INHIBITORS OF CDK2/4/6 KINASE

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of US Patent Application No. 63/515,748, filed on July 26, 2023, which is hereby incorporated by reference in its entirety.

BACKGROUND

[0002] Cyclin-dependent kinases (CDKs) are a conserved family of proline-directed serine/threonine kinases that perform critical roles in the regulation of cell division and proliferation. Dysregulation of CDK2, CDK4 and CDK6 (CDK2/4/6) has been demonstrated to be a key driver of many cancers, and inhibition of CDK2/4/6 has become a validated treatment modality in some disease, such as breast cancer. Accordingly, therapies that target CDK2/4/6 kinase activity are desired for use in the treatment of cancer and other disorders characterized by aberrant CDK2/4/6 pathway signaling.

BRIEF SUMMARY OF THE INVENTION

[0003] Provided herein are inhibitors of CDK2/4/6 kinase, pharmaceutical compositions comprising said inhibitory compounds, and methods for using said inhibitory compounds for the treatment of disease.

[0004] One embodiment provides a CDK2/4/6 kinase inhibitory compound, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, having a structure presented in Table 1.

[0005] One embodiment provides a pharmaceutical composition comprising a compound of Table 1, or pharmaceutically acceptable salt or solvate, or stereoisomer thereof, and at least one pharmaceutically acceptable excipient.

[0006] One embodiment provides a method of treating a disease or disorder in a patient in need thereof comprising administering to the patient a compound of Table 1, or pharmaceutically acceptable salt or solvate, or stereoisomer thereof. Another embodiment provides the method wherein the disease or disorder is cancer.

INCORPORATION BY REFERENCE

[0007] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference for the specific purposes identified herein.

DETAILED DESCRIPTION OF THE INVENTION

[0008] As used herein and in the appended claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an agent" includes a plurality of such agents, and reference to "the cell" includes reference to

one or more cells (or to a plurality of cells) and equivalents thereof known to those skilled in the art, and so forth. When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range, in some instances, will vary between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, "consist of" or "consist essentially of" the described features.

Definitions

[0009] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

[0010] "Amino" refers to the $-NH_2$ radical.

[0011] "Cyano" refers to the -CN radical.

[0012] "Nitro" refers to the $-NO_2$ radical.

[0013] "Oxa" refers to the -O- radical.

[0014] "Oxo" refers to the =O radical.

[0015] "Thioxo" refers to the =S radical.

[0016] "Imino" refers to the =N-H radical.

[0017] "Oximo" refers to the =N-OH radical.

[0018] "Hydrazino" refers to the $=N-NH_2$ radical.

[0019] "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to fifteen carbon atoms (*e.g.*, C_1-C_{15} alkyl). In certain embodiments, an alkyl comprises one to thirteen carbon atoms (*e.g.*, C_1-C_{13} alkyl). In certain embodiments, an alkyl comprises one to eight carbon atoms (*e.g.*, C_1-C_8 alkyl). In other embodiments, an alkyl comprises one to five carbon atoms (*e.g.*, C_1-C_5 alkyl). In other embodiments, an alkyl comprises one to four carbon atoms (*e.g.*, C_1-C_4 alkyl). In other embodiments, an alkyl comprises one to three carbon atoms (*e.g.*, C_1-C_3 alkyl). In other embodiments, an alkyl comprises one to two carbon atoms (*e.g.*, C_1-C_2 alkyl). In other embodiments, an alkyl comprises one carbon atom (*e.g.*, C_1 alkyl). In other embodiments, an alkyl comprises five to fifteen carbon atoms (*e.g.*, C_5-C_{15} alkyl). In other embodiments, an alkyl comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkyl). In other embodiments, an alkyl

comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkyl). In other embodiments, an alkyl comprises three to five carbon atoms (*e.g.*, C_3-C_5 alkyl). In other embodiments, the alkyl group is selected from methyl, ethyl, 1-propyl (*n*-propyl), 1-methylethyl (*iso*-propyl), 1-butyl (*n*-butyl), 1-methylpropyl (*sec*-butyl), 2-methylpropyl (*iso*-butyl), 1,1-dimethylethyl (*tert*-butyl), 1-pentyl (*n*-pentyl). The alkyl is attached to the rest of the molecule by a single bond. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-OC(O)-N(R^a)_2$, $-N(R^a)C(O)R^a$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^a$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, carbocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), carbocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl). In certain embodiments, an optionally substituted alkyl is a haloalkyl. In other embodiments, an optionally substituted alkyl is a fluoroalkyl. In other embodiments, an optionally substituted alkyl is a $-CF_3$ group.

