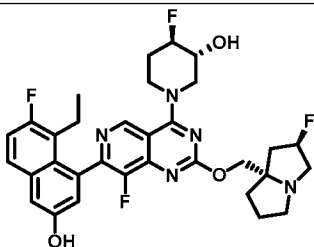
94		5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol	2,2,2-trifluoroacetate	Step 1: piperidine (CAS#: 110-89-4, Spectrum Chemicals & Laboratory Products)	
95		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-4-one	2,2,2-trifluoroacetate	Step 1: azepan-4-one hydrochloride (CAS#: 50492-22-3, Tyger Sci. Inc.)	
96		<i>rac</i> -(3R,5S)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5-methylpiperidin-3-ol	2,2,2-trifluoroacetate	Step 1: <i>rac</i> -(3R,5S)-5-methylpiperidin-3-ol hydrochloride (CAS#: 955028-53-2, ChemSpace)	
97		3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-	2,2,2-trifluoroacetate	Step 1: 3-azabicyclo[3.2.1]octan-8-ol (CAS#: 1331847-92-7, Aurum Pharmatech LLC)	

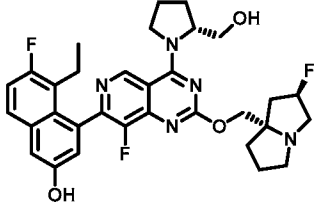
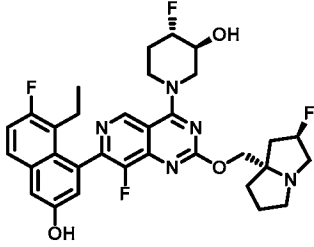
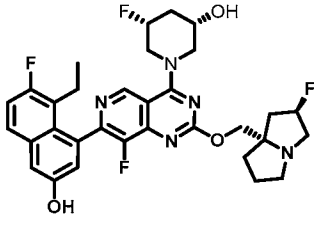
		4-yl)-3-azabicyclo[3.2.1]octan-8-ol			
98		3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-8-methyl-3-azabicyclo[3.2.1]octan-8-ol	2,2,2-trifluoroacetate	Step 1: 8-methyl-3-azabicyclo[3.2.1]octan-8-ol hydrochloride (CAS#: 1131846-59-3, Enamine)	
99		3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[4.1.0]heptan-1-ol	2,2,2-trifluoroacetate	Step 1: 3-azabicyclo[4.1.0]heptan-1-ol hydrochloride (CAS#: 1394042-85-3, Pharmablock, Inc.)	
100		<i>rel</i> -(3R,4S)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3,4-diol	2,2,2-trifluoroacetate	Step 1: <i>cis</i> -3,4-piperidinediol hydrochloride (CAS#: 443648-89-3, eNovation Chemicals LLC)	

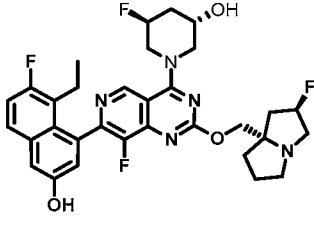
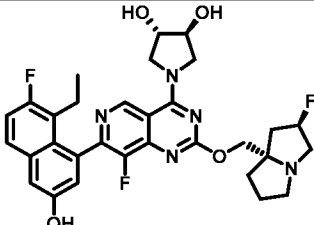
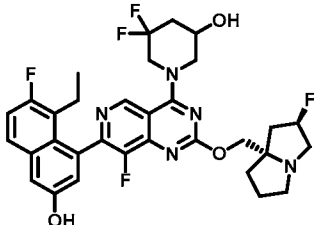
101		<i>rel</i> -(3 <i>S</i> ,4 <i>S</i>)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)piperidine-3,4-diol	2,2,2-trifluoroacetate	Step 1: <i>trans</i> -piperidine-3,4-diol hydrochloride (CAS#: 443648-97-3, eNovation Chemicals LLC)	
102		(3 <i>R</i> ,5 <i>R</i>)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)piperidine-3,5-diol	2,2,2-trifluoroacetate	Step 1: (3 <i>R</i> ,5 <i>R</i>)-piperidine-3,5-diol (CAS#: 1043449-04-2, ChemBridge)	None
103		<i>rel</i> -(3 <i>aR</i> ,7 <i>aR</i>)-5-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)octahydro-3 <i>H</i> -pyrrolo[3,4- <i>c</i>]pyridin-3-one	2,2,2-trifluoroacetate	Step 1: <i>rac</i> -(3 <i>aR</i> ,7 <i>aR</i>)-octahydro-1 <i>H</i> -pyrrolo[3,4- <i>c</i>]pyridin-3-one (CAS#: 868551-69-3, Enamine)	

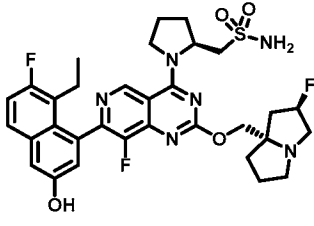
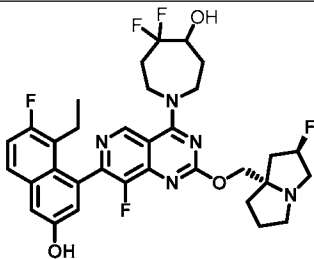
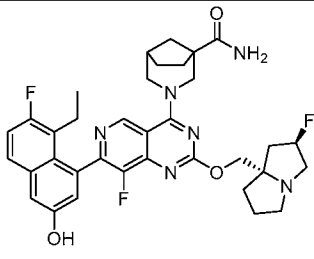
104		4-(4-((<i>S</i>)-3-Aminopiperidin-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol	bis(2,2,2-trifluoroacetate)	Step 1: (<i>S</i>)-3-Boc-aminopiperidine (CAS#: 216854-23-8, Aurum Pharmatech LLC)	Additional step similar to Example 44 after Step 1
105		4-(4-(3-Azabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol	2,2,2-trifluoroacetate	Step 1: 3-azabicyclo[3,2,1]octane hydrochloride (CAS#: 279-82-3, Ryan Scientific Inc.)	
106		4-(4-(3-(1 <i>H</i> -Imidazol-4-yl)piperidin-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol	bis(2,2,2-trifluoroacetate)	Step 1: 3-(1 <i>H</i> -imidazol-3-ium-4-yl)piperidin-1-ium dichloride (CAS#: 784080-46-2, Enamine)	

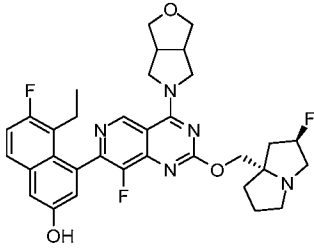
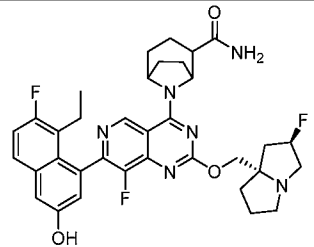
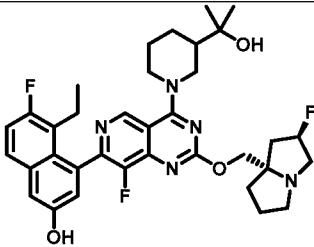
107		4-(4-(3-(1H-Pyrazol-5-yl)piperidin-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol	bis(2,2,2-trifluoroacetate)	Step 1: 3-(1H-pyrazol-5-yl)piperidine dichloride (CAS#: 774479-26-4, Enamine)	
108		5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(3-(oxazol-5-yl)piperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol	Free base	Step 1: 3-(1,3-oxazol-5-yl)piperidine dihydrochloride (CAS#: 1864062-33-8, Enamine)	After Step 2 , fractions were washed with aq. NaHCO ₃ to free base the product.
109		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,2,3,6-tetrahydropyridin-3-ol	bis(2,2,2-trifluoroacetate)	Step 1: 1,2,3,6-tetrahydropyridin-3-ol (CAS#: 84794-16-1, Aurum Pharmatech)	

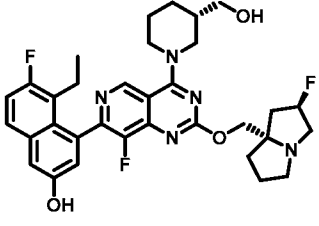
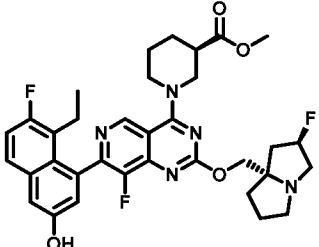
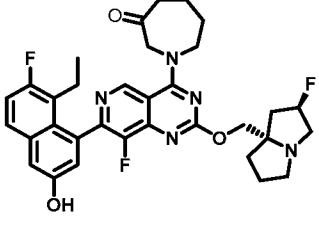
110		<i>N</i> -(1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide	Free base	Step 1: <i>N</i> -(3-piperidyl)methanesulfonamide (CAS#: 944068-21-7, AA Blocks)	After Step 2, purification was performed with 0.1% NH ₄ OH in H ₂ O and MeCN as mobile phase, XBridge column (19 x 100mm, 5 μm).
111		5-Ethyl-6-fluoro-4-(8-fluoro-4-((2 <i>S</i> ,4 <i>S</i>)-4-fluoro-2-(hydroxymethyl)pyrrolidin-1-yl)-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-7-yl)naphthalen-2-ol	2,2,2-trifluoroacetate	Step 1: (2 <i>S</i> ,4 <i>S</i>)-2-(((<i>tert</i> -butyldimethylsilyl)oxy)methyl)-4-fluoropyrrolidine (Intermediate F1)	Additional step analogous to Example 27 after Step 2 .
112		(3 <i>R</i> ,4 <i>R</i>)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-4-fluoropiperidin-3-ol	2,2,2-trifluoroacetate	Step 1: (3 <i>R</i> ,4 <i>R</i>)-4-fluoropiperidin-3-ol hydrochloride (CAS#: 2055390-10-6, J&W Pharmalab)	

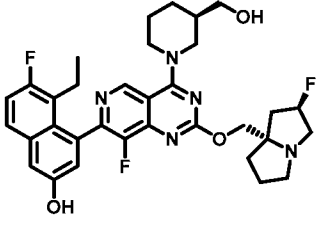
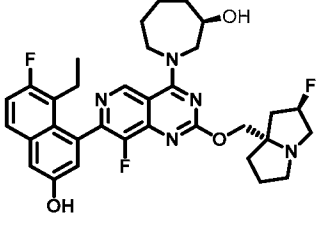
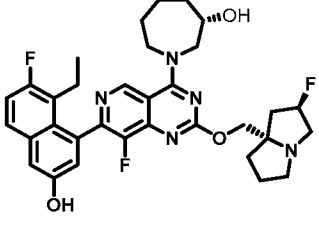
113		5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-((R)-2-(hydroxymethyl)pyrrolidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol	2,2,2-trifluoroacetate	Step 1: (R)-2-(((tert-butyl)dimethylsilyl)oxy)methylpyrrolidine (Intermediate F2)	Additional step analogous to Example 27 after Step 2 .
114		(3S,4S)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-4-fluoropiperidin-3-ol	Free base	Step 1: (3S,4S)-4-fluoropiperidin-3-ol hydrochloride (CAS#: 1523530-61-1, Combi Blocks)	After Step 2 , purification was performed with 0.1% formic acid in H ₂ O and MeCN as mobile phase, XSelect column (19 x 100 mm, 5 μm).
115		rac-(3S,5R)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5-fluoropiperidin-3-ol	2,2,2-trifluoroacetate	Step 1: rac-(3S,5S)-5-fluoropiperidin-3-ol hydrochloride (CAS#: 1955505-76-6, Enamine)	

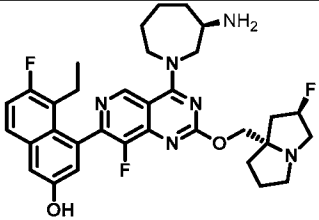
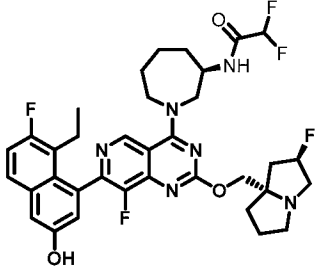
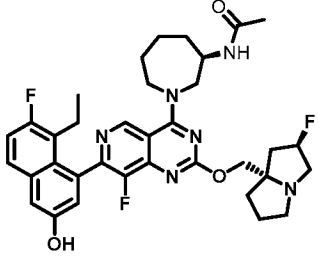
116		<i>rac</i> -(3 <i>S</i> ,5 <i>S</i>)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-5-fluoropiperidin-3-ol	2,2,2-trifluoroacetate	Step 1: <i>rac</i> -(3 <i>R</i> ,5 <i>R</i>)-5-fluoropiperidin-3-ol hydrochloride (CAS#: 195554-58-1, Enamine)	
117		(3 <i>S</i> ,4 <i>S</i>)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)pyrrolidine-3,4-diol	2,2,2-trifluoroacetate	Step 1: (3 <i>S</i> ,4 <i>S</i>)-pyrrolidine-3,4-diol (CAS#: 90481-32-6, Ambeed Inc)	
118		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-5,5-difluoropiperidin-3-ol	2,2,2-trifluoroacetate	Step 1: 5,5-difluoropiperidin-3-ol hydrochloride (CAS#: 1803584-46-4, Enamine)	

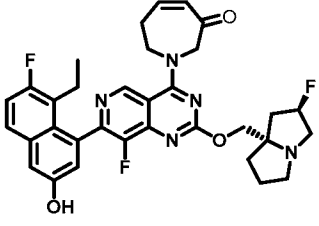
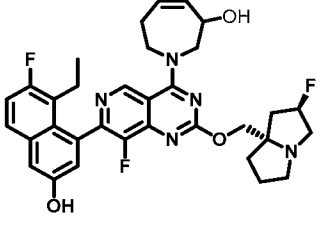
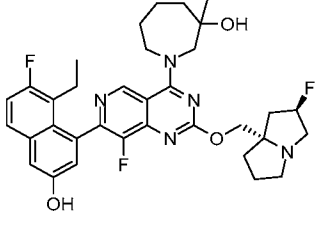
119		((S)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)pyrrolidin-2-yl)methanesulfonamide	2,2,2-trifluoroacetate	Step 1: [(2S)-pyrrolidin-2-yl]methanesulfonamide (CAS#: 1821827-86-4, Enamine)	
120		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5,5-difluoroazepan-4-ol	2,2,2-trifluoroacetate	Step 1: 5,5-difluoroazepan-4-ol hydrochloride (CAS#: 2172603-58-4, Enamine)	
121		3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octane-1-carboxamide	2,2,2-trifluoroacetate	Step 1: <i>rel</i> -(1S,5S)-8-azabicyclo[3.2.1]octane-2-carboxamide hydrochloride (Intermediate G3)	

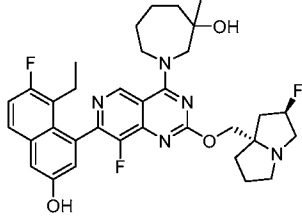
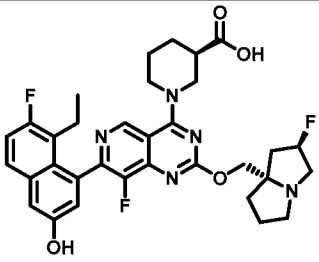
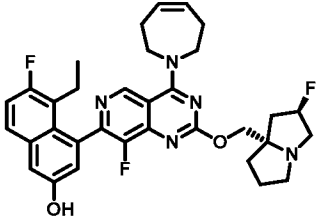
122		5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-((3aR,6aS)-tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol	2,2,2-trifluoroacetate	Step 1: hexahydro-1H-furo[3,4-c]pyrrole hydrochloride (CAS#: 60889-32-9, Aurum)	
123		<i>rac</i> -(1 <i>S</i> ,5 <i>S</i>)-8-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octane-2-carboxamide	bis(2,2,2-trifluoroacetate)	Step 1: <i>rel</i> -(1 <i>R</i> ,5 <i>R</i>)-3-azabicyclo[3.2.1]octane-1-carboxamide hydrochloride (Intermediate G2)	
124		5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(3-(2-hydroxypropan-2-yl)piperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol	2,2,2-trifluoroacetate	Step 1: 2-(piperidin-3-yl)propan-2-ol (CAS#: 252723-21-0, Chem-Bridge)	

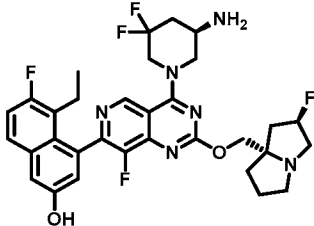
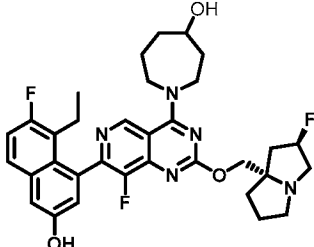
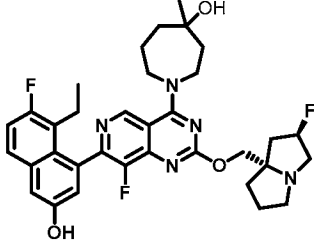
125		5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)-4-((<i>S</i>)-3-(hydroxymethyl)piperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-7-yl)naphthalen-2-ol	2,2,2-trifluoroacetate	Step 1: (3 <i>S</i>)-piperidin-3-ylmethanol (CAS#: 144539-77-5, Combi-Blocks Inc.)	
126		Methyl (<i>R</i>)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)piperidine-3-carboxylate	2,2,2-trifluoroacetate	Step 1: (<i>R</i>)-3-methylpiperidinecarboxylate (CAS#: 164323-85-7, Combi-Blocks Inc.)	Additional step after Step 1 . Procedure included below.
127		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)azepan-3-one	2,2,2-trifluoroacetate	Step 1: azepan-3-one hydrochloride (CAS#: 65326-54-7, Combi-Blocks Inc.)	

128		5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)-4-((<i>R</i>)-3-(hydroxymethyl)pyridin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-7-yl)naphthalen-2-ol	2,2,2-trifluoroacetate	Step 1: (<i>R</i>)-1- <i>N</i> -Boc-3-hydroxymethyl-piperidine (CAS#: 140695-85-8, AstaTech, Inc)	
129		(<i>R</i>)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)azepan-3-ol	2,2,2-trifluoroacetate	Step 1: (<i>R</i>)-azepan-3-ol hydrochloride (CAS#: 1956435-25-8, J&W Phamlab)	
130		(<i>S</i>)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)azepan-3-ol	2,2,2-trifluoroacetate	Step 1: (<i>S</i>)-azepan-3-ol hydrochloride (CAS#: 1956435-25-8, J&W Phamlab)	

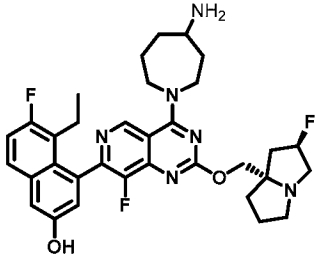
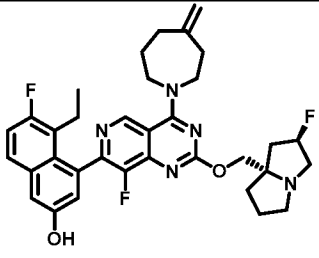
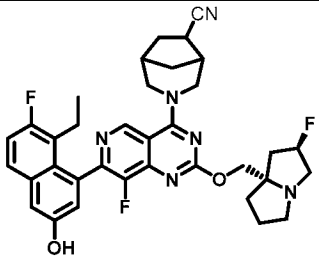
131		4-((<i>R</i>)-3-Aminoazepan-1-yl)-8-fluoro-2-(((<i>2R</i> , <i>7aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol	2,2,2-trifluoroacetate	Step 1: (<i>R</i>)- <i>tert</i> -butyl azepan-3-ylcarbamate (CAS#: 1354351-56-6, Combi-Blocks Inc.)	
132		<i>N</i> -((<i>R</i>)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((<i>2R</i> , <i>7aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)azepan-3-yl)-2,2-difluoroacetamide	2,2,2-trifluoroacetate	Step 1: (<i>R</i>)- <i>tert</i> -butyl azepan-3-ylcarbamate (CAS#: 1354351-56-6, Combi-Blocks Inc.)	Additional step after Step 2 . Procedure included below.
133		<i>N</i> -((<i>R</i>)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((<i>2R</i> , <i>7aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)azepan-3-yl)acetamide	2,2,2-trifluoroacetate	Step 1: (<i>R</i>)- <i>tert</i> -butyl azepan-3-ylcarbamate (CAS#: 1354351-56-6, Combi-Blocks Inc.)	Additional step after Step 2 analogous to Example 132 using acetyl chloride.

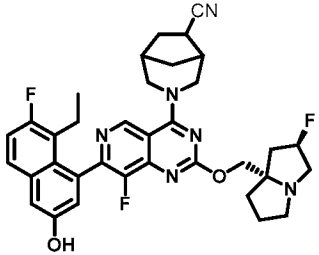
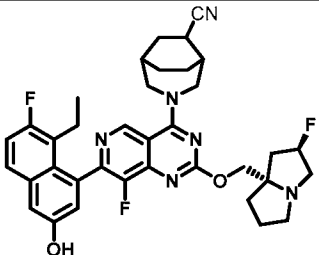
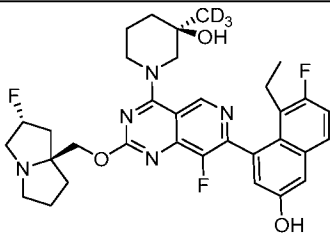
134		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,2,6,7-tetrahydro-3H-azepin-3-one	2,2,2-trifluoroacetate	Step 1: 1,2,6,7-tetrahydro-3H-azepin-3-one hydrochloride (Intermediate I)	
135		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,3,6,7-tetrahydro-1H-azepin-3-ol	2,2,2-trifluoroacetate	Step 1: 2,3,6,7-tetrahydro-1H-azepin-3-ol hydrochloride (Intermediate J)	
136		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylazepan-3-ol Isomer 1	2,2,2-trifluoroacetate	Step 1: 3-methylazepan-3-ol hydrochloride (Intermediate H1)	

137		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylazepan-3-ol Isomer 2	2,2,2-trifluoroacetate	Step 1: 3-methylazepan-3-ol hydrochloride (Intermediate H2)	
138		(R)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3-carboxylic acid	2,2,2-trifluoroacetate	Step 1: (R)-3-methylpiperidinecarboxylate (CAS#: 164323-85-7, Combi-Blocks Inc.)	Additional step after Step 1 . Details included below.
139		5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,3,6,7-tetrahydro-1H-azepin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol	2,2,2-trifluoroacetate	Step 1: 2,3,6,7-tetrahydro-1H-azepine hydrochloride (Intermediate K)	

140		4-((<i>R</i>)-5-Amino-3,3-difluoropiperidin-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol	Bis(2,2,2-trifluoroacetate)	Step 1: <i>tert</i> -butyl (<i>R</i>)-(5,5-difluoropiperidin-3-yl)carbamate (CAS#: 2089320-98-7, Advanced ChemBlocks Inc.)	Additional step after Step 1 similar to Example 44 .
141		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)azepan-4-ol	2,2,2-trifluoroacetate	Step 1: azepan-4-one hydrochloride (CAS#: 50492-22-3, Tyger Sci. Inc.)	Additional step after Step 1 . Procedure included below.
142		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-4-methylazepan-4-ol	2,2,2-trifluoroacetate	Step 1: azepan-4-one hydrochloride (CAS#: 50492-22-3, Tyger Sci. Inc.)	Additional step after Step 1 . Procedure included below.