[0020] "Alkoxy" refers to a radical bonded through an oxygen atom of the formula –O-alkyl, where alkyl is an alkyl chain as defined above.

[0021] "Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon double bond, and having from two to twelve carbon atoms. In certain embodiments, an alkenyl comprises two to eight carbon atoms. In other embodiments, an alkenyl comprises two to four carbon atoms. The alkenyl is attached to the rest of the molecule by a single bond, for example, ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. Unless stated otherwise specifically in the specification, an alkenyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-OC(O)-N(R^a)_2$, $-N(R^a)C(O)R^a$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^a$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each

R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, carbocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), carbocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl).

[0022] "Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon triple bond, having from two to twelve carbon atoms. In certain embodiments, an alkynyl comprises two to eight carbon atoms. In other embodiments, an alkynyl comprises two to six carbon atoms. In other embodiments, an alkynyl comprises two to four carbon atoms. The alkynyl is attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-OC(O)-N(R^a)_2$, $-N(R^a)C(O)R^a$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^a$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, carbocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), carbocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl).

[0023] "Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing no unsaturation and having from one to twelve carbon atoms, for example, methylene, ethylene, propylene, *n*-butylene, and the like. The alkylene chain is attached to the

rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group are through one carbon in the alkylene chain or through any two carbons within the chain. In certain embodiments, an alkylene comprises one to eight carbon atoms (*e.g.*, C_1-C_8 alkylene). In other embodiments, an alkylene comprises one to five carbon atoms (*e.g.*, C_1-C_5 alkylene). In other embodiments, an alkylene comprises one to four carbon atoms (*e.g.*, C_1-C_4 alkylene). In other embodiments, an alkylene comprises one to three carbon atoms (*e.g.*, C_1-C_3 alkylene). In other embodiments, an alkylene comprises one to two carbon atoms (*e.g.*, C_1-C_2 alkylene). In other embodiments, an alkylene comprises one carbon atom (*e.g.*, C_1 alkylene). In other embodiments, an alkylene comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkylene). In other embodiments, an alkylene comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkylene). In other embodiments, an alkylene comprises three to five carbon atoms (*e.g.*, C_3-C_5 alkylene). Unless stated otherwise specifically in the specification, an alkylene chain is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-OC(O)-N(R^a)_2$, $-N(R^a)C(O)R^a$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^a$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, carbocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), carbocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl).

[0024] "Alkenylene" or "alkenylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one carbon-carbon double bond, and having from two to twelve carbon atoms. The alkenylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. In certain embodiments, an alkenylene comprises two to eight carbon atoms (*e.g.*, C_2-C_8 alkenylene). In other embodiments, an alkenylene comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkenylene). In other embodiments, an alkenylene comprises two to four carbon atoms (*e.g.*, C_2-C_4 alkenylene). In other embodiments, an alkenylene comprises two to three carbon atoms (*e.g.*, C_2-C_3 alkenylene). In other embodiments,

an alkenylene comprises two carbon atoms (*e.g.*, C_2 alkenylene). In other embodiments, an alkenylene comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkenylene). In other embodiments, an alkenylene comprises three to five carbon atoms (*e.g.*, C_3-C_5 alkenylene). Unless stated otherwise specifically in the specification, an alkenylene chain is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-OC(O)-N(R^a)_2$, $-N(R^a)C(O)R^a$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^a$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, carbocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), carbocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl).

[0025] "Alkynylene" or "alkynylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one carbon-carbon triple bond, and having from two to twelve carbon atoms. The alkynylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. In certain embodiments, an alkynylene comprises two to eight carbon atoms (*e.g.*, C_2-C_8 alkynylene). In other embodiments, an alkynylene comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkynylene). In other embodiments, an alkynylene comprises two to four carbon atoms (*e.g.*, C_2-C_4 alkynylene). In other embodiments, an alkynylene comprises two to three carbon atoms (*e.g.*, C_2-C_3 alkynylene). In other embodiments, an alkynylene comprises two carbon atoms (*e.g.*, C_2 alkynylene). In other embodiments, an alkynylene comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkynylene). In other embodiments, an alkynylene comprises three to five carbon atoms (*e.g.*, C_3-C_5 alkynylene). Unless stated otherwise specifically in the specification, an alkynylene chain is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-OC(O)-N(R^a)_2$, $-N(R^a)C(O)R^a$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^a$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each

R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, carbocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), carbocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl).