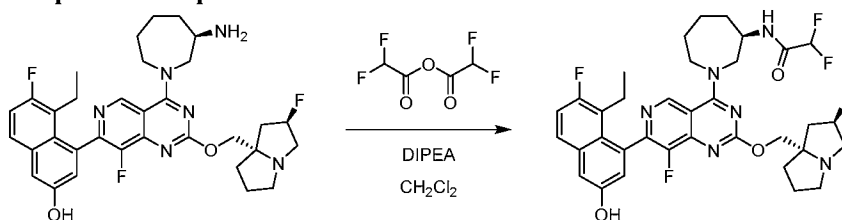
- 235 -

143		4-(4-(4-Aminoazepan-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol	2,2,2-trifluoroacetate	Step 1: azepan-4-one hydrochloride (CAS#: 50492-22-3, Tyger Sci. Inc.)	Additional step after Step 1 . Procedure included below.
144		5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)-4-(4-methyleneazepan-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-7-yl)naphthalen-2-ol	2,2,2-trifluoroacetate	Step 1: azepan-4-one hydrochloride (CAS#: 50492-22-3, Tyger Sci. Inc.)	Additional step after Step 1 . Procedure included below.
145		3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octane-6-carbonitrile Isomer Mix 1	2,2,2-trifluoroacetate	Step 1: 3-azabicyclo[3.2.1]octane-6-carbonitrile hydrochloride (Intermediate L2)	

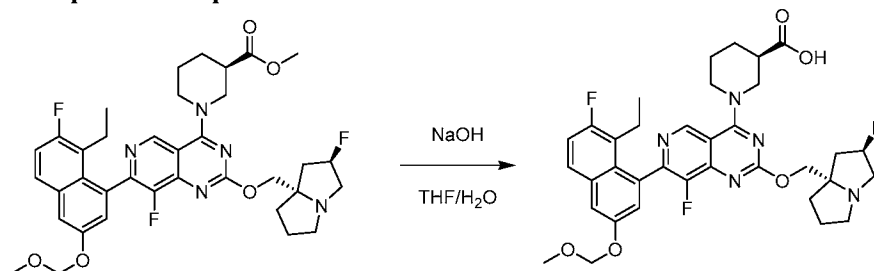
146		3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octane-6-carbonitrile Isomer Mix 2	2,2,2-trifluoroacetate	Step 1: 3-azabicyclo[3.2.1]octane-6-carbonitrile hydrochloride (Intermediate L2)	
147		3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.2]nonane-6-carbonitrile	2,2,2-trifluoroacetate	Step 1: 8-oxa-3-azabicyclo[3.2.1]octane-6-carbonitrile hydrochloride (Intermediate L1)	
176		(R)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-(methyl-d ₃)piperidin-3-ol	Free base	Step 1: Intermediate Q1	

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177		(S)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-(methyl-d3)piperidin-3-ol	Free base	Step 1: Intermediate Q2	

Additional step for Example 132

To a 10-mL round-bottomed flask was added 4-(4-((*R*)-3-aminoazepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol (30 mg, 0.05 mmol) and DIPEA (32 mg, 43 μ L, 0.25 mmol, Sigma-Aldrich Corporation) in DCM (0.5 mL). The mixture was cooled to 0 °C before difluoroacetic anhydride (13 mg, 13 μ L, 0.07 mmol, Oakwood Products, Inc.) was added. The reaction was stirred at rt for 2 h. The reaction mixture was diluted with brine (5 mL) and extracted with EtOAc (3 $\times$ 5mL). The organic layer was concentrated in vacuo. The material was further purified by reverse phase HPLC to give the desired product as TFA salt as off-white solid (12 mg, 0.02 mmol, 30% yield).

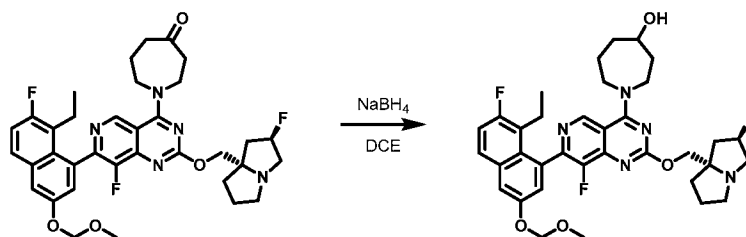
Additional step for Example 138

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To an 8-mL vial was added methyl (*R*)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-carboxylate (10 mg, 0.02 mmol) and 2 N sodium hydroxide (22 μ L, 0.04 mmol, Sigma-Aldrich) and THF (74 μ L). The reaction was stirred at rt overnight. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (2 $\times$ 10 mL). The organic extract was washed with brine (5 mL) and dried over MgSO₄. The solution was filtered and concentrated in vacuo to give the crude material, which was used in the next step without purification and determining yield.

m/z (ESI): 666.2 (M+H)⁺.

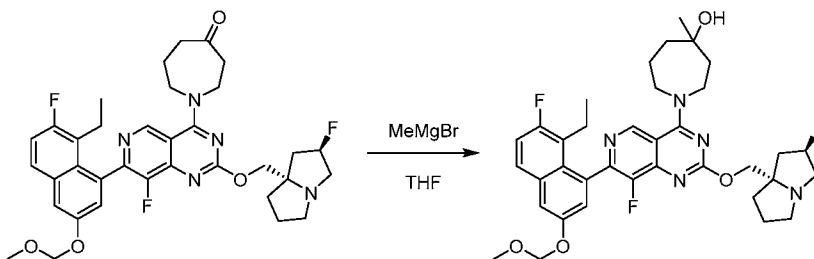
Additional step for Example 141



To a 10-mL round-bottomed flask was added 1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-4-one (30 mg, 0.046 mmol) and sodium borohydride (5.2 mg, 0.14 mmol) in DCE (0.23 mL). A small amount of MeOH was added and the reaction was stirred at rt for 1 h. The crude material was absorbed onto a plug of silica gel and purified by column chromatography on silica gel, eluting with a gradient of 0-20% 2 M NH₃·MeOH in CH₂Cl₂, to provide 1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-4-ol as white solid. *m/z* (ESI): 652.2 (M+H)⁺.

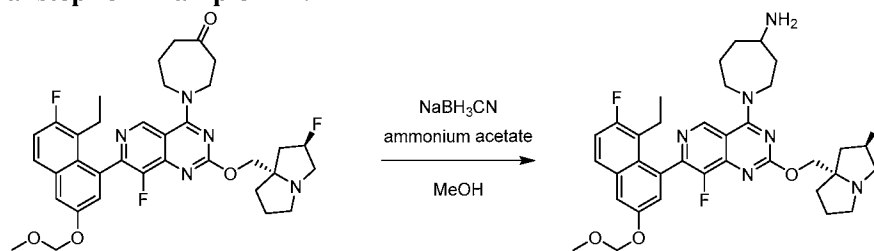
Additional step for Example 142:

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To a 10-mL round-bottomed flask was added 1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-4-one (25 mg, 0.04 mmol) and THF (0.8 mL). The mixture was cooled to 0 °C before methylmagnesium bromide solution in THF (39 μ L, 0.12 mmol, Sigma-Aldrich Corporation) was added. The reaction was stirred for 1 h. The crude material was quenched with small amount of water and then purified by column chromatography on silica gel, eluting with a gradient of 0 - 20% (2 M $\text{NH}_3 \cdot \text{MeOH}$ in CH_2Cl_2) in CH_2Cl_2 to provide 1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-4-methylazepan-4-ol as white solid, which was used directly in the next step without further manipulation and determining yield. m/z (ESI): 666.2 ($\text{M}+\text{H}$)⁺.

Additional step for Example 143:

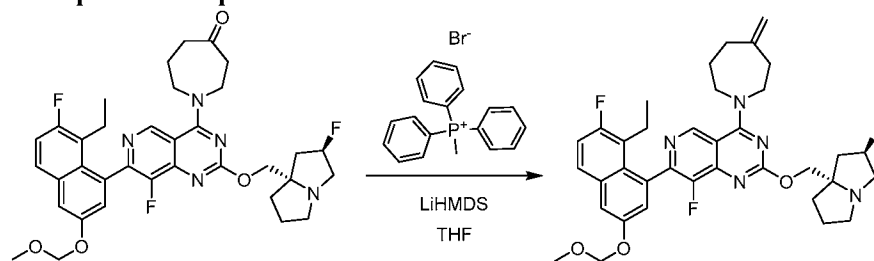


To a 10-mL round-bottomed flask was added 1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-4-methylazepan-4-ol (20 mg, 0.03 mmol), ammonium acetate (24 mg, 0.31 mmol, Oakwood Products, Inc.) and methanol (0.6 mL). To the mixture was added sodium cyanoborohydride (4 mg, 0.06 mmol, Oakwood Products, Inc.). The reaction was then stirred at rt overnight. The reaction mixture was diluted with brine (5 mL) and extracted with EtOAc (3 $\times$ 5 mL). The organic layer was concentrated in vacuo to give 1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-4-methylazepan-4-amine as white solid.

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(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-4-amine, which was used directly in the next step, without further purification and determining yield. *m/z* (ESI): 651.2 (M+H)⁺.

5 Additional Step for Example 144



To a 25-mL round-bottomed flask was added methyltriphenylphosphonium bromide in THF (41 mg, 0.12 mmol, Sigma-Aldrich Corporation) and THF (0.4 mL). LiHMDS in (1.0 M in THF, 0.1 mL, 0.11 mmol, Sigma-Aldrich Corporation) was added. The reaction was stirred for 1 h. 1-(7-(8-Ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-4-one (25 mg, 0.04 mmol) was added and the reaction was stirred at rt for 3 h. The reaction mixture was diluted with brine (5 mL) and extracted with EtOAc (2 × 5 mL). The organic extract was concentrated in vacuo. The crude material was purified by column chromatography on silica gel column, eluting with a gradient of 0 -100% 3:1 EtOAc/EtOH (with 1% TEA) in heptane to provide 7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(4-methyleneazepan-1-yl)pyrido[4,3-*d*]pyrimidine, which was used directly in the next step without further purification and determining yield. *m/z* (ESI): 648.2 (M+H)⁺.

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Table 10: Analytical Data for Examples 80 to 147 and 176-177.

Ex.#	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
80	606.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.39 (br d, <i>J</i> =3.3 Hz, 1 H), 6.89 (br dd, <i>J</i> =8.8, 5.9 Hz, 1 H), 6.39 - 6.59 (m, 2 H), 6.21 - 6.34 (m, 1 H), 4.65 - 4.88 (m, 1 H), 4.10 - 4.21 (m, 1 H), 3.77 - 3.87 (m, 2 H), 3.43 - 3.63 (m, 1 H), 2.99 - 3.32 (m, 3 H), 2.76 - 2.96 (m, 1 H), 2.63 - 2.74 (m, 1 H), 1.75 - 1.99 (m, 2 H), 1.29 - 1.73 (m, 8 H), 1.07 - 1.23 (m, 3 H), 0.89 - 1.02 (m, 1 H), 0.45 - 0.83 (m, 5 H), -0.09 - 0.07 (m, 3 H).
81	606.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.19 (d, <i>J</i> =3.3 Hz, 1 H), 7.71 (dd, <i>J</i> =9.1, 5.7 Hz, 1 H), 7.25 - 7.35 (m, 2 H), 7.09 (dd, <i>J</i> =15.7, 2.5 Hz, 1 H), 5.44 - 5.72 (m, 1 H), 4.80 - 5.06 (m, 1 H), 4.67 - 4.74 (m, 2 H), 4.27 - 4.44 (m, 1 H), 3.84 - 4.12 (m, 3 H), 3.58 - 3.77 (m, 1 H), 3.43 - 3.54 (m, 1 H), 2.56 - 2.86 (m, 2 H), 2.10 - 2.54 (m, 8 H), 1.90 - 2.08 (m, 3 H), 1.77 (q, <i>J</i> =12.1 Hz, 1 H), 1.31 - 1.59 (m, 5 H), 0.83 (q, <i>J</i> =7.2 Hz, 3 H).
82	643.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 8.99 (s, 1 H), 7.66 - 7.74 (m, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.27 (s, 1 H), 7.06 (d, <i>J</i> =2.5 Hz, 1 H), 5.48 - 5.69 (m, 1 H), 4.98 - 5.26 (m, 1 H), 4.62 - 4.74 (m, 3 H), 4.28 - 4.54 (m, 1 H), 3.81 - 4.14 (m, 3 H), 3.44 - 3.64 (m, 4 H), 3.02 (s, 1 H), 2.52 - 2.80 (m, 2 H), 2.30 - 2.51 (m, 4 H), 2.10 - 2.25 (m, 2 H), 0.80 (s, 3 H).
83	609.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.01 (s, 1 H), 7.66 - 7.73 (m, 1 H), 7.31 - 7.35 (m, 1 H), 7.23 - 7.31 (m, 1 H), 7.03 - 7.09 (m, 1 H), 5.48 - 5.70 (m, 1 H), 5.11 - 5.30 (m, 1 H), 4.79 - 4.91 (m, 1 H), 4.79 - 4.94 (m, 2 H), 4.68 (br d, <i>J</i> =3.6 Hz, 2 H), 4.30 - 4.50 (m, 1 H), 3.91 (br d, <i>J</i> =15.0 Hz, 3 H), 3.50 (s, 1 H), 2.65 (s, 2 H), 2.30 - 2.54 (m, 4 H), 2.19 (br d, <i>J</i> =3.3 Hz, 2 H), 0.81 (t, <i>J</i> =7.3 Hz, 3 H).
84	656.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.17 - 9.23 (m, 1 H), 7.66 - 7.75 (m, 1 H), 7.34 (s, 1 H), 7.23 - 7.31 (m, 1 H), 7.04 - 7.12 (m, 1 H), 5.50 - 5.72 (m, 1 H), 4.85 - 5.01 (m, 1 H), 4.81 (s, 1 H), 4.68 - 4.74 (m, 1 H), 4.38 - 4.59 (m, 1 H), 3.99 - 4.12 (m, 1 H), 3.79 - 3.98 (m, 4 H), 3.57 - 3.68 (m, 1 H), 3.45 - 3.55 (m, 1 H), 3.06 (d, <i>J</i> =4.0 Hz, 3 H), 2.55 - 2.83 (m, 2 H), 2.31 - 2.54 (m, 5 H), 2.07 - 2.30 (m, 4 H), 1.80 - 1.95 (m, 1 H), 0.75 - 0.86 (m, 3 H).
85	657.6	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.16 (s, 1 H), 7.67 - 7.75 (m, 1 H), 7.33 - 7.37 (m, 1 H), 7.23 - 7.32 (m, 1 H), 7.04 - 7.11 (m, 1 H), 5.47 - 5.69 (m, 1 H), 4.80 - 4.91 (m, 2 H), 4.65 - 4.73 (m, 2 H), 3.83 - 4.15 (m, 3 H), 3.57 - 3.72 (m, 2 H), 3.40 - 3.55 (m, 2 H), 2.55 - 2.82 (m, 2 H), 2.32 - 2.54 (m, 6 H), 1.97 - 2.31 (m, 4 H), 0.82 (s, 3 H).

Ex.#	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
86	643.6	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.30 - 9.41 (m, 1 H), 7.66 - 7.74 (m, 1 H), 7.34 (s, 1 H), 7.23 - 7.31 (m, 1 H), 7.03 - 7.11 (m, 1 H), 5.47 - 5.71 (m, 1 H), 4.77 - 4.82 (m, 1 H), 4.65 - 4.73 (m, 1 H), 4.33 - 4.60 (m, 3 H), 4.17 - 4.32 (m, 1 H), 3.82 - 4.13 (m, 4 H), 3.44 - 3.55 (m, 1 H), 2.31 - 2.82 (m, 8 H), 2.11 - 2.28 (m, 2 H), 0.76 - 0.86 (m, 3 H).
87	629.6	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 8.97 - 9.10 (m, 1 H), 7.66 - 7.75 (m, 1 H), 7.32 - 7.37 (m, 1 H), 7.24 - 7.31 (m, 1 H), 7.03 - 7.10 (m, 1 H), 5.47 - 5.71 (m, 1 H), 4.92 - 5.41 (m, 2 H), 4.74 (br s, 4 H), 4.37 - 4.50 (m, 1 H), 3.82 - 4.12 (m, 3 H), 3.42 - 3.56 (m, 1 H), 2.31 - 2.81 (m, 6 H), 2.09 - 2.26 (m, 2 H), 0.80 (s, 3 H).
88	592.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.01 (s, 1 H) 7.67 - 7.73 (m, 1 H) 7.31 - 7.36 (m, 1 H) 7.23 - 7.31 (m, 1 H) 7.03 - 7.08 (m, 1 H) 5.51 - 5.71 (m, 1 H) 4.88 - 5.21 (m, 2 H) 4.53 - 4.73 (m, 4 H) 3.73 - 4.15 (m, 4 H) 3.43 - 3.57 (m, 1 H) 2.53 - 2.81 (m, 2 H) 2.31 - 2.53 (m, 4 H) 2.11 - 2.27 (m, 2 H) 0.81 (s, 3 H).
89	635.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.13 (d, <i>J</i> =1.66 Hz, 1 H) 7.70 (dd, <i>J</i> =9.12, 5.81 Hz, 1 H) 7.33 (d, <i>J</i> =2.70 Hz, 1 H) 7.28 (t, <i>J</i> =9.43 Hz, 1 H) 7.07 (d, <i>J</i> =2.49 Hz, 1 H) 5.44 - 5.71 (m, 1 H) 4.59 - 4.76 (m, 3 H) 4.42 - 4.55 (m, 1 H) 3.63 - 4.12 (m, 5 H) 3.42 - 3.57 (m, 1 H) 2.76 (s, 6 H) 2.32 - 2.52 (m, 4 H) 2.10 - 2.28 (m, 3 H) 1.80 - 2.09 (m, 3 H) 0.78 - 0.85 (m, 3 H).
90	621.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.14 (d, <i>J</i> =2.07 Hz, 1 H) 7.67 - 7.76 (m, 1 H) 7.33 (d, <i>J</i> =2.70 Hz, 1 H) 7.23 - 7.30 (m, 1 H) 7.04 - 7.10 (m, 1 H) 5.48 - 5.70 (m, 1 H) 4.58 - 4.68 (m, 2 H) 4.42 - 4.53 (m, 1 H) 3.75 - 4.13 (m, 5 H) 3.47 - 3.54 (m, 1 H) 2.56 - 2.82 (m, 4 H) 2.35 - 2.51 (m, 4 H) 2.15 - 2.26 (m, 3 H) 1.91 - 2.09 (m, 3 H) 0.79 - 0.84 (m, 3 H).
91	616.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.29 (s, 1 H) 9.02 (s, 1 H) 8.08 - 8.14 (m, 1 H) 7.67 - 7.74 (m, 2 H) 7.34 (d, <i>J</i> =2.51 Hz, 1 H) 7.28 (t, <i>J</i> =9.41 Hz, 1 H) 7.06 (d, <i>J</i> =2.51 Hz, 1 H) 5.70 - 5.80 (m, 1 H) 5.49 - 5.69 (m, 1 H) 5.22 - 5.38 (m, 2 H) 4.94 - 5.14 (m, 2 H) 4.71 - 4.80 (m, 2 H) 3.83 - 4.14 (m, 3 H) 3.44 - 3.55 (m, 1 H) 2.55 - 2.82 (m, 2 H) 2.31 - 2.54 (m, 4 H) 2.12 - 2.27 (m, 2 H) 0.76 - 0.85 (m, 3 H).
92	580.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 10.69 - 10.88 (br s, 1 H) 9.02 (s, 1 H) 7.73 - 7.82 (m, 1 H) 7.29 - 7.40 (m, 2 H) 6.98 - 7.04 (m, 1 H) 5.47 - 5.66 (m, 1 H) 4.53 - 4.87 (m, 4 H) 4.13 - 4.36 (m, 2 H) 3.80 - 3.92 (m, 2 H) 3.26 - 3.37 (m, 1 H) 2.55 (s, 1 H) 2.00 - 2.42 (m, 7 H) 1.53 (s, 3 H) 0.73 (t, <i>J</i> =7.32 Hz, 3 H).

Ex.#	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
93	606.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 8.92 - 9.26 (m, 1 H), 7.56 - 7.93 (m, 1 H), 6.98 - 7.48 (m, 3 H), 5.09 - 5.61 (m, 1 H), 4.22 - 4.46 (m, 2 H), 4.04 - 4.19 (m, 4 H), 2.91 - 3.28 (m, 4 H), 1.56 - 2.59 (m, 18 H), 0.75 - 0.88 (m, 3 H).
94	578.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 8.86 - 9.35 (m, 1 H), 7.59 - 7.96 (m, 1 H), 7.22 - 7.46 (m, 2 H), 6.88 - 7.18 (m, 1 H), 5.26 - 5.85 (m, 1 H), 4.48 - 4.77 (m, 2 H), 3.84 - 4.27 (m, 7 H), 3.39 - 3.60 (m, 1 H), 2.06 - 2.88 (m, 8 H), 1.89 (br s, 6 H), 0.53 - 1.10 (m, 3 H).
95	606.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.01 - 9.34 (m, 1 H), 7.63 - 7.90 (m, 1 H), 7.21 - 7.46 (m, 2 H), 7.08 (d, <i>J</i> =2.7 Hz, 1 H), 5.42 - 5.78 (m, 1 H), 4.61 - 4.73 (m, 2 H), 4.26 - 4.53 (m, 4 H), 3.77 - 4.21 (m, 3 H), 3.36 - 3.59 (m, 1 H), 2.93 - 3.11 (m, 2 H), 2.03 - 2.88 (m, 12 H), 0.57 - 0.97 (m, 3 H).
96	608.3	¹ H NMR (METHANOL- <i>d</i> ₄ , 400 MHz) δ 9.15 (d, 1H, <i>J</i> =1.3 Hz), 7.70 (dd, 1H, <i>J</i> =6.0, 9.1 Hz), 7.34 (d, 1H, <i>J</i> =2.5 Hz), 7.28 (t, 1H, <i>J</i> =9.3 Hz), 7.07 (d, 1H, <i>J</i> =2.7 Hz), 5.5-5.7 (m, 1H), 3.8-4.0 (m, 4H), 3.5-3.6 (m, 3H), 3.1-3.2 (m, 1H), 2.6-2.7 (m, 2H), 2.3-2.5 (m, 5H), 2.1-2.3 (m, 3H), 2.05 (s, 1H), 1.9-1.9 (m, 1H), 1.9-2.0 (m, 1H), 1.3-1.4 (m, 1H), 1.10 (d, 3H, <i>J</i> =6.7 Hz), 0.8-0.9 (m, 3H).
97	620.3	¹ H NMR (METHANOL- <i>d</i> ₄ , 400 MHz) δ 9.23 (s, 1H), 7.70 (dd, 1H, <i>J</i> =5.9, 9.0 Hz), 7.34 (d, 1H, <i>J</i> =2.5 Hz), 7.27 (t, 1H, <i>J</i> =9.4 Hz), 7.08 (d, 1H, <i>J</i> =2.5 Hz), 5.5-5.7 (m, 1H), 4.6-4.7 (m, 2H), 4.5-4.6 (m, 2H), 4.1-4.2 (m, 3H), 3.8-4.1 (m, 3H), 3.4-3.5 (m, 1H), 3.1-3.2 (m, 1H), 2.5-2.8 (m, 2H), 2.3-2.5 (m, 4H), 2.2-2.3 (m, 4H), 1.87 (br dd, 2H, <i>J</i> =3.3, 7.3 Hz), 1.62 (br d, 2H, <i>J</i> =13.0 Hz), 0.8-0.9 (m, 3H).
98	634.3	¹ H NMR (METHANOL- <i>d</i> ₄ , 400 MHz) δ 9.22 (s, 1H), 7.70 (dd, 1H, <i>J</i> =5.7, 8.9 Hz), 7.34 (d, 1H, <i>J</i> =2.7 Hz), 7.27 (t, 1H, <i>J</i> =9.4 Hz), 7.08 (d, 1H, <i>J</i> =2.5 Hz), 5.5-5.7 (m, 1H), 4.6-4.7 (m, 1H), 4.5-4.6 (m, 2H), 4.2-4.3 (m, 2H), 3.8-4.1 (m, 3H), 3.4-3.6 (m, 2H), 2.7-2.8 (m, 1H), 2.3-2.6 (m, 6H), 2.1-2.3 (m, 2H), 2.01 (br s, 2H), 1.8-1.9 (m, 2H), 1.59 (br d, 2H, <i>J</i> =12.8 Hz), 1.38 (s, 3H), 0.8-0.9 (m, 3H).
99	606.3	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.24 (d, <i>J</i> =1.5 Hz, 1 H), 7.68 - 7.76 (m, 1 H), 7.36 (d, <i>J</i> =2.5 Hz, 1 H), 7.29 (t, <i>J</i> =9.4 Hz, 1 H), 7.11 (s, 1 H), 5.51 - 5.70 (m, 1 H), 4.33 - 4.57 (m, 2 H), 3.84 - 4.17 (m, 6 H), 3.45 - 3.60 (m, 2 H), 2.33 - 2.54 (m, 7 H), 2.15 - 2.29 (m, 3 H), 1.07 (dt, <i>J</i> =9.7, 4.7 Hz, 1 H), 0.79 - 0.87 (m, 4 H), 0.66 - 0.73 (m, 1 H)

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Ex.#	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
100	610.3	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.30 (br d, <i>J</i> =7.3 Hz, 1 H), 7.53 - 7.78 (m, 1 H), 7.15 - 7.40 (m, 3 H), 6.93 - 7.11 (m, 1 H), 5.47 - 5.70 (m, 1 H), 4.34 - 4.44 (m, 2 H), 3.66 - 4.12 (m, 9 H), 3.49 (td, <i>J</i> =10.5, 6.0 Hz, 1 H), 2.54 - 2.61 (m, 1 H), 2.32 - 2.45 (m, 3 H), 2.02 - 2.28 (m, 4 H), 1.86 - 2.00 (m, 1 H), 0.72 - 0.89 (m, 3 H).
101	610.3	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.28 (d, <i>J</i> =6.3 Hz, 1 H), 7.70 (dd, <i>J</i> =9.2, 5.9 Hz, 1 H), 7.34 (d, <i>J</i> =2.5 Hz, 1 H), 7.27 (t, <i>J</i> =9.4 Hz, 1 H), 7.08 (t, <i>J</i> =2.5 Hz, 1 H), 5.50 - 5.68 (m, 1 H), 4.69 (s, 3 H), 4.36 (dd, <i>J</i> =13.5, 2.8 Hz, 1 H), 4.05 - 4.21 (m, 2 H), 3.88 - 4.03 (m, 3 H), 3.81 - 3.87 (m, 1 H), 3.73 - 3.79 (m, 1 H), 3.45 - 3.55 (m, 1 H), 2.56 - 2.83 (m, 2 H), 2.11 - 2.54 (m, 7 H), 1.70 - 1.82 (m, 1 H), 0.82 (br t, <i>J</i> =7.4 Hz, 3 H).
102	610.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.14 - 9.45 (m, 1 H), 7.60 - 7.77 (m, 1 H), 7.23 - 7.43 (m, 2 H), 6.96 - 7.15 (m, 1 H), 5.31 - 5.90 (m, 1 H), 4.67 - 4.74 (m, 1 H), 4.20 - 4.44 (m, 4 H), 3.41 - 4.17 (m, 6 H), 1.98 - 2.91 (m, 10 H), 0.63 - 0.89 (m, 3 H).
103	633.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.23 (s, 1 H), 7.71 (dd, <i>J</i> =9.1, 5.7 Hz, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.28 (t, <i>J</i> =9.4 Hz, 1 H), 7.07 (d, <i>J</i> =2.5 Hz, 1 H), 5.48 - 5.73 (m, 1 H), 4.61 - 4.74 (m, 2 H), 4.43 - 4.50 (m, 1 H), 4.26 - 4.34 (m, 1 H), 3.73 - 4.13 (m, 5 H), 3.63 (td, <i>J</i> =8.9, 1.3 Hz, 1 H), 3.46 - 3.54 (m, 1 H), 3.13 - 3.23 (m, 1 H), 3.08 (br dd, <i>J</i> =7.4, 2.2 Hz, 1 H), 2.88 - 2.96 (m, 1 H), 2.56 - 2.80 (m, 2 H), 2.33 - 2.52 (m, 4 H), 2.17 - 2.31 (m, 4 H), 0.77 - 0.86 (m, 3 H).
104	593.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.16 (s, 1 H), 7.71 (dd, <i>J</i> =9.2, 5.9 Hz, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.28 (t, <i>J</i> =9.4 Hz, 1 H), 7.07 (d, <i>J</i> =2.5 Hz, 1 H), 5.44 - 5.72 (m, 1 H), 4.73 - 4.75 (m, 2 H), 4.61 (br d, <i>J</i> =13.4 Hz, 1 H), 4.41 (br dd, <i>J</i> =9.0, 5.6 Hz, 1 H), 3.75 - 4.14 (m, 5 H), 3.63 - 3.72 (m, 1 H), 3.46 - 3.54 (m, 1 H), 2.56 - 2.82 (m, 2 H), 2.44 - 2.52 (m, 2 H), 2.17 - 2.42 (m, 5 H), 2.08 - 2.15 (m, 1 H), 1.85 - 1.99 (m, 2 H), 0.81 (td, <i>J</i> =7.4, 1.9 Hz, 3 H).
105	604.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.16 (s, 1 H), 7.70 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.34 (d, <i>J</i> =2.5 Hz, 1 H), 7.27 (t, <i>J</i> =9.4 Hz, 1 H), 7.08 (d, <i>J</i> =2.5 Hz, 1 H), 5.46 - 5.73 (m, 1 H), 4.61 - 4.74 (m, 4 H), 3.83 - 4.17 (m, 3 H), 3.70 (br dd, <i>J</i> =12.3, 6.1 Hz, 2 H), 3.46 - 3.54 (m, 1 H), 2.55 - 2.86 (m, 2 H), 2.33 - 2.52 (m, 6 H), 2.22 (ddd, <i>J</i> =10.7, 7.1, 3.3 Hz, 2 H), 1.93 - 1.98 (m, 1 H), 1.72 - 1.84 (m, 3 H), 1.61 (br d, <i>J</i> =13.0 Hz, 2 H), 0.82 (td, <i>J</i> =7.4, 2.1 Hz, 3 H).

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Ex.#	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
106	644.4	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.14 (s, 1 H), 8.90 (dd, <i>J</i> =2.5, 1.3 Hz, 1 H), 7.71 (dd, <i>J</i> =9.2, 5.9 Hz, 1 H), 7.53 (d, <i>J</i> =4.0 Hz, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.28 (t, <i>J</i> =9.4 Hz, 1 H), 7.07 (d, <i>J</i> =2.5 Hz, 1 H), 5.46 - 5.73 (m, 1 H), 4.82 - 4.91 (m, 1 H), 4.66 - 4.73 (m, 2 H), 3.83 - 4.15 (m, 3 H), 3.59 - 3.72 (m, 2 H), 3.35 - 3.53 (m, 3 H), 2.54 - 2.85 (m, 2 H), 2.32 - 2.51 (m, 5 H), 2.14 - 2.27 (m, 2 H), 1.95 - 2.14 (m, 3 H), 0.81 (br t, <i>J</i> =7.3 Hz, 3 H).
107	644.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.16 (s, 1 H), 7.70 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.61 (dd, <i>J</i> =3.3, 2.3 Hz, 1 H), 7.34 (d, <i>J</i> =2.5 Hz, 1 H), 7.27 (t, <i>J</i> =9.4 Hz, 1 H), 7.08 (d, <i>J</i> =2.3 Hz, 1 H), 6.31 (dd, <i>J</i> =5.2, 2.1 Hz, 1 H), 5.42 - 5.66 (m, 1 H), 4.81 - 4.94 (m, 1 H), 4.63 - 4.71 (m, 2 H), 3.82 - 4.17 (m, 3 H), 3.60 - 3.75 (m, 2 H), 3.45 - 3.54 (m, 1 H), 3.20 - 3.30 (m, 2 H), 2.56 - 2.84 (m, 2 H), 2.19 - 2.48 (m, 7 H), 1.90 - 2.13 (m, 3 H), 0.82 (t, <i>J</i> =7.3 Hz, 3 H).
108	645.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 9.88 (s, 1 H), 9.10 (s, 1 H), 8.27 (d, <i>J</i> =5.9 Hz, 1 H), 7.77 (dd, <i>J</i> =9.1, 6.0 Hz, 1 H), 7.30 - 7.40 (m, 2 H), 6.98 - 7.08 (m, 2 H), 5.15 - 5.40 (m, 1 H), 4.53 - 4.72 (m, 1 H), 4.32 - 4.51 (m, 1 H), 4.07 - 4.24 (m, 2 H), 3.46 - 3.72 (m, 2 H), 3.29 - 3.39 (m, 1 H), 2.98 - 3.15 (m, 3 H), 2.77 - 2.92 (m, 1 H), 2.28 - 2.44 (m, 1 H), 2.00 - 2.25 (m, 5 H), 1.73 - 1.98 (m, 6 H), 0.75 (br t, <i>J</i> =6.8 Hz, 3 H).
109	592.15	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ ppm 10.56 - 10.86 (m, 1 H), 9.69 - 10.14 (m, 1 H), 9.45 (dd, <i>J</i> =12.3, 2.1 Hz, 1 H), 7.78 (dd, <i>J</i> =9.1, 6.0 Hz, 1 H), 7.32 - 7.40 (m, 2 H), 7.03 (d, <i>J</i> =2.7 Hz, 1 H), 5.87 - 6.07 (m, 2 H), 5.51 - 5.70 (m, 1 H), 4.53 - 4.71 (m, 3 H), 4.43 (br s, 1 H), 4.26 - 4.36 (m, 1 H), 4.19 (br dd, <i>J</i> =17.1, 13.0 Hz, 1 H), 3.88 - 4.04 (m, 3 H), 3.23 - 3.45 (m, 2 H), 2.52 - 2.71 (m, 1 H), 1.98 - 2.42 (m, 7 H), 0.74 (t, <i>J</i> =7.3 Hz, 3 H).
110	671.4	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.12 (d, <i>J</i> =2.3 Hz, 1 H), 7.68 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.32 (d, <i>J</i> =2.7 Hz, 1 H), 7.26 (t, <i>J</i> =9.4 Hz, 1 H), 7.07 (t, <i>J</i> =3.0 Hz, 1 H), 5.22 - 5.48 (m, 1 H), 4.55 - 4.70 (m, 1 H), 4.25 - 4.43 (m, 3 H), 3.48 - 3.89 (m, 3 H), 3.21 - 3.29 (m, 2 H), 3.03 (d, <i>J</i> =0.8 Hz, 4 H), 2.13 - 2.55 (m, 6 H), 1.71 - 2.08 (m, 6 H), 0.82 (q, <i>J</i> =7.4 Hz, 3 H).
111	612.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.41 (s, 1 H), 7.71 (dd, <i>J</i> =9.1, 5.7 Hz, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.28 (t, <i>J</i> =9.4 Hz, 1 H), 7.07 (dd, <i>J</i> =7.3, 2.5 Hz, 1 H), 5.62 - 5.69 (m, 1 H), 5.48 - 5.56 (m, 1 H), 5.06 - 5.15 (m, 1 H), 4.65 - 4.71 (m, 1 H), 4.50 - 4.56 (m, 1 H), 4.41 - 4.48 (m, 1 H), 4.09 - 4.15 (m, 1 H), 3.92 (br d, <i>J</i> =16.1 Hz, 3 H), 3.75 - 3.88 (m, 1 H), 3.46 - 3.55 (m, 1 H), 2.67 (br d, <i>J</i> =3.3 Hz, 3 H), 2.13 - 2.55 (m, 8 H), 0.81 (t, <i>J</i> =7.1 Hz, 3 H).

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Ex.#	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
112	612.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.32 (d, <i>J</i> =7.1 Hz, 1 H), 7.70 (dd, <i>J</i> =9.2, 5.9 Hz, 1 H), 7.34 (d, <i>J</i> =2.5 Hz, 1 H), 7.27 (t, <i>J</i> =9.4 Hz, 1 H), 7.07 (t, <i>J</i> =2.7 Hz, 1 H), 5.51 - 5.67 (m, 1 H), 4.64 - 4.72 (m, 2 H), 4.22 - 4.33 (m, 2 H), 3.86 - 4.19 (m, 6 H), 3.46 - 3.56 (m, 1 H), 2.55 - 2.82 (m, 2 H), 2.33 - 2.54 (m, 5 H), 2.15 - 2.29 (m, 2 H), 1.99 - 2.10 (m, 1 H), 0.82 (t, <i>J</i> =7.4 Hz, 3 H).
113	594.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.35 (d, <i>J</i> =4.2 Hz, 1 H), 7.70 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.27 (t, <i>J</i> =9.4 Hz, 1 H), 7.07 (dd, <i>J</i> =6.5, 2.7 Hz, 1 H), 5.49 - 5.69 (m, 1 H), 4.85 - 4.94 (m, 1 H), 4.71 (s, 2 H), 4.13 - 4.27 (m, 2 H), 3.93 (br d, <i>J</i> =3.3 Hz, 5 H), 3.49 (br dd, <i>J</i> =10.3, 4.9 Hz, 1 H), 2.66 (br s, 2 H), 2.44 - 2.57 (m, 2 H), 2.30 - 2.43 (m, 3 H), 2.07 - 2.27 (m, 5 H), 0.78 - 0.86 (m, 3 H).
114	612.2	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 9.23 (d, <i>J</i> =5.9 Hz, 1 H), 7.77 (dd, <i>J</i> =9.2, 6.0 Hz, 1 H), 7.32 - 7.37 (m, 2 H), 7.02 (dt, <i>J</i> =3.4, 1.0 Hz, 1 H), 5.32 - 5.72 (m, 1 H), 4.60 - 4.77 (m, 1 H), 3.68 - 4.10 (m, 4 H), 1.84 - 2.41 (m, 7 H), 0.70 - 0.76 (m, 3 H).
115	612.3	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.43 (d, <i>J</i> =7.3 Hz, 1 H), 7.70 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.20 - 7.37 (m, 2 H), 7.08 (t, <i>J</i> =2.4 Hz, 1 H), 5.47 - 5.74 (m, 1 H), 4.92 - 5.14 (m, 1 H), 4.73 (br dd, <i>J</i> =8.3, 3.2 Hz, 3 H), 4.52 (br s, 1 H), 3.72 - 4.35 (m, 8 H), 3.44 - 3.57 (m, 1 H), 2.59 - 2.91 (m, 2 H), 2.29 - 2.55 (m, 5 H), 2.10 - 2.28 (m, 3 H), 0.82 (t, <i>J</i> =7.3 Hz, 3 H).
116	612.3	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.26 (d, <i>J</i> =7.7 Hz, 1 H), 9.12 (s, 1 H), 7.70 (dd, <i>J</i> =9.1, 6.0 Hz, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.27 (t, <i>J</i> =9.4 Hz, 1 H), 6.93 - 7.19 (m, 1 H), 5.52 - 5.69 (m, 1 H), 5.49 (s, 1 H), 5.04 - 5.22 (m, 1 H), 4.57 (br t, <i>J</i> =12.4 Hz, 1 H), 4.47 (br dd, <i>J</i> =9.2, 5.2 Hz, 1 H), 4.26 (br dd, <i>J</i> =8.2, 4.0 Hz, 1 H), 4.08 (br dd, <i>J</i> =14.3, 2.6 Hz, 1 H), 3.86 - 4.03 (m, 3 H), 3.45 - 3.66 (m, 2 H), 2.73 - 2.81 (m, 1 H), 2.53 - 2.72 (m, 2 H), 2.43 - 2.52 (m, 2 H), 2.37 (br dd, <i>J</i> =11.2, 5.7 Hz, 4 H), 2.14 - 2.26 (m, 3 H), 0.81 (br t, <i>J</i> =7.3 Hz, 4 H).
117	596.3	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.36 (d, <i>J</i> =6.7 Hz, 1 H), 7.70 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.21 - 7.44 (m, 2 H), 7.09 (dd, <i>J</i> =11.3, 2.5 Hz, 1 H), 5.47 - 5.70 (m, 1 H), 4.63 - 4.77 (m, 3 H), 4.20 (br s, 1 H), 4.13 - 4.53 (m, 2 H), 4.12 - 4.60 (m, 1 H), 3.84 - 4.10 (m, 1 H), 3.78 - 4.02 (m, 3 H), 3.42 - 3.55 (m, 1 H), 2.56 - 2.82 (m, 2 H), 2.31 - 2.53 (m, 4 H), 2.11 - 2.26 (m, 2 H), 1.24 (s, 3 H), 0.82 (dt, <i>J</i> =10.6, 7.4 Hz, 3 H).

Ex.#	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
118	630.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.33 - 9.41 (m, 1 H), 7.67 - 7.74 (m, 1 H), 7.32 - 7.37 (m, 1 H), 7.24 - 7.31 (m, 1 H), 7.06 - 7.12 (m, 1 H), 5.51 - 5.71 (m, 1 H), 4.67 - 4.76 (m, 2 H), 4.26 - 4.47 (m, 4 H), 3.83 - 4.11 (m, 4 H), 3.46 - 3.57 (m, 1 H), 2.32 - 2.82 (m, 7 H), 2.12 - 2.31 (m, 3 H), 0.77 - 0.86 (m, 3 H).
119	657.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.32 - 9.44 (m, 1 H), 7.65 - 7.75 (m, 1 H), 7.33 - 7.41 (m, 1 H), 7.28 (s, 1 H), 7.00 - 7.10 (m, 1 H), 5.50 - 5.71 (m, 1 H), 5.16 - 5.30 (m, 1 H), 4.84 - 4.92 (m, 1 H), 4.12 - 4.35 (m, 2 H), 3.83 - 4.10 (m, 4 H), 3.44 - 3.55 (m, 1 H), 3.35 - 3.41 (m, 1 H), 2.10 - 2.89 (m, 13 H), 0.75 - 0.87 (m, 3 H).
120	644.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.26 - 9.31 (m, 1 H), 7.66 - 7.74 (m, 1 H), 7.32 - 7.36 (m, 1 H), 7.24 - 7.31 (m, 1 H), 7.05 - 7.12 (m, 1 H), 5.49 - 5.70 (m, 1 H), 4.62 - 4.74 (m, 2 H), 4.22 - 4.45 (m, 3 H), 3.83 - 4.15 (m, 5 H), 3.45 - 3.56 (m, 1 H), 2.55 - 2.93 (m, 3 H), 2.32 - 2.54 (m, 6 H), 2.11 - 2.31 (m, 3 H), 0.75 - 0.86 (m, 3 H).
121	647.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.18 (s, 1 H), 7.66 - 7.73 (m, 1 H), 7.34 (d, <i>J</i> =2.5 Hz, 1 H), 7.27 (s, 1 H), 7.08 (s, 1 H), 5.46 - 5.72 (m, 1 H), 5.05 - 5.22 (m, 1 H), 4.52 - 4.73 (m, 3 H), 3.72 - 4.14 (m, 4 H), 3.45 - 3.66 (m, 2 H), 2.67 (s, 3 H), 2.31 - 2.54 (m, 4 H), 2.05 - 2.30 (m, 4 H), 1.95 (s, 3 H), 1.54 - 1.66 (m, 1 H), 0.75 - 0.87 (m, 3 H).
122	642.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.33 - 9.40 (m, 1 H), 7.66 - 7.74 (m, 1 H), 7.31 - 7.37 (m, 1 H), 7.22 - 7.31 (m, 1 H), 7.03 - 7.11 (m, 1 H), 5.48 - 5.72 (m, 1 H), 4.82 - 4.91 (m, 2 H), 4.63 - 4.73 (m, 1 H), 4.26 - 4.49 (m, 1 H), 3.68 - 4.16 (m, 9 H), 3.45 - 3.58 (m, 1 H), 2.54 - 2.82 (m, 4 H), 2.30 - 2.54 (m, 4 H), 2.13 - 2.27 (m, 2 H), 0.70 - 0.93 (m, 3 H).
123	647.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.23 (s, 1 H), 7.66 - 7.74 (m, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.23 - 7.31 (m, 1 H), 7.06 - 7.10 (m, 1 H), 5.45 - 5.71 (m, 2 H), 5.21 - 5.32 (m, 1 H), 4.73 (br s, 2 H), 3.82 - 4.15 (m, 3 H), 3.44 - 3.56 (m, 1 H), 2.94 - 3.04 (m, 1 H), 2.53 - 2.82 (m, 2 H), 2.34 - 2.53 (m, 4 H), 1.91 - 2.25 (m, 10 H), 0.83 (s, 3 H).
124	636.4	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.04 - 9.37 (m, 1 H), 7.61 - 7.79 (m, 1 H), 7.22 - 7.43 (m, 2 H), 6.88 - 7.17 (m, 1 H), 5.27 - 5.79 (m, 1 H), 4.96 - 5.15 (m, 1 H), 4.54 - 4.80 (m, 2 H), 3.79 - 4.16 (m, 3 H), 3.25 - 3.65 (m, 3 H), 3.00 - 3.26 (m, 1 H), 1.46 - 2.82 (m, 13 H), 1.26 (s, 3 H), 1.31 (s, 3 H), 0.71 - 0.97 (m, 3 H).

Ex.#	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
125	608.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.18 (s, 1 H), 7.65 - 7.88 (m, 1 H), 7.34 (d, <i>J</i> =2.5 Hz, 2 H), 6.94 - 7.14 (m, 1 H), 5.07 - 5.88 (m, 1 H), 4.53 - 4.74 (m, 4 H), 3.76 - 4.17 (m, 3 H), 3.35 - 3.68 (m, 5 H), 1.76 - 2.83 (m, 12 H), 1.35 - 1.59 (m, 1 H), 0.78 - 0.83 (m, 3 H).
126	636.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.02 - 9.24 (m, 1 H), 7.66 - 7.91 (m, 1 H), 6.96 - 7.38 (m, 3 H), 5.46 - 5.72 (m, 1 H), 4.48 - 4.75 (m, 3 H), 3.83 - 4.41 (m, 6 H), 3.71 (m, 3 H), 3.40 - 3.58 (m, 1 H), 1.70 - 3.03 (m, 13 H), 0.80 - 0.85 (m, 3 H).
127	606.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.06 - 9.71 (m, 1 H), 7.57 - 7.83 (m, 1 H), 7.22 - 7.37 (m, 2 H), 6.87 - 7.11 (m, 1 H), 5.30 - 6.03 (m, 1 H), 4.55 - 4.75 (m, 4 H), 4.24 - 4.46 (m, 2 H), 3.75 - 4.11 (m, 3 H), 3.43 - 3.58 (m, 1 H), 2.31 - 2.80 (m, 8 H), 2.10 - 2.27 (m, 4 H), 1.89 - 2.05 (m, 2 H), 0.72 - 0.93 (m, 3 H).
128	608.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.14 - 9.43 (m, 1 H), 7.61 - 7.92 (m, 1 H), 7.20 - 7.39 (m, 2 H), 7.00 - 7.18 (m, 1 H), 5.36 - 5.85 (m, 1 H), 4.56 - 4.83 (m, 4 H), 3.78 - 4.17 (m, 3 H), 3.36 - 3.71 (m, 5 H), 1.73 - 2.82 (m, 12 H), 1.39 - 1.63 (m, 1 H), 0.74 - 0.92 (m, 3 H).
129	608.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.26 - 9.47 (m, 1 H), 7.52 - 7.94 (m, 1 H), 7.18 - 7.37 (m, 2 H), 6.91 - 7.11 (m, 1 H), 5.47 - 5.79 (m, 1 H), 4.64 - 4.74 (m, 2 H), 4.34 - 4.51 (m, 1 H), 3.74 - 4.22 (m, 7 H), 3.41 - 3.58 (m, 1 H), 2.56 - 2.91 (m, 2 H), 2.27 - 2.54 (m, 4 H), 1.90 - 2.27 (m, 6 H), 1.39 - 1.83 (m, 2 H), 1.44 - 1.79 (m, 2 H), 0.51 - 0.99 (m, 3 H).
130	608.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.28 - 9.59 (m, 1 H), 7.62 - 7.99 (m, 1 H), 7.20 - 7.49 (m, 2 H), 7.03 - 7.13 (m, 1 H), 5.21 - 6.01 (m, 1 H), 4.65 - 4.77 (m, 2 H), 4.35 - 4.50 (m, 1 H), 3.74 - 4.29 (m, 7 H), 3.43 - 3.56 (m, 1 H), 2.29 - 2.81 (m, 6 H), 1.88 - 2.26 (m, 6 H), 1.41 - 1.84 (m, 2 H), 0.73 - 0.94 (m, 3 H).
131	607.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.12 - 9.41 (m, 1 H), 7.71 (dd, <i>J</i> =9.1, 6.0 Hz, 1 H), 7.16 - 7.45 (m, 2 H), 6.90 - 7.12 (m, 1 H), 5.37 - 6.01 (m, 1 H), 4.67 - 4.77 (m, 2 H), 3.78 - 4.48 (m, 8 H), 3.42 - 3.66 (m, 1 H), 1.95 - 2.87 (m, 12 H), 1.51 - 1.90 (m, 2 H), 0.79 - 0.85 (m, 3 H).
132	685.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.03 - 9.54 (m, 1 H), 7.57 - 7.80 (m, 1 H), 7.21 - 7.40 (m, 2 H), 6.95 - 7.14 (m, 1 H), 5.87 - 6.38 (m, 1 H), 5.40 - 5.71 (m, 1 H), 4.90 - 5.03 (m, 1 H), 4.51 - 4.65 (m, 3 H), 4.01 - 4.37 (m, 3 H), 3.83 - 3.99 (m, 2 H), 3.61 - 3.78 (m, 1 H), 3.43 - 3.56 (m, 1 H), 1.90 - 2.89 (m, 12 H), 1.34 - 1.78 (m, 2 H), 0.66 - 0.94 (m, 3 H).

Ex.#	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
133	649.4	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.13 - 9.54 (m, 1 H), 7.70 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.24 - 7.44 (m, 2 H), 7.04 - 7.15 (m, 1 H), 5.16 - 5.90 (m, 1 H), 4.89 - 4.93 (m, 1 H), 4.23 - 4.67 (m, 4 H), 3.80 - 4.20 (m, 4 H), 3.38 - 3.68 (m, 2 H), 2.01 (s, 15 H), 1.26 - 1.76 (m, 2 H), 0.66 - 0.92 (m, 3 H).
134	604.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.06 - 9.36 (m, 1 H), 7.66 - 7.77 (m, 1 H), 7.19 - 7.49 (m, 2 H), 6.98 - 7.12 (m, 1 H), 6.81 - 6.93 (m, 1 H), 5.85 - 6.33 (m, 1 H), 5.51 - 5.76 (m, 1 H), 4.55 - 4.73 (m, 4 H), 4.28 - 4.50 (m, 2 H), 3.80 - 4.11 (m, 3 H), 3.46 - 3.55 (m, 1 H), 2.91 - 3.06 (m, 2 H), 2.55 - 2.80 (m, 2 H), 2.33 - 2.50 (m, 4 H), 2.14 - 2.28 (m, 2 H), 0.67 - 0.93 (m, 3 H).
135	606.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.32 - 9.60 (m, 1 H), 7.64 - 7.94 (m, 1 H), 7.34 (m, 2 H), 6.89 - 7.14 (m, 1 H), 5.76 - 6.26 (m, 2 H), 5.32 - 5.69 (m, 1 H), 4.62 - 4.78 (m, 3 H), 4.49 - 4.62 (m, 1 H), 3.81 - 4.46 (m, 7 H), 3.42 - 3.54 (m, 1 H), 2.55 - 2.89 (m, 3 H), 2.30 - 2.54 (m, 4 H), 1.86 - 2.25 (m, 3 H), 0.71 - 0.93 (m, 3 H).
136	622.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.45 - 9.71 (m, 1 H), 7.65 - 7.84 (m, 1 H), 7.18 - 7.39 (m, 2 H), 6.94 - 7.15 (m, 1 H), 5.46 - 5.96 (m, 1 H), 4.32 - 4.72 (m, 4 H), 3.80 - 4.11 (m, 5 H), 3.38 - 3.59 (m, 1 H), 2.32 - 2.87 (m, 6 H), 2.10 - 2.27 (m, 3 H), 1.62 - 2.10 (m, 5 H), 1.40 (s, 3 H), 0.67 - 0.83 (m, 3 H).
137	622.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.38 - 9.84 (m, 1 H), 7.62 - 7.77 (m, 1 H), 7.32 - 7.37 (m, 1 H), 7.24 - 7.31 (m, 1 H), 7.04 - 7.12 (m, 1 H), 5.51 - 5.78 (m, 1 H), 4.62 - 4.78 (m, 2 H), 4.26 - 4.62 (m, 2 H), 3.72 - 4.14 (m, 5 H), 3.42 - 3.57 (m, 1 H), 2.55 - 2.93 (m, 2 H), 2.29 - 2.53 (m, 4 H), 2.07 - 2.29 (m, 3 H), 1.66 - 2.07 (m, 5 H), 1.40 (s, 3 H), 0.57 - 1.00 (m, 3 H).
138	622.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.14 - 9.38 (m, 1 H), 7.65 - 7.75 (m, 1 H), 7.24 - 7.41 (m, 2 H), 7.04 - 7.17 (m, 1 H), 5.50 - 5.90 (m, 1 H), 4.46 - 4.73 (m, 3 H), 3.79 - 4.36 (m, 6 H), 3.42 - 3.61 (m, 1 H), 1.77 - 3.02 (m, 13 H), 0.80 - 0.85 (m, 3 H).
139	590.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.23 (s, 1 H), 7.70 (dd, <i>J</i> =9.0, 5.9 Hz, 1 H), 7.17 - 7.49 (m, 2 H), 6.81 - 7.14 (m, 1 H), 5.80 (s, 2 H), 5.46 - 5.71 (m, 1 H), 4.51 - 4.76 (m, 3 H), 4.25 - 4.35 (m, 3 H), 3.76 - 4.16 (m, 3 H), 3.41 - 3.60 (m, 1 H), 2.09 - 2.85 (m, 12 H), 1.36 - 1.75 (m, 1 H), 0.68 - 1.08 (m, 3 H).

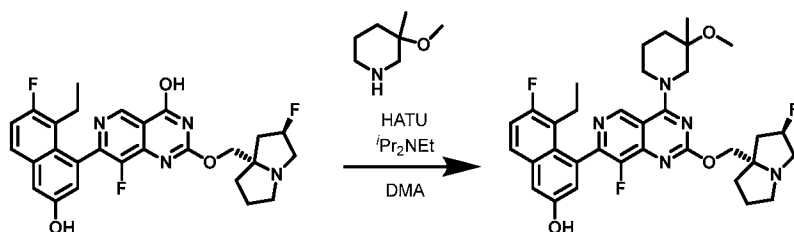
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Ex.#	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
140	629.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.24 (s, 1 H), 7.71 (dd, <i>J</i> =9.1, 6.0 Hz, 1 H), 7.26 - 7.36 (m, 2 H), 7.08 (dd, <i>J</i> =6.8, 2.6 Hz, 1 H), 5.51 - 5.77 (m, 1 H), 4.80 - 4.86 (m, 2 H), 4.55 - 4.69 (m, 2 H), 4.14 - 4.31 (m, 1 H), 3.87 - 4.08 (m, 5 H), 3.43 - 3.60 (m, 1 H), 2.72 - 2.85 (m, 1 H), 2.56 - 2.72 (m, 2 H), 2.33 - 2.54 (m, 5 H), 2.12 - 2.31 (m, 2 H), 0.80 (t, <i>J</i> =7.1 Hz, 3 H).
141	608.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 8.88 - 9.27 (m, 1 H), 7.59 - 7.80 (m, 1 H), 7.20 - 7.37 (m, 2 H), 6.93 - 7.14 (m, 1 H), 5.13 - 5.47 (m, 1 H), 4.32 - 4.51 (m, 2 H), 3.86 - 4.30 (m, 5 H), 3.36 - 3.56 (m, 3 H), 3.07 - 3.17 (m, 1 H), 1.72 - 2.58 (m, 16 H), 0.82 (s, 3 H).
142	622.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.14 - 9.28 (m, 1 H), 7.56 - 8.03 (m, 1 H), 7.20 - 7.44 (m, 2 H), 6.85 - 7.18 (m, 1 H), 5.35 - 5.95 (m, 1 H), 4.62 - 4.76 (m, 2 H), 3.77 - 4.33 (m, 7 H), 3.46 - 3.61 (m, 1 H), 1.81 - 2.89 (m, 13 H), 1.47 - 1.72 (m, 1 H), 1.31 (d, <i>J</i> =4.2 Hz, 3 H), 0.69 - 0.97 (m, 3 H).
143	607.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 8.97 - 9.35 (m, 1 H), 7.59 - 7.90 (m, 1 H), 7.20 - 7.47 (m, 2 H), 6.89 - 7.18 (m, 1 H), 5.40 - 5.78 (m, 1 H), 4.65 - 4.78 (m, 3 H), 4.29 - 4.56 (m, 2 H), 3.74 - 4.17 (m, 5 H), 3.40 - 3.69 (m, 2 H), 2.03 - 2.91 (m, 13 H), 1.66 - 1.83 (m, 1 H), 0.60 - 0.93 (m, 3 H).
144	604.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.13 - 9.30 (m, 1 H), 7.64 - 7.79 (m, 1 H), 7.22 - 7.46 (m, 2 H), 6.86 - 7.13 (m, 1 H), 5.32 - 5.90 (m, 1 H), 4.83 - 5.01 (m, 2 H), 4.60 - 4.76 (m, 2 H), 4.20 - 4.40 (m, 4 H), 3.80 - 4.11 (m, 3 H), 3.43 - 3.60 (m, 1 H), 1.95 - 2.91 (m, 14 H), 0.63 - 0.93 (m, 3 H).
145	629.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.15 (s, 1 H), 7.70 (dd, <i>J</i> =9.1, 6.0 Hz, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.28 (t, <i>J</i> =9.4 Hz, 1 H), 7.06 (t, <i>J</i> =2.5 Hz, 1 H), 5.47 - 5.73 (m, 1 H), 4.82 - 4.98 (m, 1 H), 4.52 - 4.75 (m, 3 H), 3.58 - 4.15 (m, 5 H), 3.45 - 3.55 (m, 1 H), 3.01 - 3.12 (m, 1 H), 2.54 - 2.87 (m, 4 H), 2.30 - 2.54 (m, 4 H), 1.99 - 2.29 (m, 6 H), 0.73 - 0.88 (m, 3 H).
146	629.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.13 - 9.25 (m, 1 H), 7.69 (br d, <i>J</i> =3.6 Hz, 1 H), 7.34 (d, <i>J</i> =2.5 Hz, 1 H), 7.26 (s, 1 H), 7.03 - 7.14 (m, 1 H), 5.48 - 5.70 (m, 1 H), 4.82 - 5.14 (m, 3 H), 4.61 - 4.73 (m, 1 H), 3.83 - 4.13 (m, 4 H), 3.45 - 3.73 (m, 2 H), 3.10 - 3.23 (m, 1 H), 2.53 - 2.81 (m, 4 H), 2.31 - 2.53 (m, 5 H), 2.07 - 2.26 (m, 3 H), 1.84 - 1.99 (m, 2 H), 0.80 (s, 3 H).

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Ex.#	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
147	643.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.16 - 9.22 (m, 1 H), 7.66 - 7.73 (m, 1 H), 7.34 (d, <i>J</i> =2.7 Hz, 1 H), 7.24 - 7.30 (m, 1 H), 7.04 - 7.14 (m, 1 H), 5.49 - 5.70 (m, 1 H), 4.83 (br d, <i>J</i> =7.1 Hz, 1 H), 4.30 - 4.75 (m, 4 H), 3.91 (br d, <i>J</i> =14.8 Hz, 4 H), 3.44 - 3.56 (m, 1 H), 3.06 - 3.19 (m, 1 H), 2.53 - 2.86 (m, 3 H), 2.29 - 2.52 (m, 6 H), 1.93 - 2.27 (m, 5 H), 1.79 - 1.92 (m, 1 H), 1.64 - 1.76 (m, 1 H), 0.76 - 0.87 (m, 3 H).
176	611.2	¹ H NMR (500 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.22 (s, 1 H), 7.68 (dd, <i>J</i> =8.89, 5.90 Hz, 1 H), 7.23 - 7.34 (m, 2 H), 7.07 (s, 1 H), 5.21 - 5.42 (m, 1 H), 4.52 (br d, <i>J</i> =12.33 Hz, 1 H), 4.24 - 4.36 (m, 3 H), 3.55 - 3.68 (m, 1 H), 3.42 - 3.50 (m, 1 H), 3.20 - 3.29 (m, 3 H), 3.00 - 3.09 (m, 1 H), 2.44 - 2.52 (m, 1 H), 2.12 - 2.39 (m, 6 H), 1.83 - 2.05 (m, 5 H), 1.75 - 1.82 (m, 2 H), 0.82 (dt, <i>J</i> =11.22, 7.43 Hz, 3 H).
177	611.2	¹ H NMR (500 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.22 (s, 1 H), 7.68 (dd, <i>J</i> =8.95, 5.84 Hz, 1 H), 7.31 (d, <i>J</i> =2.47 Hz, 1 H), 7.26 (t, <i>J</i> =9.34 Hz, 1 H), 7.07 (s, 1 H), 5.24 - 5.40 (m, 1 H), 4.53 (br d, <i>J</i> =9.86 Hz, 1 H), 4.25 - 4.37 (m, 3 H), 3.57 - 3.68 (m, 1 H), 3.43 - 3.50 (m, 1 H), 3.18 - 3.29 (m, 3 H), 3.00 - 3.07 (m, 1 H), 2.49 (br dd, <i>J</i> =14.34, 7.20 Hz, 1 H), 2.33 - 2.39 (m, 1 H), 2.12 - 2.31 (m, 5 H), 1.84 - 2.05 (m, 5 H), 1.76 - 1.83 (m, 2 H), 0.82 (q, <i>J</i> =7.14 Hz, 3 H).

5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(3-methoxy-3-methylpiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol (Example 148)



Example 148

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7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol (80 mg, 0.16 mmol, **Intermediate D**) was dissolved in *N,N*-dimethylacetamide (1.3 mL), HATU (0.24 mg, 0.63 mmol) and *N,N*-diisopropylethylamine (0.10 g, 0.14 mL, 0.78 mmol) and 3-methoxy-3-

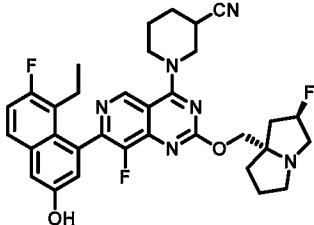
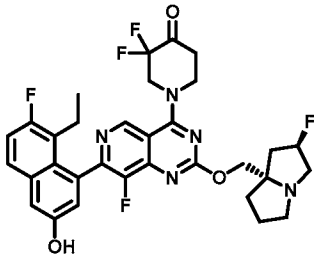
- 252 -

methylpiperidine (41 mg, 0.31 mmol, Enamine) were added and the mixture was stirred at rt overnight. Water (0.5 mL) was added and the mixture was stirred overnight. The crude residue was purified by reverse phase HPLC to yield 5-ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(3-methoxy-3-methylpiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol as TFA salt and as off-white solid (16 mg, 22 μ mol, 14 % yield). *m/z* (ESI): 622.0 (M+H)⁺. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 9.28 - 9.40 (m, 1 H), 7.65 - 7.74 (m, 1 H), 7.32 - 7.38 (m, 1 H), 7.23 - 7.31 (m, 1 H), 7.07 - 7.11 (m, 1 H), 5.49 - 5.70 (m, 1 H), 4.51 - 4.75 (m, 3 H), 3.83 - 4.15 (m, 3 H), 3.35 - 3.75 (m, 4 H), 3.11 - 3.23 (m, 3 H), 2.53 - 2.83 (m, 2 H), 2.31 - 2.53 (m, 4 H), 2.11 - 2.28 (m, 3 H), 1.95 - 2.10 (m, 1 H), 1.61 - 1.85 (m, 2 H), 1.27 (d, *J*=7.3 Hz, 3 H), 0.78 - 0.86 (m, 3 H).

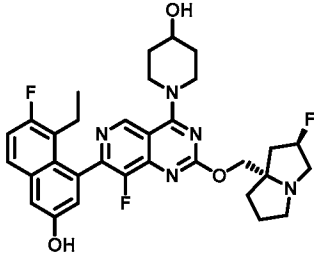
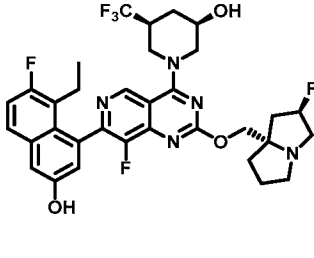
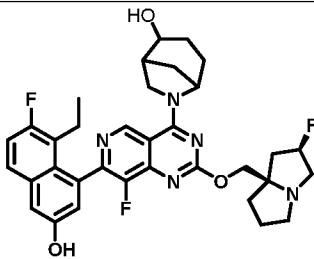
Table 11: Examples 149 to 161. prepared in an analogous manner to Example 148.

Ex. #	Structure	Name	Salt Form	Reagent	Method Change
149		4-(4-(4,4-Difluoroazepan-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol	2,2,2-trifluoroacetate	4,4-difluoroazepane hydrochloride (CAS#: 1094073-72-9, Combi-Blocks Inc.)	
150		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyrido[4,3- <i>d</i>]pyrimidin-4-yl)-5,5-difluoroazepan-4-one	2,2,2-trifluoroacetate	5,5-difluoroazepan-4-one hydrochloride (CAS#: 2097991-20-1, Enamine)	

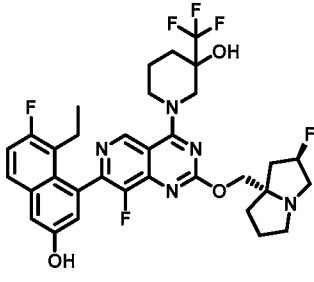
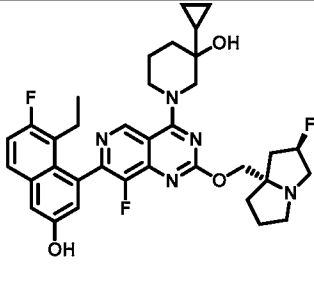
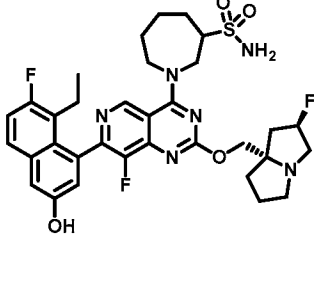
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		yl)-5,5-difluoroazepan-4-one			
151		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyridino[4,3- <i>d</i>]pyrimidin-4-yl)piperidine-3-carbonitrile	Free base	3-cyanopiperidine (CAS#: 7492-88-8, Combi Blocks)	Purification was performed with 0.1% formic acid in H ₂ O and MeCN as mobile phase, XSelect column (19 x 100 mm, 5 μm)
152		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyridino[4,3- <i>d</i>]pyrimidin-4-yl)-3,3-difluoropiperidin-4-one	2,2,2-trifluoroacetate	3,3-difluoro-4-piperidinone hydrochloride (CAS#: 1283720-75-1, Advanced ChemBlocks Inc.)	

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153		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyridin-4-yl)piperidin-4-ol	2,2,2-trifluoroacetate	piperidin-4-ol (CAS#: 5382-16-1, Combi-Blocks Inc.)	
154		(3 <i>R</i> ,5 <i>S</i>)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyridin-4-yl)-5-(trifluoromethyl)piperidin-3-ol	2,2,2-trifluoroacetate	(3 <i>R</i> ,5 <i>S</i>)-5-(trifluoromethyl)piperidin-3-ol (CAS#: 2227198-76-5, AA Blocks)	
155		6-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyridin-4-yl)-6-azabicyclo[3.2.1]octan-2-ol	2,2,2-trifluoroacetate	6-azabicyclo[3.2.1]octan-2-ol (CAS#: 1934420-45-7, Enamine)	

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156		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyridin-4-yl)-3-(trifluoromethyl)piperidin-3-ol	2,2,2-trifluoroacetate	3-(trifluoromethyl)piperidin-3-ol (CAS#: 1052713-79-7, Enamine)	
157		3-Cyclopropyl-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyridin-4-yl)piperidin-3-ol	2,2,2-trifluoroacetate	3-cyclopropylpiperidin-3-ol (CAS#: 1494822-71-7, Enamine)	
158		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyridin-4-yl)azepane-3-sulfonamide	2,2,2-trifluoroacetate	azepane-3-sulfonamide (CAS#: 1934897-80-9, Chemspace)	

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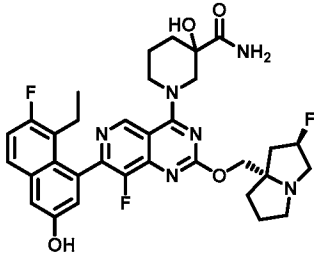
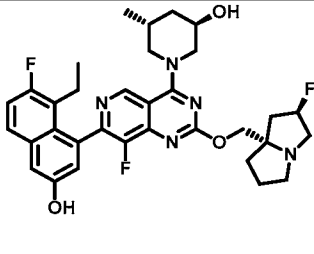
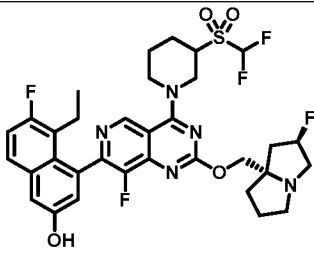
159		1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyridine-4,3- <i>d</i>]pyrimidin-4-yl)-3-hydroxypiperidine-3-carboxamide	2,2,2-trifluoroacetate	3-hydroxypiperidine-3-carboxamide hydrochloride (CAS#: 1803570-33-3, Aurum Pharmatech LLC)	
160		<i>rel</i> -(3 <i>R</i> ,5 <i>R</i>)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyridine-4,3- <i>d</i>]pyrimidin-4-yl)-5-methylpiperidine-3-ol	2,2,2-trifluoroacetate	<i>rac</i> -(3 <i>R</i> ,5 <i>R</i>)-5-methylpiperidine-3-ol (CAS#: 1354392-05-4, ChemSpace)	
161		4-(4-(3-((difluoromethyl)sulfonyl)piperidine-1-yl)-8-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)pyridine-4,3- <i>d</i>]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol	2,2,2-trifluoroacetate	3-((difluoromethyl)sulfonyl)piperidine hydrochloride (CAS#: of free base: 1783321-40-3, ChemSpace)	

Table 12. Analytical Data of Examples 149 to 161.

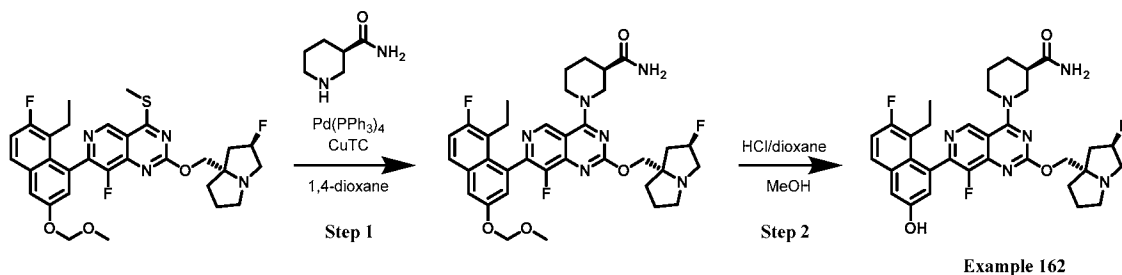
Ex. #	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
149	628.0	¹ H NMR (METHANOL- <i>d</i> ₄ , 400 MHz) δ 9.26 (s, 1H), 7.71 (dd, 1H, <i>J</i> =5.9, 9.0 Hz), 7.36 (d, 1H, <i>J</i> =2.7 Hz), 7.28 (t, 1H, <i>J</i> =9.4 Hz), 7.11 (d, 1H, <i>J</i> =2.5 Hz), 5.5-5.7 (m, 1H), 4.79 (s, 1H), 4.7-4.7 (m, 1H), 4.2-4.3 (m, 4H), 3.8-4.1 (m, 3H), 3.4-3.6 (m, 1H), 2.3-2.8 (m, 8H), 2.1-2.3 (m, 6H), 0.83 (dt, 3H, <i>J</i> =1.6, 7.3 Hz).
150	660.0 (M+H ₃ O) ⁺	¹ H NMR (METHANOL- <i>d</i> ₄ , 400 MHz) δ 9.1-9.3 (m, 1H), 7.69 (dd, 1H, <i>J</i> =5.9, 9.0 Hz), 7.32 (d, 1H, <i>J</i> =2.5 Hz), 7.26 (t, 1H, <i>J</i> =9.4 Hz), 7.0-7.1 (m, 1H), 5.4-5.7 (m, 1H), 4.6-4.7 (m, 2H), 4.20 (dt, 2H, <i>J</i> =6.1, 11.0 Hz), 3.8-4.1 (m, 5H), 3.5-3.6 (m, 2H), 2.99 (br dd, 1H, <i>J</i> =6.2, 8.7 Hz), 2.6-2.7 (m, 3H), 2.3-2.5 (m, 5H), 2.1-2.3 (m, 2H), 0.8-0.9 (m, 3H).
151	603.2	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 9.20 (d, <i>J</i> =1.2 Hz, 1 H), 7.74 - 7.82 (m, 1 H), 7.33 - 7.38 (m, 2 H), 7.00 - 7.05 (m, 1 H), 5.50 - 5.64 (m, 1 H), 4.56 - 4.68 (m, 2 H), 4.33 - 4.48 (m, 1 H), 4.12 - 4.24 (m, 1 H), 4.01 - 4.10 (m, 1 H), 3.70 - 3.92 (m, 3 H), 1.78 - 2.41 (m, 9 H), 0.66 - 0.76 (m, 3 H).
152	646.0 (M+H ₃ O) ⁺	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.17 - 9.23 (m, 1 H), 7.66 - 7.74 (m, 1 H), 7.32 - 7.36 (m, 1 H), 7.24 - 7.32 (m, 1 H), 7.06 - 7.11 (m, 1 H), 5.51 - 5.70 (m, 1 H), 4.67 - 4.77 (m, 2 H), 4.37 - 4.53 (m, 2 H), 4.13 - 4.32 (m, 2 H), 3.84 - 4.11 (m, 3 H), 3.45 - 3.58 (m, 1 H), 2.55 - 2.83 (m, 2 H), 2.31 - 2.53 (m, 4 H), 2.09 - 2.29 (m, 4 H), 0.76 - 0.86 (m, 3 H).
153	594.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.11 - 9.17 (m, 1 H), 7.70 (s, 1 H), 7.32 - 7.37 (m, 1 H), 7.23 - 7.32 (m, 1 H), 7.05 - 7.11 (m, 1 H), 5.48 - 5.71 (m, 1 H), 4.63 - 4.75 (m, 2 H), 4.37 - 4.51 (m, 2 H), 3.82 - 4.15 (m, 6 H), 3.43 - 3.56 (m, 1 H), 2.55 - 2.82 (m, 2 H), 2.31 - 2.55 (m, 4 H), 2.07 - 2.29 (m, 4 H), 1.72 - 1.89 (m, 2 H), 0.75 - 0.89 (m, 3 H).
154	662.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.16 - 9.23 (m, 1 H), 7.67 - 7.74 (m, 1 H), 7.32 - 7.38 (m, 1 H), 7.23 - 7.32 (m, 1 H), 7.05 - 7.11 (m, 1 H), 5.49 - 5.73 (m, 1 H), 4.82 - 4.91 (m, 1 H), 4.68 - 4.77 (m, 3 H), 3.84 - 4.11 (m, 4 H), 3.45 - 3.57 (m, 1 H), 3.35 - 3.43 (m, 1 H), 3.25 - 3.30 (m, 1 H), 2.84 - 3.03 (m, 1 H), 2.56 - 2.80 (m, 2 H), 2.32 - 2.53 (m, 5 H), 2.13 - 2.30 (m, 2 H), 1.61 - 1.81 (m, 1 H), 0.82 (s, 3 H).
155	620.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.15 - 9.59 (m, 1 H), 7.66 - 7.76 (m, 1 H), 7.33 - 7.38 (m, 1 H), 7.23 - 7.32 (m, 1 H), 7.04 - 7.13 (m, 1 H), 5.47 - 5.69 (m, 1 H), 4.94 - 5.12 (m, 1 H), 4.59 - 4.77 (m, 2 H), 3.81 - 4.32 (m, 6 H), 3.43 - 3.57 (m, 1 H), 2.31 - 2.85 (m, 8 H), 2.12 - 2.30 (m, 3 H), 1.59 - 2.09 (m, 3 H), 1.20 - 1.44 (m, 1 H), 0.75 - 0.89 (m, 3 H).

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Ex. #	MS <i>m/z</i> (ESI): (M+H) ⁺	¹ H NMR
156	622.8	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.27 - 9.36 (m, 1 H), 7.67 - 7.74 (m, 1 H), 7.32 - 7.36 (m, 1 H), 7.23 - 7.31 (m, 1 H), 7.06 - 7.10 (m, 1 H), 5.49 - 5.70 (m, 1 H), 4.65 - 4.77 (m, 4 H), 3.69 - 4.11 (m, 4 H), 3.40 - 3.55 (m, 2 H), 2.54 - 2.81 (m, 2 H), 2.31 - 2.51 (m, 4 H), 2.14 - 2.31 (m, 3 H), 2.05 - 2.13 (m, 2 H), 1.87 - 1.99 (m, 1 H), 0.77 - 0.88 (m, 3 H).
157	634.9	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.31 - 9.41 (m, 1 H), 7.66 - 7.74 (m, 1 H), 7.32 - 7.37 (m, 1 H), 7.24 - 7.31 (m, 1 H), 7.07 - 7.11 (m, 1 H), 5.49 - 5.69 (m, 1 H), 4.63 - 4.75 (m, 3 H), 4.36 - 4.48 (m, 1 H), 3.83 - 4.11 (m, 3 H), 3.63 - 3.74 (m, 1 H), 3.39 - 3.55 (m, 2 H), 2.54 - 2.83 (m, 2 H), 2.31 - 2.51 (m, 4 H), 2.08 - 2.30 (m, 3 H), 1.80 - 1.92 (m, 3 H), 0.92 - 1.04 (m, 1 H), 0.83 (s, 3 H), 0.30 - 0.57 (m, 4 H).
158	671.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.12 - 9.34 (m, 1 H), 7.65 - 7.76 (m, 1 H), 7.32 - 7.36 (m, 1 H), 7.22 - 7.31 (m, 1 H), 7.01 - 7.11 (m, 1 H), 5.50 - 5.71 (m, 1 H), 4.96 - 5.13 (m, 1 H), 4.80 - 4.94 (m, 2 H), 4.27 - 4.41 (m, 1 H), 4.13 - 4.26 (m, 1 H), 3.82 - 4.13 (m, 4 H), 3.64 - 3.80 (m, 1 H), 3.44 - 3.58 (m, 1 H), 2.03 - 2.86 (m, 12 H), 1.83 - 1.98 (m, 1 H), 1.37 - 1.57 (m, 1 H), 0.74 - 0.90 (m, 3 H).
159	637.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.28 - 9.38 (m, 1 H), 7.65 - 7.75 (m, 1 H), 7.31 - 7.38 (m, 1 H), 7.23 - 7.31 (m, 1 H), 7.05 - 7.12 (m, 1 H), 5.48 - 5.70 (m, 1 H), 4.63 - 4.75 (m, 3 H), 4.44 - 4.55 (m, 1 H), 3.83 - 4.11 (m, 4 H), 3.46 - 3.58 (m, 2 H), 2.54 - 2.82 (m, 2 H), 2.29 - 2.52 (m, 5 H), 2.11 - 2.28 (m, 3 H), 1.88 - 1.99 (m, 2 H), 0.76 - 0.88 (m, 3 H).
160	607.9	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.28 - 9.37 (m, 1 H), 7.66 - 7.74 (m, 1 H), 7.32 - 7.37 (m, 1 H), 7.28 (t, <i>J</i> =9.4 Hz, 1 H), 7.04 - 7.11 (m, 1 H), 5.49 - 5.70 (m, 1 H), 4.60 - 4.75 (m, 4 H), 4.20 (br s, 1 H), 3.91 (br d, <i>J</i> =15.0 Hz, 3 H), 3.61 - 3.78 (m, 1 H), 3.44 - 3.56 (m, 1 H), 2.95 - 3.17 (m, 1 H), 2.54 - 2.81 (m, 2 H), 2.39 (br d, <i>J</i> =6.1 Hz, 5 H), 2.14 - 2.29 (m, 2 H), 1.97 - 2.06 (m, 1 H), 1.55 - 1.67 (m, 1 H), 1.02 - 1.11 (m, 3 H), 0.77 - 0.88 (m, 3 H).
161	692.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 9.17 - 9.22 (m, 1 H), 7.65 - 7.75 (m, 1 H), 7.31 - 7.37 (m, 1 H), 7.24 - 7.31 (m, 1 H), 7.05 - 7.11 (m, 1 H), 6.70 - 7.02 (m, 1 H), 5.50 - 5.71 (m, 1 H), 4.67 - 4.76 (m, 1 H), 4.21 - 4.35 (m, 1 H), 4.02 - 4.14 (m, 1 H), 3.88 - 4.01 (m, 4 H), 3.45 - 3.57 (m, 1 H), 3.07 (s, 1 H), 2.94 (s, 1 H), 2.56 - 2.84 (m, 2 H), 2.33 - 2.52 (m, 5 H), 2.12 - 2.32 (m, 4 H), 2.09 (s, 1 H), 1.82 - 1.95 (m, 1 H), 0.76 - 0.85 (m, 3 H).

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(*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-carboxamide (Example 162)



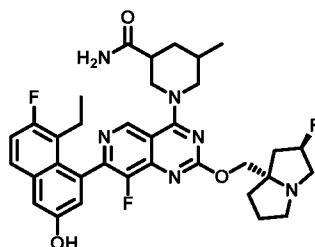
5 **Step 1: (*R*)-1-(7-(8-Ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-carboxamide.** A vial was charged with 7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(methylthio)pyrido[4,3-*d*]pyrimidine (20 mg, 0.034 mmol),
 10 copper(I) thiophene-2-carboxylate (13 mg, 0.068 mmol), Pd(PPh₃)₄ (4.0 mg, 3.42 μmol), and (*R*)-piperidine-3-carboxamide (8.8 mg, 0.068 mmol). The solids were suspended in degassed 1,4-dioxane (0.17 mL), and the reaction was capped and stirred at 90 °C. After stirring overnight, the reaction was absorbed onto a silica plug and purified via column
 15 chromatography on silica gel, eluting with a gradient of 0-100% of 3:1 EtOAc/EtOH blend in heptane with 2% triethylamine additive to provide (*R*)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-carboxamide, which was used directly in the subsequent step. *m/z* (ESI): 666.0 (M+H)⁺.

20 **Step 2: (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-carboxamide.** Synthesized in an analogous manner to **Example 1**. The product was isolated as TFA salt (9.0 mg, 0.11 mmol, 31 % yield over 2 steps). *m/z* (ESI): 621.2 (M+H)⁺. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 9.15 (d, J=1.88 Hz, 1 H) 7.71 (br d, J=9.20 Hz, 1 H) 7.34 (d, J=2.51 Hz, 1 H) 7.23 - 7.30 (m, 1 H) 7.08 (s, 1 H) 5.47 - 5.70 (m, 1 H) 4.74 (br s, 3 H) 4.38 - 4.51 (m, 1 H) 3.71 - 4.13 (m, 5 H)
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3.42 - 3.57 (m, 1 H) 2.53 - 2.83 (m, 3 H) 2.32 - 2.52 (m, 4 H) 2.13 - 2.29 (m, 3 H) 1.97 - 2.10 (m, 2 H) 1.77 - 1.94 (m, 1 H) 0.76 - 0.86 (m, 3 H).

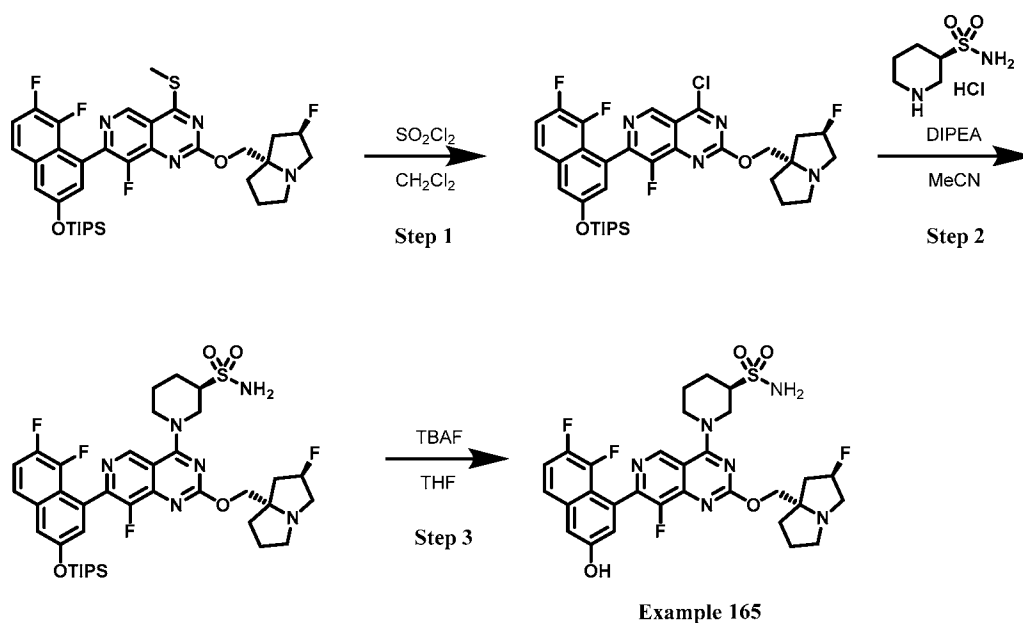
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-methylpiperidine-3-carboxamide (Example 163 and Example 164)



Synthesized in an analogous manner to **Example 162**, using 5-methylpiperidine-3-carboxamide hydrochloride (CAS#: 2228678-05-3, Enamine). Isomer 1 (**Example 163**) was isolated as bis(2,2,2-trifluoroacetate) and as light-yellow solid. *m/z* (ESI): 635.3 (M+H)⁺. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 9.14 (d, *J*=1.67 Hz, 1 H) 7.70 (s, 1 H) 7.34 (d, *J*=2.51 Hz, 1 H) 7.27 (s, 1 H) 7.07 (d, *J*=1.88 Hz, 1 H) 5.48 - 5.70 (m, 1 H) 4.39 - 4.69 (m, 3 H) 3.64 - 4.15 (m, 5 H) 3.43 - 3.57 (m, 1 H) 2.76 (s, 6 H) 2.34 - 2.52 (m, 4 H) 2.13 - 2.30 (m, 3 H) 1.76 - 2.10 (m, 3 H) 0.76 - 0.87 (m, 3 H). Isomers 2 (**Example 164**) was isolated as bis(2,2,2-trifluoroacetate) and as light-yellow solid. *m/z* (ESI): 635.3 (M+H)⁺. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 9.12 (s, 1 H) 7.68 - 7.74 (m, 1 H) 7.34 (d, *J*=2.72 Hz, 1 H) 7.23 - 7.31 (m, 1 H) 7.05 - 7.10 (m, 1 H) 5.51 - 5.71 (m, 1 H) 4.81 - 4.96 (m, 3 H) 4.57 - 4.71 (m, 2 H) 3.87 - 4.15 (m, 3 H) 3.40 - 3.58 (m, 1 H) 3.03 - 3.16 (m, 1 H) 2.53 - 2.89 (m, 3 H) 2.32 - 2.53 (m, 4 H) 2.13 - 2.29 (m, 3 H) 1.97 - 2.10 (m, 1 H) 1.51 - 1.65 (m, 1 H) 1.06 - 1.12 (m, 3 H) 0.78 - 0.86 (m, 3 H).

(*R*)-1-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-sulfonamide (Example 165)

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Step 1: 4-Chloro-7-(7,8-difluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine. To a solution of 7-(7,8-difluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(methylthio)pyrido[4,3-d]pyrimidine (54 mg, 0.079 mmol) in DCM (1 mL) at 0 °C was added sulfuryl chloride (1.0 M in DCM, 0.24 mL, 0.24 mmol) slowly. The reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was concentrated under reduced pressure and the crude product was used directly in the subsequent step. *m/z* (ESI): 676.0 (M+H)⁺.

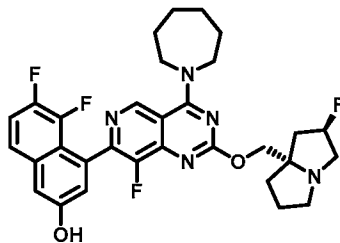
Step 2: (R)-1-(7-(7,8-Difluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3-sulfonamide. A mixture of 4-chloro-7-(7,8-difluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (26 mg, 0.039 mmol), (3R)-piperidine-3-sulfonamide hydrochloride (16 mg, 0.078 mmol), and Hunig's base (15 mg, 0.02 mL, 0.12 mmol) was stirred in acetonitrile (0.5 mL) at rt for 30 min. The reaction mixture was purified by reverse phase HPLC to afford (R)-1-(7-(7,8-difluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-

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pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3-sulfonamide (5.0 mg, 6.23 μ mol, 16 % yield) as white solid. m/z (ESI): 803.2 (M+H)⁺.

Step 3: (R)-1-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3-sulfonamide. To a solution of (R)-1-(7-(7,8-difluoro-3-
 (((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-
 pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3-sulfonamide (5.0
 mg, 6.23 μ mol) in tetrahydrofuran (0.5 mL) at 0 °C was added tetrabutylammonium fluoride
 solution (1.0 M in THF, 16 mg, 0.018 mL, 0.062 mmol) slowly. The resulting mixture was
 stirred at 0 °C for 0.5 h. The reaction mixture was purified twice by reverse phase HPLC to
 afford (R)-1-(7-(7,8-difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-
 fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3-
 sulfonamide as TFA salt (2.0 mg, 2.3 μ mol, 37 % yield) as light yellow solid. m/z (ESI):
 647.0 (M+H)⁺. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 9.20 (s, 1 H), 7.64 (ddd, J =9.1,
 4.9, 1.5 Hz, 1 H), 7.36 - 7.46 (m, 2 H), 7.28 (d, J =9.8 Hz, 1 H), 5.50 - 5.73 (m, 1 H), 5.02 (br
 d, J =13.2 Hz, 1 H), 4.77 - 4.84 (m, 2 H), 4.56 - 4.66 (m, 1 H), 3.73 - 4.14 (m, 5 H), 3.46 -
 3.57 (m, 2 H), 2.54 - 2.84 (m, 2 H), 2.33 - 2.49 (m, 4 H), 2.04 - 2.26 (m, 3 H), 1.79 - 1.92 (m,
 1 H).

4-(4-(Azepan-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5,6-difluoronaphthalen-2-ol (Example 166)



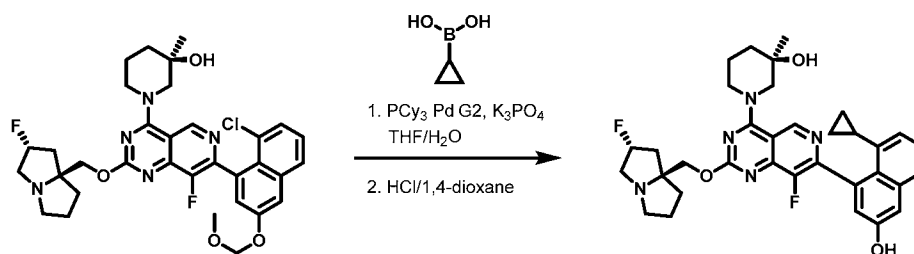
Example 166

Synthesized in an analogous manner to **Example 165** using azepane (CAS#: 111-49-9, Sigma-Aldrich Corporation). The product was isolated as its TFA salt. m/z (ESI, +ve ion):
 582.0 (M+H)⁺. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 9.23 (s, 1 H), 7.65 (ddd, J =9.2,

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4.8, 1.7 Hz, 1 H), 7.36 - 7.46 (m, 2 H), 7.28 (d, $J=2.3$ Hz, 1 H), 5.47 - 5.71 (m, 1 H), 4.60 - 4.74 (m, 2 H), 4.11 - 4.22 (m, 4 H), 3.84 - 4.02 (m, 3 H), 3.46 - 3.53 (m, 1 H), 2.53 - 2.82 (m, 2 H), 2.33 - 2.48 (m, 3 H), 2.13 - 2.24 (m, 1 H), 2.04 - 2.13 (m, 4 H), 1.71 - 1.79 (m, 4 H).

5 **(*R*)-1-(7-(8-Cyclopropyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol (Example 167)**



Example 167

10 **(*R*)-1-(7-(8-Chloro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol** (46 mg, 0.07 mmol, synthesized in an analogous manner to **Example 1** using 2-[8-chloro-3-(methoxymethoxy)-1-naphthalenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, CAS#: 2621938-40-5, LabNetwork) was suspended in toluene (0.7 mL) and

15 water (0.04 mL). Cyclopropylboronic acid (7.4 mg, 0.09 mmol), PCy₃ Pd G2 (4.0 mg, 7.0 μmol) and potassium phosphate, monohydrate (66 mg, 0.29 mmol) were added. The mixture was degassed for 5 minutes and then stirred at 80 °C for 16 h. The crude mixture was purified by reverse phase HPLC. The product obtained was dissolved in THF (1.5 mL). HCl (4 M in 1,4-dioxane, 0.5 mL) was added and the mixture was stirred at rt for 2 h. Volatiles were

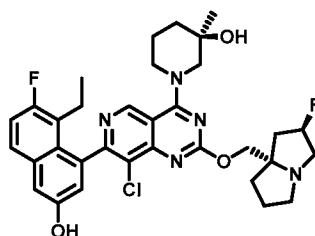
20 removed under reduced pressure. The crude product was purified by reverse phase HPLC to yield (*R*)-1-(7-(8-cyclopropyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol (5.5 mg, 9.14 μmol, 13% yield). m/z (ESI): 602.2 (M+H)⁺. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 9.23 - 9.33 (m, 1 H), 7.65 (s, 1 H), 7.31 - 7.39 (m, 2 H), 7.19 - 7.25 (m, 1 H), 7.07 - 7.13 (m, 1 H), 5.50 - 5.69 (m, 1 H), 4.57 - 4.74 (m, 3 H), 4.31 - 4.43 (m, 1 H), 3.86 - 4.12 (m, 3 H), 3.40 - 3.71 (m, 4 H), 2.53 - 2.84 (m, 2 H), 2.31 - 2.50 (m,

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3 H), 2.12 - 2.27 (m, 2 H), 1.76 - 1.94 (m, 3 H), 1.55 - 1.68 (m, 1 H), 1.32 (d, $J=7.3$ Hz, 5 H), 0.53 - 0.72 (m, 1 H), 0.27 - 0.48 (m, 2 H).

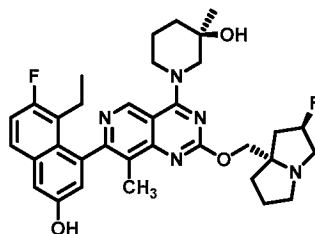
(R)-1-(8-Chloro-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (Example 168)



Example 168

Synthesized in an analogous manner to **Example 43** using 2,4,7,8-tetrachloropyrido[4,3-d]pyrimidine (CAS#: 2454396-63-3, LabNetwork) and (3R)-3-methylpiperidin-3-ol hydrochloride (CAS#: 2305080-34-4, PharmaBlock, Inc.). The product was isolated as 2,2,2-trifluoroacetate and as light-yellow solid. m/z (ESI): 623.8 (M+H)⁺. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 9.35 - 9.43 (m, 1 H), 7.65 - 7.74 (m, 1 H), 7.30 - 7.33 (m, 1 H), 7.23 - 7.30 (m, 1 H), 6.98 - 7.05 (m, 1 H), 5.48 - 5.68 (m, 1 H), 4.67 - 4.76 (m, 2 H), 4.59 - 4.67 (m, 1 H), 4.30 - 4.42 (m, 1 H), 3.98 - 4.15 (m, 1 H), 3.84 - 3.97 (m, 2 H), 3.58 - 3.71 (m, 1 H), 3.40 - 3.56 (m, 2 H), 2.55 - 2.82 (m, 2 H), 2.43 - 2.53 (m, 1 H), 2.25 - 2.42 (m, 4 H), 2.10 - 2.24 (m, 2 H), 1.75 - 1.94 (m, 3 H), 1.31 (d, $J=6.3$ Hz, 3 H), 0.80 - 0.91 (m, 3 H).

(R)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8-methylpyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (Example 169)

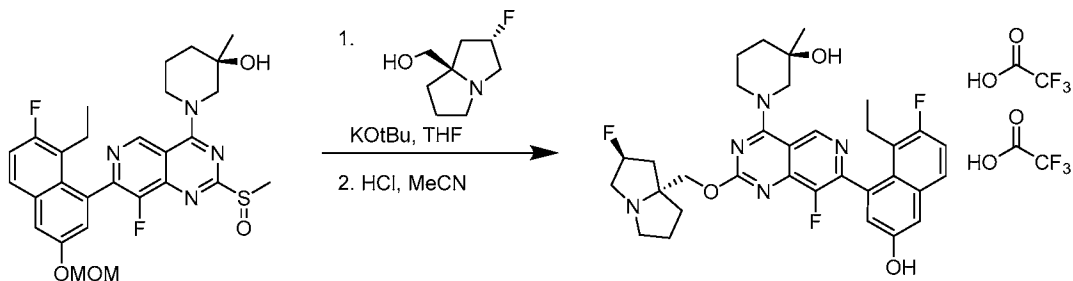


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Example 169

Synthesized in an analogous manner to **Example 43** using 2,4,7-trichloro-8-methylpyrido[4,3-*d*]pyrimidine (CAS#: 2454396-72-4, WuXi App Tec Co. Ltd.) and (3*R*)-3-methylpiperidin-3-ol hydrochloride (CAS#: 2305080-34-4, PharmaBlock, Inc.). The product was isolated as 2,2,2-trifluoroacetate and as white solid. *m/z* (ESI): 604.0 (M+H)⁺. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 9.65 - 9.74 (m, 1 H), 7.73 - 7.82 (m, 1 H), 7.40 - 7.48 (m, 1 H), 7.29 - 7.39 (m, 1 H), 7.13 - 7.19 (m, 1 H), 5.51 - 5.73 (m, 1 H), 4.85 - 4.91 (m, 1 H), 4.73 - 4.80 (m, 2 H), 4.26 - 4.44 (m, 1 H), 3.83 - 4.11 (m, 3 H), 3.55 - 3.66 (m, 1 H), 3.45 - 3.55 (m, 1 H), 3.35 - 3.44 (m, 1 H), 2.57 - 2.87 (m, 2 H), 2.44 - 2.54 (m, 1 H), 2.35 - 2.44 (m, 3 H), 2.32 - 2.35 (m, 4 H), 2.22 - 2.31 (m, 1 H), 2.08 - 2.20 (m, 1 H), 1.77 - 1.96 (m, 3 H), 1.34 (d, *J*=2.7 Hz, 3 H), 0.87 (br d, *J*=4.4 Hz, 3 H).

(*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*S*,7*aR*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol bis(2,2,2-trifluoroacetate) (Example 178)

**Example 178**

To an 8-mL vial was added ((2*S*,7*aR*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methanol (24 mg, 0.15 mmol, Pharmablock, Inc.) in THF (1.1 mL). The vial was then cooled to 0 °C and potassium *tert*-butoxide, 1.0 M in THF (220 μL, 0.22 mmol) was added. After stirring for 45 min, (3*R*)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(methylsulfinyl)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol (60 mg, 0.11 mmol, Intermediate Q) in tetrahydrofuran (1.1 mL) was added. After stirring at rt for 30 min, the reaction was quenched via the addition of saturated aqueous NH₄Cl solution (2 mL) and water (2 mL). The mixture was then diluted with dichloromethane (5 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 5 mL) and the

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combined organic layers were dried with sodium sulfate, filtered and concentrated under reduced pressure to afford a colorless oil. The crude oil was then purified via column chromatography on silica gel using a gradient of 0-70% of a3:1 EtOAc/EtOH (with 2% triethylamine) in heptane, to provide crude (R)-1-(7-(8-ethyl-7-fluoro-3-

(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*S*,7*aR*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol) as light yellow solid. *m/z* (ESI): 652.2 (M+H)⁺.

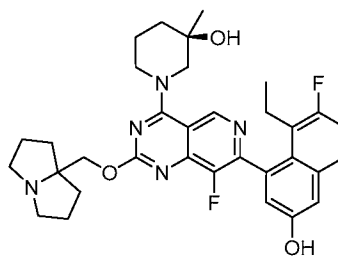
The crude (R)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*S*,7*aR*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-

yl)-3-methylpiperidin-3-ol was dissolved in MeCN (3.4 mL) and 4 M HCl in 1,4-dioxane (680 μ L, 2.69 mmol) was added. After stirring for 1 h at rt, the reaction was concentrated under reduced pressure and purified via reverse phase HPLC to provide (R)-1-(7-(8-ethyl-7-

fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*S*,7*aR*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol bis(2,2,2-trifluoroacetate) (11 mg, 0.014 mmol, 13 % yield) as light yellow solid. *m/z* (ESI): 608.2 (M+H)⁺. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 9.32 (s, 1 H) 7.65 - 7.75 (m, 1 H) 7.34 (d, *J*=2.51 Hz, 1 H) 7.28 (s, 1 H) 7.08 (s, 1 H) 5.49 - 5.71 (m, 1 H) 4.59 - 4.78 (m, 3 H) 4.33 - 4.45 (m, 1 H) 3.85 - 4.15 (m, 3 H) 3.57 - 3.72 (m, 1 H) 3.42 - 3.55 (m, 2 H) 2.52 - 2.83 (m, 2 H) 2.31 - 2.52 (m, 4 H) 2.11 - 2.30 (m, 3 H) 1.78 - 1.94 (m, 3 H) 1.33 (d, *J*=8.15 Hz, 3 H)

0.77 - 0.88 (m, 3 H).

(R)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol (Example 179).

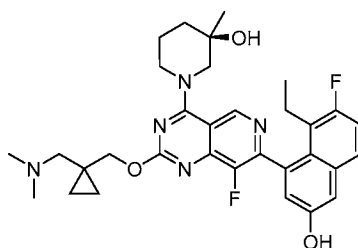


Example 179

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Synthesized in an analogous manner to **Example 178** using 1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethanol (CAS#: 78449-72-6, Advanced ChemBlocks Inc.). The product was isolated as 2,2,2-trifluoroacetate and as white solid. *m/z* (ESI): 590.0. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 9.31 (s, 1 H), 7.70 (dd, *J*=9.0, 5.9 Hz, 1 H), 7.34 (d, *J*=2.5 Hz, 1 H), 7.28 (t, *J*=9.4 Hz, 1 H), 7.08 (t, *J*=2.2 Hz, 1 H), 4.69 (s, 3 H), 4.32 - 4.43 (m, 1 H), 3.58 - 3.79 (m, 4 H), 3.43 - 3.52 (m, 1 H), 3.28 - 3.31 (m, 1 H), 2.31 - 2.53 (m, 3 H), 2.11 - 2.31 (m, 8 H), 1.76 - 1.95 (m, 3 H), 1.32 (d, *J*=8.6 Hz, 3 H), 0.77 - 0.90 (m, 3 H).

(*R*)-1-(2-((1-((Dimethylamino)methyl)cyclopropyl)methoxy)-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol (Example 180).



Example 180

Synthesized in an analogous manner to **Example 178** using (1-((dimethylamino)methyl)cyclopropyl)methanol (CAS#: 39943-41-4, Enamine) and Lithium bis(trimethylsilyl)amide in THF solution (1 M). The product was isolated as off-white solid. *m/z* (ESI): 578.3 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.91 (d, *J*=2.5 Hz, 1 H), 9.27 (s, 1 H), 7.77 (dd, *J*=9.0, 6.1 Hz, 1 H), 7.27 - 7.42 (m, 2 H), 7.03 (d, *J*=2.5 Hz, 1 H), 4.72 (d, *J*=1.9 Hz, 1 H), 4.22 - 4.46 (m, 3 H), 4.09 (br dd, *J*=19.8, 13.3 Hz, 1 H), 3.50 - 3.72 (m, 1 H), 3.30 - 3.45 (m, 3 H), 3.04 - 3.21 (m, 1 H), 2.69 - 2.88 (m, 5 H), 2.28 - 2.41 (m, 1 H), 2.10 - 2.23 (m, 1 H), 1.95 - 2.07 (m, 1 H), 1.61 - 1.79 (m, 3 H), 1.19 (d, *J*=9.4 Hz, 3 H), 0.86 (br s, 2 H), 0.67 - 0.80 (m, 5 H).

Biological Evaluation

Provided in this section is the biological evaluation of the specific examples provided herein.

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KRAS G12D TR-FRET Assay

Compounds of interest were prepared in a dose-response titration in DMSO, and 80 nL were added via Labcyte Echo to each well of a 384-well plate (Perkin Elmer 6008280). The His-tagged KRAS G12D protein (Amgen) was diluted to 20 nM in Assay Buffer (20 mM HEPES, pH 7.4, 10 mM MgCl₂, 50 mM NaCl, 0.1% BSA, 0.01% Tween-20, 10 μM GDP) and 2 uL was added to the appropriate wells of the 384-well plate. The plate was incubated for 30 minutes at room temperature. Biotinylated KRPeP-2d substrate (Amgen) was diluted to 20 nM in Assay Buffer and 2 μL was added to all wells and incubated for 1 hour at room temperature. Detection Reagent (0.4 nM LANCE Eu-W1024 Anti-6xHis (Perkin Elmer AD0401), 5 nM streptavidin-d2 (Cisbio 610SADLA)) was prepared in Assay Buffer, then 4 μL was added to the plate and incubated for 1 hour at room temperature. Plates were read using PerkinElmer EnVision (ex: 320 nm, em1: 665 nm, em2: 615 nm) and em1/em2 data was used to generate curve fits using a 4-parameter logistic model to calculate IC₅₀ values.

KRAS G12D Coupled Nucleotide Exchange Assay

Purified GDP-bound KRAS protein (aa 1-169), containing both G12D and C118A amino acid substitutions and an *N*-terminal His-tag, was pre-incubated in assay buffer (25 mM HEPES pH 7.4, 10 mM MgCl₂, and 0.01% Triton X-100) with a compound dose-response titration for 2 hours. Following compound pre-incubation, purified SOS protein (aa 564-1049) and GTP (Roche 10106399001) were added to the assay wells and incubated for an additional 30 min. To determine the extent of inhibition of SOS-mediated nucleotide exchange, purified GST-tagged cRAF (aa 1-149), nickel chelate AlphaLISA acceptor beads (PerkinElmer AL108R), and AlphaScreen glutathione donor beads (PerkinElmer 6765302) were added to the assay wells and incubated for 10 minutes. The assay plates were then read on a PerkinElmer EnVision Multilabel Reader, using AlphaScreen® technology, and data were analyzed using a 4-parameter logistic model to calculate IC₅₀ values.

Phospho-ERK1/2 MSD Assay

AsPC-1 (ATCC® CRL-1682™) cells were cultured in RPMI 1640 Medium (ThermoFisher Scientific 11875093) containing 10% fetal bovine serum (ThermoFisher

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Scientific 16000044) and 1x penicillin-streptomycin-glutamine (ThermoFisher Scientific 10378016). Sixteen hours prior to compound treatment, AsPC-1 cells were seeded in 96-well cell culture plates at a density of 25,000 cells/well and incubated at 37 °C, 5% CO₂. A compound dose-response titration was diluted in growth media, added to appropriate wells of a cell culture plate, and then incubated at 37 °C, 5% CO₂ for 2 hours. Following compound treatment, cells were washed with ice-cold Dulbecco's phosphate-buffered saline, no Ca²⁺ or Mg²⁺ (ThermoFisher Scientific 14190144), and then lysed in RIPA buffer (50 mM Tris-HCl pH 7.5, 1% Igepal, 0.5% sodium deoxycholate, 150 mM NaCl, and 0.5% sodium dodecyl sulfate) containing protease inhibitors (Roche 4693132001) and phosphatase inhibitors (Roche 4906837001). Phosphorylation of ERK1/2 in compound-treated lysates was assayed using Phospho-ERK1/2 Whole Cell Lysate kits (Meso Scale Discovery K151DWD) according to the manufacturer's protocol. Assay plates were read on a Meso Scale Discovery Sector Imager 6000, and data were analyzed using a 4-parameter logistic model to calculate IC₅₀ values.

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Table 13: Biochemical and cellular activity of examples.

Ex.#	KRAS G12D Binding IC ₅₀ (μM)	KRAS G12D Coupled Exchange IC ₅₀ (μM)	2 h p-ERK (AsPC-1 cells), IC ₅₀ (μM)
1	0.001	0.002	0.165
2	0.001	0.001	0.115
3	0.009	0.006	>10
4	0.021	0.008	>10
5	0.019	0.010	NT
6	0.055	0.025	>10
7	0.037	0.025	>10
8	0.082	0.039	>10
9	0.005	0.005	1.340
10	0.002	0.002	NT

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Ex.#	KRAS G12D Binding IC ₅₀ (μM)	KRAS G12D Coupled Exchange IC ₅₀ (μM)	2 h p-ERK (AsPC- 1 cells), IC ₅₀ (μM)
11	0.003	0.003	>10
12	0.002	0.003	0.377
13	0.002	0.004	0.107
14	0.012	0.007	1.100
15	0.017	0.012	1.480
16	0.031	0.013	2.860
17	0.038	0.039	3.180
18	0.003	0.003	0.105
19	0.026	0.034	NT
20	0.039	0.044	NT
21	0.032	0.032	NT
22	0.004	0.007	0.297
23	0.031	0.034	2.380
24	0.002	0.003	0.014
25	0.011	0.015	NT
26	0.004	0.006	NT
27	0.006	0.007	1.030
28	0.001	0.002	0.036
29	0.001	0.002	0.031
30	0.003	0.003	0.399
31	0.002	0.003	0.032
32	0.009	0.010	NT
33	0.013	0.008	NT
34	0.054	0.027	NT

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Ex.#	KRAS G12D Binding IC ₅₀ (μM)	KRAS G12D Coupled Exchange IC ₅₀ (μM)	2 h p-ERK (AsPC- 1 cells), IC ₅₀ (μM)
35	0.025	0.019	NT
36	0.007	0.005	0.344
37	0.042	0.023	NT
38	0.002	0.003	0.005
39	0.002	0.002	0.013
40	0.015	0.012	0.571
41	0.001	0.002	0.025
42	0.038	0.034	0.810
43	0.004	0.004	NT
44	0.004	0.008	NT
45	0.025	0.030	2.960
46	0.003	0.006	0.213
47	0.002	0.005	0.222
48	0.01	0.013	0.341
49	0.017	0.026	0.991
50	0.008	0.010	NT
51	0.025	0.019	NT
52	0.001	0.002	0.008
53	0.001	0.003	0.013
54	0.003	0.006	0.116
55	0.003	0.006	0.259
56	0.001	0.002	0.033
57	0.002	0.003	0.115
58	0.001	0.001	0.009

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Ex.#	KRAS G12D Binding IC₅₀ (μM)	KRAS G12D Coupled Exchange IC₅₀ (μM)	2 h p-ERK (AsPC- 1 cells), IC₅₀ (μM)
59	0.001	0.002	0.033
60	0.002	0.003	0.330
61	0.005	0.004	NT
62	0.04	0.042	NT
63	0.039	0.039	NT
64	0.006	0.005	NT
65	0.003	0.005	0.153
66	0.018	0.016	0.754
67	0.019	0.022	0.816
68	0.008	0.010	1.690
69	0.036	0.038	NT
70	0.032	0.035	NT
71	0.024	0.023	1.170
72	0.034	0.020	3.240
73	0.004	0.004	NT
74	0.007	0.006	2.710
75	0.027	0.035	NT
76	0.016	0.017	1.100
77	0.027	0.030	1.530
78	0.001	0.000	0.244
79	0.005	0.007	2.190
80	0.002	0.003	0.253
81	0.019	0.008	1.160
82	0.033	0.027	>10

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Ex.#	KRAS G12D Binding IC₅₀ (μM)	KRAS G12D Coupled Exchange IC₅₀ (μM)	2 h p-ERK (AsPC- 1 cells), IC₅₀ (μM)
83	0.002	0.003	>10
84	0.005	0.007	1.290
85	0.037	0.015	>10
86	0.064	0.022	>10
87	0.063	0.028	>10
88	0.006	0.002	>10
89	0.009	0.011	>3
90	0.016	0.008	NT
91	0.007	0.008	5.130
92	0.083	0.046	6.620
93	0.002	0.002	0.100
94	0.003	0.004	0.179
95	0.003	0.004	0.074
96	0.005	0.006	0.119
97	0.033	0.010	1.560
98	0.08	0.029	2.840
99	0.011	0.005	0.794
100	0.009	0.009	3.700
101	0.02	0.017	>10
102	0.002	0.002	1.900
103	0.004	0.007	NT
104	0.02	0.008	NT
105	0.009	0.008	0.939
106	0.01	0.007	NT

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Ex.#	KRAS G12D Binding IC ₅₀ (μM)	KRAS G12D Coupled Exchange IC ₅₀ (μM)	2 h p-ERK (AsPC- 1 cells), IC ₅₀ (μM)
107	0.008	0.007	NT
108	0.011	0.007	NT
109	0.012	0.011	NT
110	0.006	0.011	NT
111	0.017	0.011	NT
112	0.012	0.009	NT
113	0.066	0.043	NT
114	0.011	0.008	NT
115	0.003	0.005	0.083
116	0.004	0.007	0.792
117	0.009	0.014	>10
118	0.003	0.002	0.105
119	0.035	0.017	NT
120	0.004	0.008	0.222
121	0.006	0.006	NT
122	0.033	0.013	NT
123	0.047	0.024	NT
124	0.07	0.037	NT
125	0.004	0.004	NT
126	0.037	0.024	3.340
127	0.002	0.003	0.008
128	0.002	0.003	0.293
129	0.001	0.004	0.064
130	0.004	0.006	NT

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Ex.#	KRAS G12D Binding IC₅₀ (μM)	KRAS G12D Coupled Exchange IC₅₀ (μM)	2 h p-ERK (AsPC- 1 cells), IC₅₀ (μM)
131	0.004	0.004	NT
132	0.001	0.001	0.119
133	0.002	0.004	0.661
134	0.002	0.019	0.259
135	0.001	0.002	0.081
136	0.01	0.014	0.614
137	0.002	0.002	0.040
138	0.016	0.013	>10
139	0.005	0.012	0.116
140	0.003	0.004	0.081
141	0.004	0.004	0.198
142	0.014	0.011	NT
143	0.062	0.036	>10
144	0.006	0.013	NT
145	0.008	0.008	0.593
146	0.002	0.002	0.233
147	0.015	0.013	0.714
148	0.038	0.041	NT
149	0.012	0.008	0.702
150	0.003	0.004	1.430
151	0.011	0.009	NT
152	0.004	0.006	2.670
153	0.004	0.007	0.353
154	0.016	0.022	NT

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Ex.#	KRAS G12D Binding IC ₅₀ (μM)	KRAS G12D Coupled Exchange IC ₅₀ (μM)	2 h p-ERK (AsPC- 1 cells), IC ₅₀ (μM)
155	0.033	0.030	NT
156	0.001	0.002	0.172
157	0.017	0.016	1.240
158	0.002	0.004	1.420
159	0.002	0.003	3.080
160	0.003	0.004	0.414
161	0.076	0.049	NT
162	0.002	0.004	1.610
163	0.011	0.010	2.730
164	0.003	0.005	1.200
165	0.001	0.001	1.160
166	0.003	0.004	0.094
167	0.002	0.003	0.012
168	0.002	0.003	0.034
169	0.003	0.003	0.040
170	0.005	0.003	0.018
171	0.003	0.002	0.002
172	0.012	0.006	0.086
173	0.004	0.006	0.022
174	0.335	0.325	NT
175	0.008	0.005	0.01
176	0.005	0.003	0.005
177	0.024	0.012	0.109
178	0.005	0.003	0.008

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Ex.#	KRAS G12D Binding IC ₅₀ (μM)	KRAS G12D Coupled Exchange IC ₅₀ (μM)	2 h p-ERK (AsPC- 1 cells), IC ₅₀ (μM)
179	0.005	0.002	0.018
180	0.003	0.003	0.012

NT: not tested.

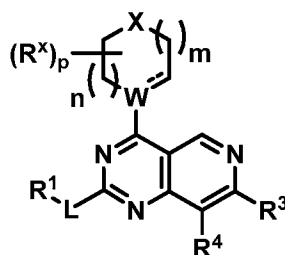
REFERENCES

All references, for example, a scientific publication or patent application publication,
5 cited herein are incorporated herein by reference in their entirety and for all purposes to the
same extent as if each reference was specifically and individually indicated to be
incorporated by reference in its entirety for all purposes.

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What is claimed is:

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt of said compound, wherein;

--- is a single bond or a double bond;

W is C, CH or N, wherein when W is CH or N, --- is a single bond;

X is CH_2 or $CH=CH$;

10 n is 0, 1 or 2;

m is 0, 1 or 2;

p is 0, 1, 2, 3 or 4;

each R^x is hydroxyl, halogen, oxo, cyano, $-N(R^z)_2$, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, 5-7 membered heteroaryl, $-T-R^y$ or two R^x taken together with adjacent carbon atoms can form C_{3-7} cycloalkyl, a 5-7 membered heterocycloalkyl, wherein each C_{3-7} cycloalkyl or 5-7 membered heterocycloalkyl is further substituted with 0-3 occurrences of R^y or two R^x taken together can form a bridged ring where the bridge is selected from one of the following: $-C_{1-4}$ alkylene, $-C_{1-4}$ alkylene- O - C_{1-4} alkylene-, $-O$ -, $-S$ - or $-C_{1-4}$ alkylene- S - C_{1-4} alkylene- and wherein each C_{1-4} alkylene is further substituted with 0-2 occurrences of R^y ;

L is C_{1-6} alkylene, $-O$ - C_{1-6} alkylene, $-S$ - C_{1-6} alkylene, NR^z , O or S , wherein each C_{1-6} alkylene, $-O$ - C_{1-6} alkylene and $-S$ - C_{1-6} alkylene chain is substituted with 0-2 occurrences of R^2 ;

25 R^1 is hydroxyl, aryl, heteroaryl, C_{3-8} cycloalkyl or heterocycloalkyl substituted with 0-3 occurrences of R^5 ;

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R^2 is halogen, hydroxyl, C_{1-4} alkyl or two R^2 on the same or adjacent carbon atoms can be taken together to form a C_{3-7} cycloalkyl;

R^3 is aryl or heteroaryl substituted with 0-3 occurrences of R^6 ;

R^4 is hydrogen, hydroxyl, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl or cyano;

each R^5 is halogen, oxo, hydroxyl, amino or C_{1-4} alkyl;

each R^6 is halogen, hydroxyl, cyano, $-N(R^Z)_2$, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{2-4} alkynyl or C_{3-6} cycloalkyl;

T is C_{1-4} alkylene, $-S(O)_2-$, $-C(O)-$, $-C_{1-4}$ alkylene- $C(O)-$, $-N(H)-C(O)-$, $-N(H)-S(O)_2-$, C_{1-4} alkylene- $S(O)_2-$ or $-S-$;

R^y is halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, hydroxyl, cyano or $-N(R^Z)_2$; and

R^Z is hydrogen or C_{1-4} alkyl.

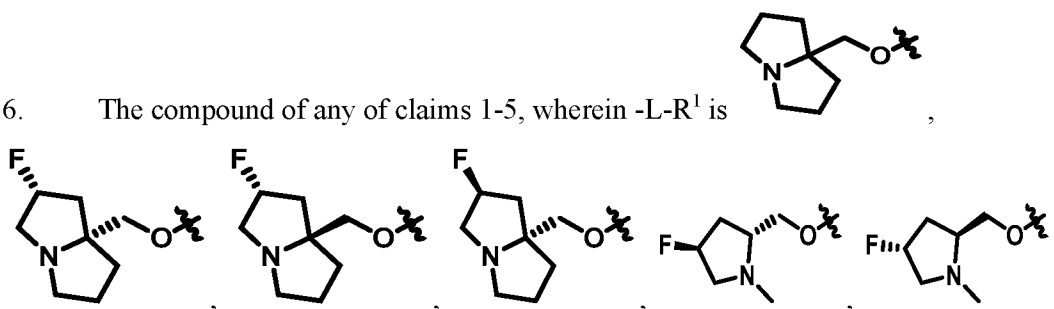
2. The compound of claim 1, wherein L is $-O-C_{1-6}$ alkylene (e.g., $-O$ -methylene-, $-O$ -ethylene- or $-O$ -*n*-propylene) substituted with 0-2 occurrences of R^2 .

3. The compound of any of claims 1-2, wherein L is $-O$ -ethylene or $-O$ -*n*-propylene substituted with 0-2 occurrences of R^2 .

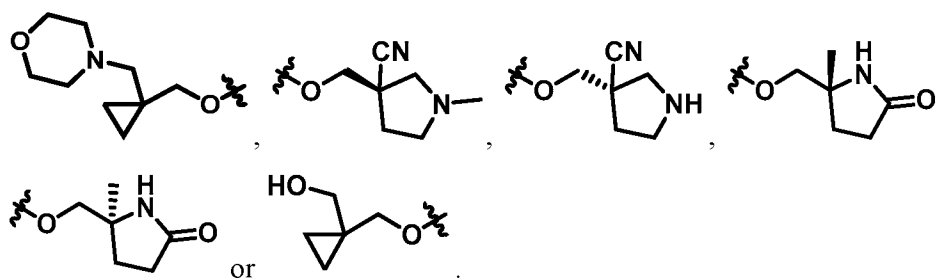
4. The compound of any of claims 1-3, wherein R^1 is hydroxyl or heterocycloalkyl substituted with 0-3 occurrences of R^5 .

5. The compound of any of claims 1-4, wherein R^5 is halogen, cyano, C_{1-4} alkyl or oxo.

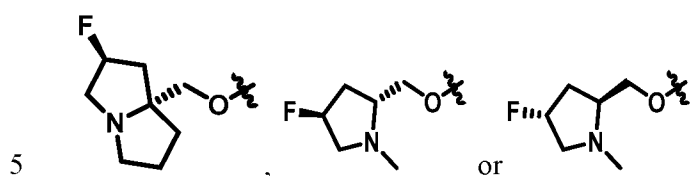
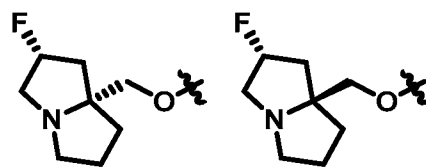
6. The compound of any of claims 1-5, wherein $-L-R^1$ is



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7. The compound of claim 6, wherein -L-R¹ is



8. The compound of any of claims 1-7, wherein R³ is aryl substituted with 0-3 occurrences of R⁶.

10 9. The compound of claim 8, wherein R³ is phenyl or naphthyl substituted with 0-3 occurrences of R⁶.

10. The compound of any of claims 1-7, wherein R³ is heteroaryl substituted with 0-3 occurrences of R⁶.

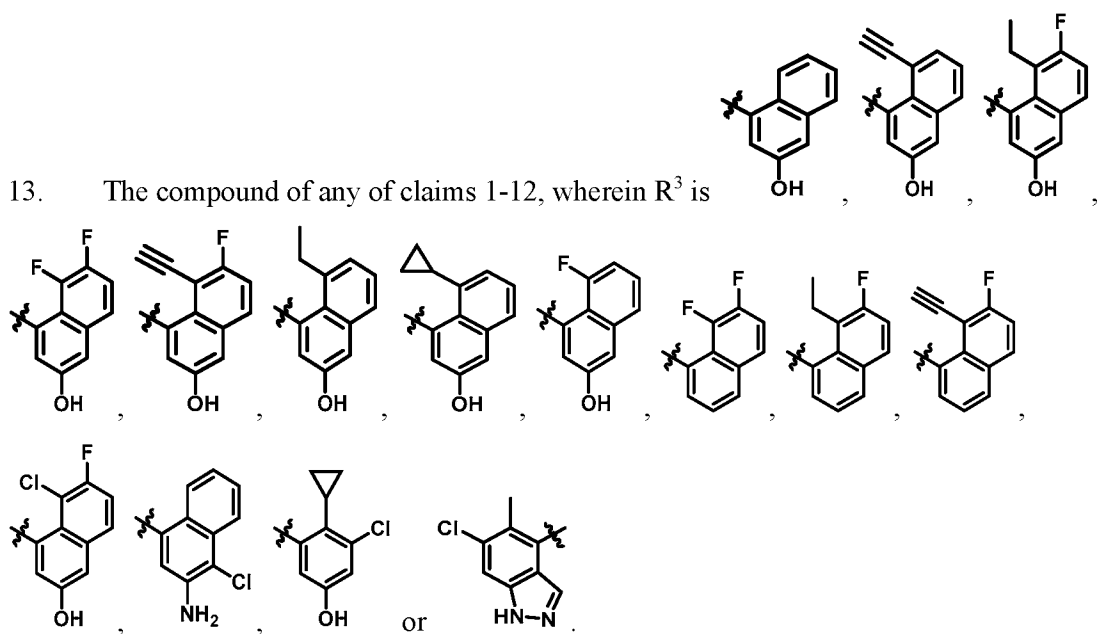
15

11. The compound of any of claims 8-10, wherein R⁶ is hydroxyl, halogen, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl or -N(R^z)₂.

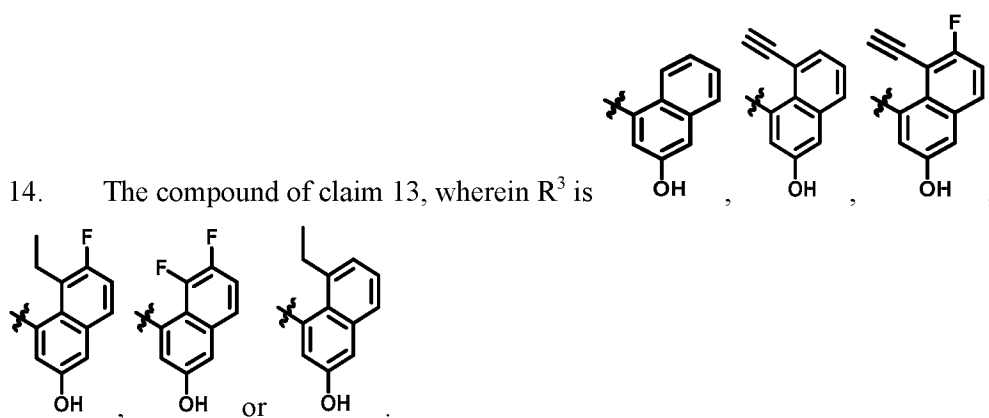
12. The compound of claim 11, wherein R⁶ is hydroxyl, methyl, ethyl, trifluoromethyl, difluoromethyl, ethynyl, fluorine, chlorine, cyclopropyl or -NH₂.

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5 14. The compound of claim 13, wherein R^3 is

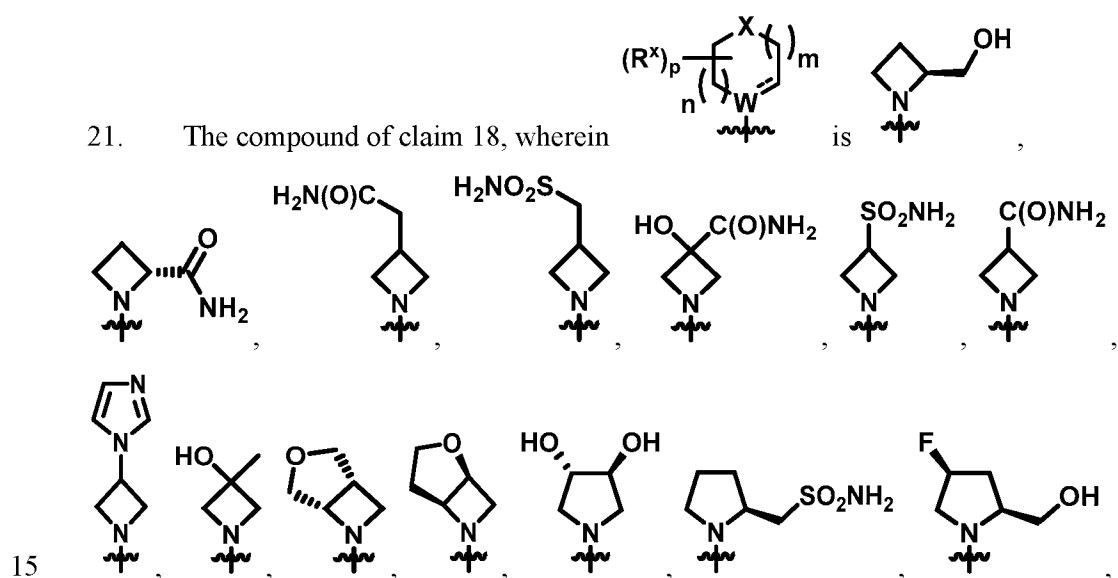


15. The compound of any of claims 1-14, wherein W is N and --- is a single bond.

10 16. The compound of any of claims 1-15, wherein X is CH_2 .

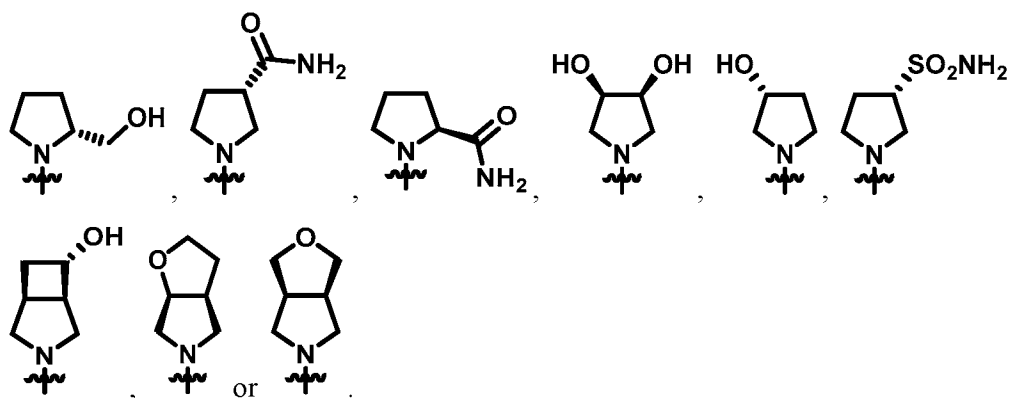
17. The compound of claim 16, wherein n is 0 and m is 0; n is 1 and m is 0; or n is 0 and m is 1.

18. The compound of claim 17, wherein p is 0, 1 or 2.
19. The compound of claim 18, wherein each R^x is hydroxyl, halogen, C₁₋₄ alkyl, 5-7 membered heteroaryl, -T-R_y or two R^x are taken together with adjacent carbon atoms to form a C₃₋₇ cycloalkyl or 5-7 membered heterocycloalkyl substituted with 0-3 occurrences of R^y.
20. The compound of claim 18, wherein each R^x is hydroxyl, methyl, fluorine, -CH₂OH, -C(O)NH₂, -CH₂C(O)NH₂, -CH₂S(O)₂NH₂, -S(O)NH₂, 1-imidazolyl or two R^x are taken together with adjacent carbon atoms to form a cyclobutyl, 1-tetrahydrofuranyl or 2-tetrahydrofuranyl, each of which is substituted with 0-3 occurrences of R^y.



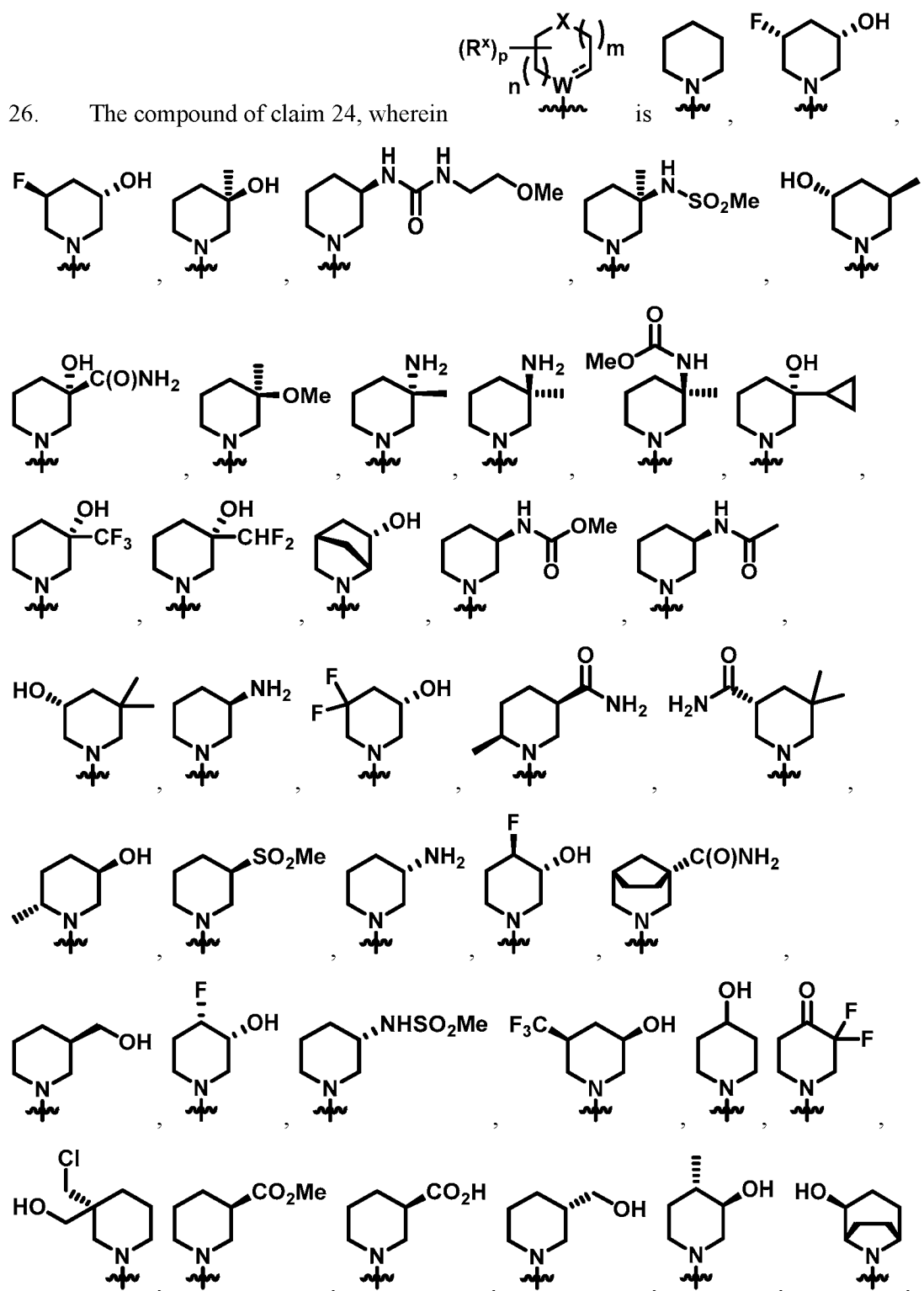
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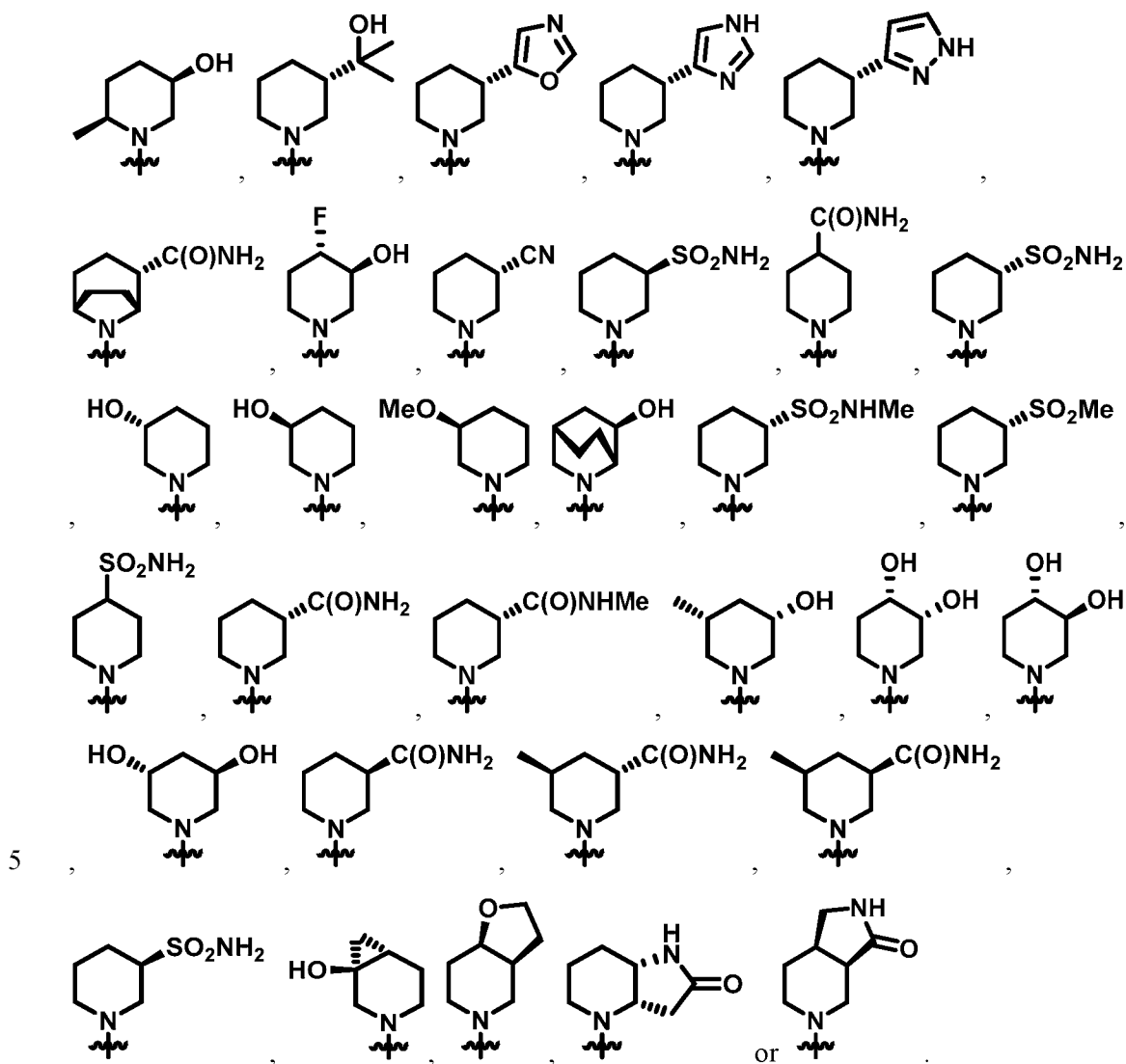


22. The compound of claim 16, wherein n is 1 and m is 1.
- 5 23. The compound of claim 22, wherein p is 0, 1, 2 or 3.
24. The compound of claim 23, wherein each R^x is hydroxyl, cyano, oxo, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₇ cycloalkyl, 5-7 membered heteroaryl, -N(R^z)₂, -T-R^y,
 10 two R^x are taken together with adjacent carbon atoms to form a C₃₋₇ cycloalkyl or 5-7 membered heterocycloalkyl substituted with 0-3 occurrences of R^y or two R^x taken together can form a -C₁₋₄ alkylene bridged ring substituted with 0-2 occurrences of R^y.
25. The compound of claim 24, wherein each R^x is hydroxyl, cyano, oxo, fluorine,
 15 methyl, methoxy, trifluoromethyl, difluoromethyl, chloromethyl, cyclopropyl, -NH₂, 5-oxazolyl, 4-imidazolyl, -pyrazolyl, -NHC(O)OMe, -S(O)₂Me, -NHC(O)Me, -NHC(O)-N(H)CH₂CH₂OMe, -CH₂OH, -NHS(O)₂Me, -CO₂H, -C(O)₂Me, 1-isopropanol, -S(O)₂NH₂, -C(O)NH₂, -S(O)₂N(H)Me, -C(O)N(H)Me or two R^x are taken together with adjacent carbon atoms to form a cyclopropyl, 1-tetrahydrofuranyl, 1-pyrrolidinyl or 2-pyrrolidinyl substituted with
 20 0-3 occurrences of R^y or two R^x taken together can form a methylene or ethylene bridged ring substituted with 0-2 occurrences of R^y.

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27. The compound of claim 16, wherein n is 1 and m is 2; n is 2 and m is 1; or n is 2 and m is 2.

28. The compound of claim 27, wherein p is 0, 1, 2 or 3.

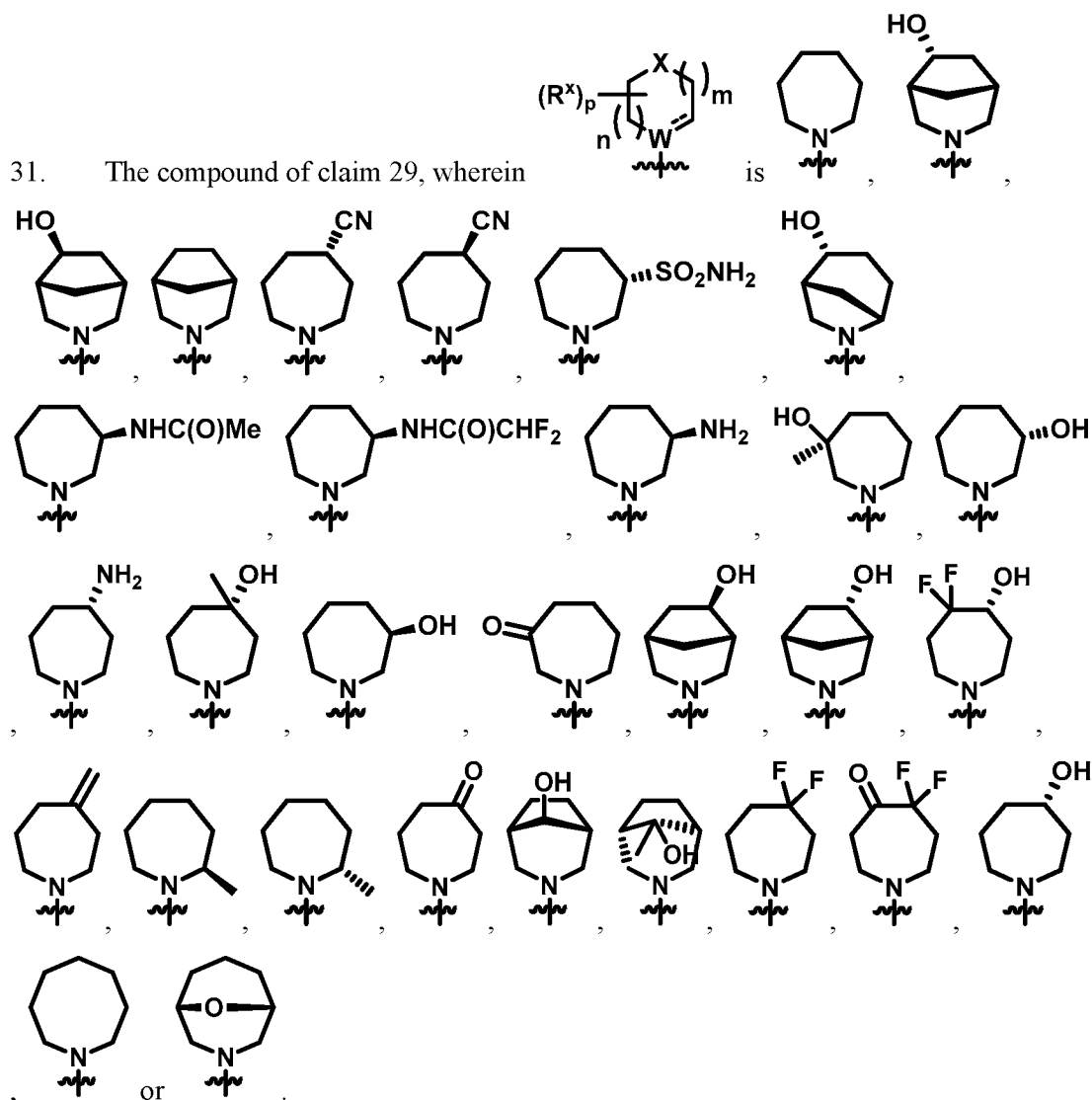
29. The compound of claim 28, wherein R^x is C_{1-4} alkyl, C_{1-4} alkenyl, cyano, hydroxy, halogen, oxo, $-N(R^z)_2$, $-T-R^y$ or two R^x taken together can form a -O- or $-C_{1-4}$ alkylene

15 bridged ring substituted with 0-2 occurrences of R^y .

30. The compound of claim 29, wherein Rx is hydroxy, cyano, oxo, fluorine, methyl, methenyl, -SO₂NH₂, -NHC(O)Me, -NHC(O)CF₂H or two R^x taken together can form a -O- or methylene bridged ring substituted with 0-2 occurrences of R^y.

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31. The compound of claim 29, wherein



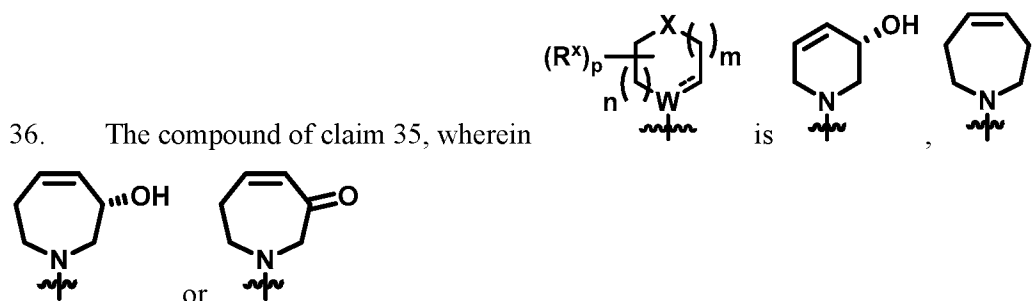
32. The compound of any of claims 1-15, wherein X is CH=CH.

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33. The compound of claim 32, wherein n is 0 and m is 1 or n is 1 and m is 1.

34. The compound of claim 33, wherein p is 0 or 1.

35. The compound of claim 34, wherein each Rx is hydroxyl or oxo.



37. The compound of claim 1, wherein the compound is selected from one of the following compounds:
- (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-sulfonamide;
- 4-(4-(Azepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidine-3-carboxamide;
- (*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidine-2-carboxamide;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azetidine-2-carboxamide;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide;

- (*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-sulfonamide;
- 2-(1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azetidin-3-yl)acetamide;
- 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.0]heptan-6-ol;
- (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;
- (3*S*,4*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidine-3,4-diol;
- (*R*)-1-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;
- (*R*)-1-(7-(8-Ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;
- (*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(3-methoxypiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidin-3-ol;
- (1*R*,4*S*)-2-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-azabicyclo[2.2.2]octan-6-ol;
- 3-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol;

- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*S*)-2-(hydroxymethyl)azetidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 4-(4-((1*S*,5*R*)-3-Oxa-6-azabicyclo[3.2.0]heptan-6-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 5 *rel*-4-(4-((1*R*,5*R*)-2-Oxa-6-azabicyclo[3.2.0]heptan-6-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 10 4-(4-(3-(Chloromethyl)-3-(hydroxymethyl)piperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-
- 15 azabicyclo[3.2.1]octan-6-ol (Isomer 1);
- 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-
- azabicyclo[3.2.1]octan-6-ol (Isomer 2);
- (1*R*,5*R*,6*R*)-3-(7-(8-ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-
- 20 azabicyclo[3.2.1]octan-6-ol (Isomer 1);
- (1*R*,5*R*,6*R*)-3-(7-(3-chloro-2-cyclopropyl-5-hydroxyphenyl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-
- azabicyclo[3.2.1]octan-6-ol (Isomer 1);
- 25 (1*R*,5*R*,6*R*)-3-(7-(8-ethynyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-
- azabicyclo[3.2.1]octan-6-ol (Isomer 1);
- 1-(7-(8-Ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-
- 30 dimethylpiperidin-3-ol;

- (3*R*,6*S*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-methylpiperidin-3-ol;
- 8-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octan-2-ol 2,2,2-trifluoroacetate;
- (3*R*,6*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-methylpiperidin-3-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(hexahydro-5*H*-furo[2,3-*c*]pyrrol-5-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 3-(Difluoromethyl)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol (Isomer 1);
- 3-(Difluoromethyl)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol (Isomer 2);
- 3-(Difluoromethyl)-1-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol (Isomer 1);
- rel*-5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((3*aR*,7*aR*)-hexahydrofuro[3,2-*b*]pyridin-4(2*H*)-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-(fluoromethyl)piperidin-3-ol (Isomer 1);

- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-(fluoromethyl)piperidin-3-ol (Isomer 2);
- (3*R*)-1-(7-(8-ethyl-3-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol (Isomer 2);
- (3*R*)-1-(7-(8-ethyl-3-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol (Isomer 1);
- (3*R*)-1-(7-(8-Allyl-3-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-dimethylpiperidine-3-carboxamide;
- 4-(4-((*R*)-3-Aminopiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 4-(4-((*S*)-3-Amino-3-methylpiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 4-(4-((*R*)-3-Amino-3-methylpiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- (3*R*,4*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-4-fluoropiperidin-3-ol;
- (*R*)-1-(7-(7,8-Difluoronaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (*R*)-1-(7-(8-Ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 2-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-azabicyclo[2.2.1]heptan-6-ol;

- (*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aR*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (*R*)-1-(7-(8-Chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 5 (*R*)-1-(8-Fluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (*R*)-1-(7-(8-Ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 10 (*R*)-1-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (*R*)-1-(8-Fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-7-(3-hydroxynaphthalen-1-yl)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 15 *rel*-(3*aR*,6*aS*)-5-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)hexahydropyrrolo[3,4-*c*]pyrrol-1(2*H*)-one;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-*rel*-((3*aR*,7*aS*)-hexahydrofuro[3,2-*c*]pyridin-5(4*H*)-yl)pyrido[4,3-*d*]pyrimidin-
- 20 7-yl)naphthalen-2-ol;
- rel*-(3*aR*,7*aR*)-4-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)octahydro-2*H*-pyrrolo[3,2-*b*]pyridin-2-one;
- rel*-(3*S*,6*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-
- 25 methylpiperidine-3-carboxamide;
- 3-Ethyl-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;

- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(((*S*)-3-(hydroxymethyl)-3-methylpiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(((*R*)-3-(hydroxymethyl)-3-methylpiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidine-3-carboxamide;
- 8-(7-(8-Ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-methyl-8-azabicyclo[3.2.1]octan-2-ol;
- 8-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-methyl-8-azabicyclo[3.2.1]octan-2-ol;
- 2-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-methyl-2-azabicyclo[2.2.1]heptan-6-ol;
- 2-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-azabicyclo[2.2.1]heptan-6-one;
- N*-(((*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-yl)acetamide;
- 1-(((*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-yl)-3-(2-methoxyethyl)thiourea;
- N*-(((*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-yl)methanesulfonamide;

- N*-((*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-yl)acetamide;
- Methyl ((*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-yl)carbamate;
- Methyl ((*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-yl)carbamate;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-*N*-methylpiperidine-3-sulfonamide;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*R*)-2-methylazepan-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*S*)-2-methylazepan-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- (1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azetidin-3-yl)methanesulfonamide;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-hydroxyazetidine-3-carboxamide;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(3-(methylsulfonyl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-4-sulfonamide;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidine-3-sulfonamide;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azetidine-3-sulfonamide;

- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azetidine-3-carboxamide;
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-*N*-methylpiperidine-3-
5 carboxamide;
(*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-carboxamide;
4-(4-(3-(1*H*-Imidazol-1-yl)azetidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-
10 pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylazetidin-3-ol;
4-(4-(Azocan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
15 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-4-one;
rac-(3*R*,5*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-methylpiperidin-3-ol;
20 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-ol;
3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-8-methyl-3-
25 azabicyclo[3.2.1]octan-8-ol;
3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[4.1.0]heptan-1-ol;
rel-(3*R*,4*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-
30 3,4-diol;

- rel*-(3*S*,4*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3,4-diol;
- rel*-(3*aR*,7*aR*)-5-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)octahydro-3*H*-pyrrolo[3,4-*c*]pyridin-3-one;
- 4-(4-((*S*)-3-Aminopiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 4-(4-(3-Azabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 4-(4-(3-(1*H*-Imidazol-4-yl)piperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 4-(4-(3-(1*H*-Pyrazol-5-yl)piperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(3-(oxazol-5-yl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-1,2,3,6-tetrahydropyridin-3-ol;
- N*-(1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide;
- 5-Ethyl-6-fluoro-4-(8-fluoro-4-((2*S*,4*S*)-4-fluoro-2-(hydroxymethyl)pyrrolidin-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- (3*R*,4*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-4-fluoropiperidin-3-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*R*)-2-(hydroxymethyl)pyrrolidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;

- rac*-(3*S*,5*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-fluoropiperidin-3-ol;
- (3*S*,4*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidine-3,4-diol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-difluoropiperidin-3-ol;
- ((*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidin-2-yl)methanesulfonamide;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-difluoroazepan-4-ol;
- 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octane-1-carboxamide;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((3*aR*,6*aS*)-tetrahydro-1*H*-furo[3,4-*c*]pyrrol-5(3*H*)-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- rac*-(1*S*,5*S*)-8-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octane-2-carboxamide;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(3-(2-hydroxypropan-2-yl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*S*)-3-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- Methyl (*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-carboxylate;

- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-one;
5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*R*)-3-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
5
(*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-ol;
(*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-ol;
10 4-(4-((*R*)-3-Aminoazepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
N-((*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-yl)-2,2-difluoroacetamide;
15 *N*-((*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-yl)acetamide;
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-1,2,6,7-tetrahydro-3*H*-azepin-3-one;
20 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2,3,6,7-tetrahydro-1*H*-azepin-3-ol;
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylazepan-3-ol (Isomer 1);
25 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylazepan-3-ol (Isomer 2);

- (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-carboxylic acid;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(2,3,6,7-tetrahydro-1*H*-azepin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 4-(4-((*R*)-5-Amino-3,3-difluoropiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-4-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-4-methylazepan-4-ol;
- 4-(4-(4-Aminoazepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(4-methyleneazepan-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octane-6-carbonitrile (Isomer Mix 1);
- 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octane-6-carbonitrile (Isomer Mix 2);
- 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.2]nonane-6-carbonitrile;
- (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-(methyl-*d*3)piperidin-3-ol;
- (*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-(methyl-*d*3)piperidin-3-ol;

- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(3-methoxy-3-methylpiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 4-(4-(4,4-Difluoroazepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-difluoroazepan-4-one;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-carbonitrile;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3,3-difluoropiperidin-4-one;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-4-ol;
- (3*R*,5*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-(trifluoromethyl)piperidin-3-ol;
- 6-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-(trifluoromethyl)piperidin-3-ol;
- 3-Cyclopropyl-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepane-3-sulfonamide;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-hydroxypiperidine-3-carboxamide;

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- 4-(4-(3-((Difluoromethyl)sulfonyl)piperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-methylpiperidine-3-carboxamide;
- (*R*)-1-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-sulfonamide;
- 4-(4-(Azepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5,6-difluoronaphthalen-2-ol;
- (*R*)-1-(7-(8-Cyclopropyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (*R*)-1-(8-Chloro-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-8-methylpyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*S*,7*aR*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol bis(2,2,2-trifluoroacetate);
- (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol; or
- (*R*)-1-(2-((1-((Dimethylamino)methyl)cyclopropyl)methoxy)-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol.

38. The compound of claim 1, wherein the compound is selected from one of the following compounds:

- (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-sulfonamide;
- 4-(4-(Azepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidine-3-carboxamide;
- (*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidine-2-carboxamide;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azetidine-2-carboxamide;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide;
- (*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-sulfonamide;
- 2-(1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azetidin-3-yl)acetamide;
- 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.0]heptan-6-ol;
- (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;
- (3*S*,4*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidine-3,4-diol;
- (*R*)-1-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;

- (*R*)-1-(7-(8-Ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;
(*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;
5 ol;
5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(3-methoxypiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidin-3-ol;
10 (1*R*,4*S*)-2-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-azabicyclo[2.2.2]octan-6-ol;
3-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol;
15 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*S*)-2-(hydroxymethyl)azetidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
4-(4-((1*S*,5*R*)-3-Oxa-6-azabicyclo[3.2.0]heptan-6-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
20 *rel*-4-(4-((1*R*,5*R*)-2-Oxa-6-azabicyclo[3.2.0]heptan-6-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
4-(4-(3-(Chloromethyl)-3-(hydroxymethyl)piperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
25 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 1);

- 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 2);
- (1*R*,5*R*,6*R*)-3-(7-(8-ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 1);
- (1*R*,5*R*,6*R*)-3-(7-(3-chloro-2-cyclopropyl-5-hydroxyphenyl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 1);
- (1*R*,5*R*,6*R*)-3-(7-(8-ethynyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 1);
- 1-(7-(8-Ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-dimethylpiperidin-3-ol;
- (3*R*,6*S*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-methylpiperidin-3-ol;
- 8-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octan-2-ol 2,2,2-trifluoroacetate;
- (3*R*,6*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-methylpiperidin-3-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(hexahydro-5*H*-furo[2,3-*c*]pyrrol-5-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 3-(Difluoromethyl)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol (Isomer 1);

- 3-(Difluoromethyl)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol (Isomer 2);
- 3-(Difluoromethyl)-1-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol (Isomer 1);
- rel*-5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((3*aR*,7*aR*)-hexahydrofuro[3,2-*b*]pyridin-4(2*H*)-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-dimethylpiperidine-3-carboxamide;
- 4-(4-((*R*)-3-Aminopiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 4-(4-((*S*)-3-Amino-3-methylpiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 4-(4-((*R*)-3-Amino-3-methylpiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- (3*R*,4*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-4-fluoropiperidin-3-ol;
- (*R*)-1-(7-(7,8-Difluoronaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (*R*)-1-(7-(8-Ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 2-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-azabicyclo[2.2.1]heptan-6-ol;
- (*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aR*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;

- (*R*)-1-(7-(8-Chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (*R*)-1-(8-Fluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (*R*)-1-(7-(8-Ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (*R*)-1-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (*R*)-1-(8-Fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-7-(3-hydroxynaphthalen-1-yl)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- rel*-(3*aR*,6*aS*)-5-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)hexahydropyrrolo[3,4-*c*]pyrrol-1(2*H*)-one;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-*rel*-((3*aR*,7*aS*)-hexahydrofuro[3,2-*c*]pyridin-5(4*H*)-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- rel*-(3*aR*,7*aR*)-4-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)octahydro-2*H*-pyrrolo[3,2-*b*]pyridin-2-one;
- rel*-(3*S*,6*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-methylpiperidine-3-carboxamide;
- 3-Ethyl-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*S*)-3-(hydroxymethyl)-3-methylpiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;

- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*R*)-3-(hydroxymethyl)-3-methylpiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidine-3-carboxamide;
- 8-(7-(8-Ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-methyl-8-azabicyclo[3.2.1]octan-2-ol;
- 8-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-methyl-8-azabicyclo[3.2.1]octan-2-ol;
- 2-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-methyl-2-azabicyclo[2.2.1]heptan-6-ol;
- 2-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-azabicyclo[2.2.1]heptan-6-one;
- N*-((*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-yl)acetamide;
- 1-((*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-yl)-3-(2-methoxyethyl)thiourea;
- N*-((*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-yl)methanesulfonamide;
- N*-((*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-yl)acetamide;

- Methyl ((*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-yl)carbamate;
- Methyl ((*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-yl)carbamate;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-*N*-methylpiperidine-3-sulfonamide;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*R*)-2-methylazepan-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*S*)-2-methylazepan-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- (1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azetidin-3-yl)methanesulfonamide;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-hydroxyazetidine-3-carboxamide;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(3-(methylsulfonyl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-4-sulfonamide;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidine-3-sulfonamide;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azetidine-3-sulfonamide;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azetidine-3-carboxamide;

- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-*N*-methylpiperidine-3-carboxamide;
- (*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-carboxamide;
- 4-(4-(3-(1*H*-Imidazol-1-yl)azetidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylazetidin-3-ol;
- 4-(4-(Azocan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-4-one;
- rac*-(3*R*,5*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-methylpiperidin-3-ol;
- 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-ol;
- 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-8-methyl-3-azabicyclo[3.2.1]octan-8-ol;
- 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[4.1.0]heptan-1-ol;
- rel*-(3*R*,4*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3,4-diol;

- rel*-(3*S*,4*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3,4-diol;
- rel*-(3*aR*,7*aR*)-5-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)octahydro-3*H*-pyrrolo[3,4-*c*]pyridin-3-one;
- 4-(4-((*S*)-3-Aminopiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 4-(4-(3-Azabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 4-(4-(3-(1*H*-Imidazol-4-yl)piperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 4-(4-(3-(1*H*-Pyrazol-5-yl)piperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(3-(oxazol-5-yl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-1,2,3,6-tetrahydropyridin-3-ol;
- N*-(1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide;
- 5-Ethyl-6-fluoro-4-(8-fluoro-4-((2*S*,4*S*)-4-fluoro-2-(hydroxymethyl)pyrrolidin-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- (3*R*,4*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-4-fluoropiperidin-3-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*R*)-2-(hydroxymethyl)pyrrolidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;

- rac*-(3*S*,5*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-fluoropiperidin-3-ol;
- (3*S*,4*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidine-3,4-diol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-difluoropiperidin-3-ol;
- ((*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidin-2-yl)methanesulfonamide;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-difluoroazepan-4-ol;
- 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octane-1-carboxamide;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((3*aR*,6*aS*)-tetrahydro-1*H*-furo[3,4-*c*]pyrrol-5(3*H*)-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- rac*-(1*S*,5*S*)-8-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octane-2-carboxamide;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(3-(2-hydroxypropan-2-yl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*S*)-3-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- Methyl (*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-carboxylate;

- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-one;
5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*R*)-3-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
5 (R)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-ol;
(*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-ol;
10 4-(4-((*R*)-3-Aminoazepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
N-((*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-yl)-2,2-difluoroacetamide;
15 *N*-((*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-yl)acetamide;
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-1,2,6,7-tetrahydro-3*H*-azepin-3-one;
20 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2,3,6,7-tetrahydro-1*H*-azepin-3-ol;
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylazepan-3-ol (Isomer 1);
25 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylazepan-3-ol (Isomer 2);

- (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-carboxylic acid;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(2,3,6,7-tetrahydro-1*H*-azepin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 4-(4-((*R*)-5-Amino-3,3-difluoropiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-4-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-4-methylazepan-4-ol;
- 4-(4-(4-Aminoazepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(4-methyleneazepan-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octane-6-carbonitrile (Isomer Mix 1);
- 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octane-6-carbonitrile (Isomer Mix 2);
- 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.2]nonane-6-carbonitrile;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(3-methoxy-3-methylpiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 4-(4-(4,4-Difluoroazepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;

- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-difluoroazepan-4-one;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-carbonitrile;
- 5 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3,3-difluoropiperidin-4-one;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-4-ol;
- (3*R*,5*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-
- 10 fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-(trifluoromethyl)piperidin-3-ol;
- 6-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-2-ol;
- 15 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-(trifluoromethyl)piperidin-3-ol;
- 3-Cyclopropyl-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-
- 20 ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepane-3-sulfonamide;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-hydroxypiperidine-3-
- 25 carboxamide;
- 4-(4-(3-((Difluoromethyl)sulfonyl)piperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-
- 30 1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-methylpiperidine-3-carboxamide;

- (*R*)-1-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-sulfonamide;
 4-(4-(Azepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5,6-difluoronaphthalen-2-ol;
- 5 (*R*)-1-(7-(8-Cyclopropyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (*R*)-1-(8-Chloro-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-
- 10 methylpiperidin-3-ol; or
- (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-8-methylpyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol.
- 15 39. The compound of claim 1, wherein the compound is selected from one of the following compounds:
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidine-3-carboxamide;
- (*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-
- 20 fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidine-2-carboxamide;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azetidine-2-carboxamide;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-
- 25 1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide;
- 2-(1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azetidin-3-yl)acetamide;
- 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-
- 30 1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.0]heptan-6-ol;

- (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;
- (3*S*,4*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidine-3,4-diol;
- (*R*)-1-(7-(8-Ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(3-methoxypiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidin-3-ol;
- (1*R*,4*S*)-2-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-azabicyclo[2.2.2]octan-6-ol;
- 3-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*S*)-2-(hydroxymethyl)azetidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 4-(4-((1*S*,5*R*)-3-Oxa-6-azabicyclo[3.2.0]heptan-6-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- rel*-4-(4-((1*R*,5*R*)-2-Oxa-6-azabicyclo[3.2.0]heptan-6-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 4-(4-(3-(Chloromethyl)-3-(hydroxymethyl)piperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;

- 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 1);
- 3-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 2);
- (1*R*,5*R*,6*R*)-3-(7-(8-ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 1);
- (1*R*,5*R*,6*R*)-3-(7-(3-chloro-2-cyclopropyl-5-hydroxyphenyl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (Isomer 1);
- 1-(7-(8-Ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-dimethylpiperidin-3-ol;
- (3*R*,6*S*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-methylpiperidin-3-ol;
- 8-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octan-2-ol 2,2,2-trifluoroacetate;
- (3*R*,6*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-methylpiperidin-3-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(hexahydro-5*H*-furo[2,3-*c*]pyrrol-5-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 3-(Difluoromethyl)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol (Isomer 1);

- 3-(Difluoromethyl)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol (Isomer 2);
- 3-(Difluoromethyl)-1-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol (Isomer 1);
- rel*-5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((3*aR*,7*aR*)-hexahydrofuro[3,2-*b*]pyridin-4(2*H*)-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-dimethylpiperidine-3-carboxamide;
- 4-(4-((*R*)-3-Aminopiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 4-(4-((*S*)-3-Amino-3-methylpiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 4-(4-((*R*)-3-Amino-3-methylpiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- (3*R*,4*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-4-fluoropiperidin-3-ol;
- (*R*)-1-(7-(7,8-Difluoronaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- (*R*)-1-(7-(8-Ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
- 2-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-azabicyclo[2.2.1]heptan-6-ol;
- (*R*)-1-(7-(8-Chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;

- (*R*)-1-(8-Fluoro-7-(8-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
(*R*)-1-(7-(8-Ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
5 (*R*)-1-(7-(7,8-Difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
(*R*)-1-(8-Fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-7-(3-hydroxynaphthalen-1-yl)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;
rel-(3*aR*,6*aS*)-5-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)hexahydropyrrolo[3,4-*c*]pyrrol-1(2*H*)-one;
5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-*rel*-((3*aR*,7*aS*)-hexahydrofuro[3,2-*c*]pyridin-5(4*H*)-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
15 *rel*-(3*aR*,7*aR*)-4-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)octahydro-2*H*-pyrrolo[3,2-*b*]pyridin-2-one;
rel-(3*S*,6*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-methylpiperidine-3-carboxamide;
20 3-Ethyl-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;
5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*S*)-3-(hydroxymethyl)-3-methylpiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
25 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*R*)-3-(hydroxymethyl)-3-methylpiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;

- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidine-3-carboxamide;
- 8-(7-(8-Ethyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-methyl-8-azabicyclo[3.2.1]octan-2-ol;
- 8-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-methyl-8-azabicyclo[3.2.1]octan-2-ol;
- 2-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-methyl-2-azabicyclo[2.2.1]heptan-6-ol;
- 2-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-azabicyclo[2.2.1]heptan-6-one;
- N*-(((*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-yl)acetamide;
- 1-(((*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-yl)-3-(2-methoxyethyl)thiourea;
- N*-(((*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-yl)acetamide;
- Methyl (((*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-yl)carbamate;
- Methyl (((*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-yl)carbamate;

- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(((*R*)-2-methylazepan-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(((*S*)-2-methylazepan-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
5 (1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azetidin-3-yl)methanesulfonamide;
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-hydroxyazetidine-3-
10 carboxamide;
5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(3-(methylsulfonyl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidine-3-sulfonamide;
15 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azetidine-3-sulfonamide;
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azetidine-3-carboxamide;
20 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-*N*-methylpiperidine-3-carboxamide;
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylazetidin-3-ol;
25 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-4-one;
3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-ol;

- 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-8-methyl-3-azabicyclo[3.2.1]octan-8-ol;
- 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[4.1.0]heptan-1-ol;
- rel*-(3*R*,4*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3,4-diol;
- rel*-(3*S*,4*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3,4-diol;
- rel*-(3*aR*,7*aR*)-5-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)octahydro-3*H*-pyrrolo[3,4-*c*]pyridin-3-one;
- 4-(4-((*S*)-3-Aminopiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 4-(4-(3-(1*H*-Imidazol-4-yl)piperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 4-(4-(3-(1*H*-Pyrazol-5-yl)piperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(3-(oxazol-5-yl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- N*-(1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide;
- 5-Ethyl-6-fluoro-4-(8-fluoro-4-((2*S*,4*S*)-4-fluoro-2-(hydroxymethyl)pyrrolidin-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;

- (3*R*,4*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-4-fluoropiperidin-3-ol;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((*R*)-2-(hydroxymethyl)pyrrolidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
- rac*-(3*S*,5*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-fluoropiperidin-3-ol;
- 10 (3*S*,4*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidine-3,4-diol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-difluoropiperidin-3-ol;
- 15 ((*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)pyrrolidin-2-yl)methanesulfonamide;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-difluoroazepan-4-ol;
- 20 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octane-1-carboxamide;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-((3*aR*,6*aS*)-tetrahydro-1*H*-furo[3,4-*c*]pyrrol-5(3*H*)-yl)pyrido[4,3-*d*]pyrimidin-
- 25 7-yl)naphthalen-2-ol;
- rac*-(1*S*,5*S*)-8-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octane-2-carboxamide;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(3-(2-hydroxypropan-2-yl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-
- 30 yl)naphthalen-2-ol;

- Methyl (*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-carboxylate;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-one;
- 4-(4-(((*R*)-3-Aminoazepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
- N*-(((*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-yl)-2,2-difluoroacetamide;
- N*-(((*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-yl)acetamide;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-1,2,6,7-tetrahydro-3*H*-azepin-3-one;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2,3,6,7-tetrahydro-1*H*-azepin-3-ol;
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylazepan-3-ol (Isomer 1);
- 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylazepan-3-ol (Isomer 2);
- (*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-carboxylic acid;
- 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(2,3,6,7-tetrahydro-1*H*-azepin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;

- 4-(4-((*R*)-5-Amino-3,3-difluoropiperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-4-ol;
5 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-4-methylazepan-4-ol;
4-(4-(4-Aminoazepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(4-methyleneazepan-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
10 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octane-6-carbonitrile (Isomer Mix 1);
3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octane-6-carbonitrile (Isomer Mix 2);
15 3-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.2]nonane-6-carbonitrile;
20 5-Ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-4-(3-methoxy-3-methylpiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol;
4-(4-(4,4-Difluoroazepan-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;
25 1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5,5-difluoroazepan-4-one;
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidine-3-carbonitrile;
1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3,3-difluoropiperidin-4-one;
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(3*R*,5*S*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-(trifluoromethyl)piperidin-3-ol;

1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-(trifluoromethyl)piperidin-3-ol;

3-Cyclopropyl-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;

1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-hydroxypiperidine-3-carboxamide;

4-(4-(3-((Difluoromethyl)sulfonyl)piperidin-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol;

1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-methylpiperidine-3-carboxamide;

(*R*)-1-(7-(8-Cyclopropyl-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;

(*R*)-1-(8-Chloro-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol; or

(*R*)-1-(7-(8-Ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-8-methylpyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol.

40. A pharmaceutical composition comprising the compound according to any one of claims 1-39 or a pharmaceutically acceptable salt of said compound, and a pharmaceutically acceptable excipient.

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41. A compound according to any one of claims 1-39, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound, or the pharmaceutical composition according to claim 40 for use as a medicament.

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42. A compound according to any one of claims 1-39 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 40 for use in treating cancer.

10 43. A compound according to any one of claims 1-39 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 40 for use in treating cancer, wherein one or more cells express KRAS G12D mutant protein.

44. The compound or pharmaceutical composition for use of claims 42 or 43, wherein
15 the cancer is pancreatic cancer, colorectal cancer, non-small cell lung cancer, small bowel cancer, appendiceal cancer, cancer of unknown primary, endometrial cancer, mixed cancer types, hepatobiliary cancer, small cell lung cancer, cervical cancer, germ cell cancer, ovarian cancer, gastrointestinal neuroendocrine cancer, bladder cancer,
myelodysplastic/myeloproliferative neoplasms, head and neck cancer, esophagogastric
20 cancer, soft tissue sarcoma, mesothelioma, thyroid cancer, leukemia, or melanoma.

45. A use of the compound according to any one of claims 1-39 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 40 in the preparation of a medicament for treating cancer.

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46. A use of the compound according to any one of claims 1-39 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 40 in the preparation of a medicament for treating cancer, wherein one or more cells express KRAS G12D mutant protein.

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47. The use according to claim 45 or 46, wherein the cancer is non-small cell lung cancer, small bowel cancer, appendiceal cancer, colorectal cancer, cancer of unknown primary, endometrial cancer, mixed cancer types, pancreatic cancer, hepatobiliary cancer, small cell lung cancer, cervical cancer, germ cell cancer, ovarian cancer, gastrointestinal
5 neuroendocrine cancer, bladder cancer, myelodysplastic/myeloproliferative neoplasms, head and neck cancer, esophagogastric cancer, soft tissue sarcoma, mesothelioma, thyroid cancer, leukemia, or melanoma.

48. A method of treating cancer in a subject in need thereof, the method comprising
10 administering to the subject a therapeutically effective amount of the compound according to any one of to any one of claims 1-39 or a pharmaceutically acceptable salt thereof or a pharmaceutical composition according to claim 40.

49. A method of treating cancer in a subject in need thereof, the method comprising
15 administering to the subject a therapeutically effective amount of the compound according to any one of to any one of claims 1-39 or a pharmaceutically acceptable salt thereof or a pharmaceutical composition according to claim 40, wherein one or more cells express KRAS G12D mutant protein.

20 50. The method according to claim 48 or 49, wherein the cancer is non-small cell lung cancer, small bowel cancer, appendiceal cancer, colorectal cancer, cancer of unknown primary, endometrial cancer, mixed cancer types, pancreatic cancer, hepatobiliary cancer, small cell lung cancer, cervical cancer, germ cell cancer, ovarian cancer, gastrointestinal neuroendocrine cancer, bladder cancer, myelodysplastic/myeloproliferative neoplasms, head
25 and neck cancer, esophagogastric cancer, soft tissue sarcoma, mesothelioma, thyroid cancer, leukemia, or melanoma.

51. The method according to claim 48 or 49, wherein the cancer is non-small cell lung cancer, colorectal cancer, pancreatic cancer, appendiceal cancer, endometrial cancer,
30 esophageal cancer, cancer of unknown primary, ampullary cancer, gastric cancer, small bowel cancer, sinonasal cancer, bile duct cancer, or melanoma.

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52. The method according to claim 51, wherein the cancer is non-small cell lung cancer.
53. The method according to claim 51, wherein the cancer is colorectal cancer.
- 5 54. The method according to claim 51, wherein the cancer is pancreatic cancer.
55. The method according to anyone of claims 48-54, wherein the subject has a cancer
that was determined to have one or more cells expressing the KRAS G12D mutant protein
10 prior to administration of the compound or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 22/39971

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 31/33, A61K 31/395, A61K 31/519 (2022.01)

ADD. A61K 31/395 (2022.01)

CPC - INV. A61K 31/33, A61K 31/395, A61K 31/519

ADD. A61K 31/395

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

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

See Search History document

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2021/041671 A1 (MIRATI THERAPEUTICS INC) 4 March 2021 (04.03.2021), especially: pg 19, bottom, first formula.	1-3,37-39
A	US 2020/0331911 A1 (MIRATI THERAPEUTICS INC) 22 October 2020 (22.10.2020), especially: pg 12, col 2, first formula.	1-3,37-39
A	US 2015/0368274 A1 (SHANGHAI INSTITUTE OF MATERIA MEDICA) 24 December 2015 (24.12.2015), especially: pg 7, formula 22.	1-3,37-39

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

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

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

9 October 2022

Date of mailing of the international search report

OCT 26 2022

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 22/39971

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 4-36,40-55
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.