[0026] "Aryl" refers to a radical derived from an aromatic monocyclic or multicyclic hydrocarbon ring system by removing a hydrogen atom from a ring carbon atom. The aromatic monocyclic or multicyclic hydrocarbon ring system contains only hydrogen and carbon from five to eighteen carbon atoms, where at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. The ring system from which aryl groups are derived include, but are not limited to, groups such as benzene, fluorene, indane, indene, tetralin and naphthalene. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals optionally substituted by one or more substituents independently selected from optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, halo, cyano, nitro, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, cycloalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), cycloalkylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), each R^b is independently a direct bond or a straight or branched alkylene or

alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the R^a, R^b, or R^c substituents is unsubstituted unless otherwise indicated.

[0027] "Aralkyl" refers to a radical of the formula -R^c-aryl where R^c is an alkylene chain as defined above, for example, methylene, ethylene, and the like. The alkylene chain part of the aralkyl radical is optionally substituted as described above for an alkylene chain. The aryl part of the aralkyl radical is optionally substituted as described above for an aryl group.

[0028] "Aralkenyl" refers to a radical of the formula –R^d-aryl where R^d is an alkenylene chain as defined above. The aryl part of the aralkenyl radical is optionally substituted as described above for an aryl group. The alkenylene chain part of the aralkenyl radical is optionally substituted as defined above for an alkenylene group.

[0029] "Aralkynyl" refers to a radical of the formula -R^e-aryl, where R^e is an alkynylene chain as defined above. The aryl part of the aralkynyl radical is optionally substituted as described above for an aryl group. The alkynylene chain part of the aralkynyl radical is optionally substituted as defined above for an alkynylene chain.

[0030] "Aralkoxy" refers to a radical bonded through an oxygen atom of the formula -O-R^c-aryl where R^c is an alkylene chain as defined above, for example, methylene, ethylene, and the like. The alkylene chain part of the aralkyl radical is optionally substituted as described above for an alkylene chain. The aryl part of the aralkyl radical is optionally substituted as described above for an aryl group.

[0031] "Carbocyclyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which includes fused or bridged ring systems, having from three to fifteen carbon atoms. In certain embodiments, a carbocyclyl comprises three to ten carbon atoms. In other embodiments, a carbocyclyl comprises five to seven carbon atoms. The carbocyclyl is attached to the rest of the molecule by a single bond. Carbocyclyl is saturated (*i.e.*, containing single C-C bonds only) or unsaturated (*i.e.*, containing one or more double bonds or triple bonds). A fully saturated carbocyclyl radical is also referred to as "cycloalkyl." Examples of monocyclic cycloalkyls include, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. An unsaturated carbocyclyl is also referred to as "cycloalkenyl." Examples of monocyclic cycloalkenyls include, *e.g.*, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Polycyclic carbocyclyl radicals include, for example, adamantyl, norbornyl (*i.e.*, bicyclo[2.2.1]heptanyl), norbornenyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, the term "carbocyclyl" is meant to include carbocyclyl radicals that are optionally substituted by one or more substituents independently selected from optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, halo,

oxo, thioxo, cyano, nitro, -R^b-OR^a, -R^b-OC(O)-R^a, -R^b-OC(O)-OR^a, -R^b-OC(O)-$N(R^a)_2$, -R^b-$N(R^a)_2$, -R^b-C(O)R^a, -R^b-C(O)OR^a, -R^b-C(O)$N(R^a)_2$, -R^b-O-R^c-C(O)$N(R^a)_2$, -R^b-N(R^a)C(O)OR^a, -R^b-N(R^a)C(O)R^a, -R^b-N(R^a)$S(O)_tR^a$ (where t is 1 or 2), -R^b-$S(O)_tR^a$ (where t is 1 or 2), -R^b-$S(O)_tOR^a$ (where t is 1 or 2) and -R^b-$S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, cycloalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), cycloalkylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the R^a, R^b, or R^c substituents is unsubstituted unless otherwise indicated.

[0032] "Carbocyclylalkyl" refers to a radical of the formula –R^c-carbocyclyl where R^c is an alkylene chain as defined above. The alkylene chain and the carbocyclyl radical is optionally substituted as defined above.

[0033] "Carbocyclylalkynyl" refers to a radical of the formula –R^c-carbocyclyl where R^c is an alkynylene chain as defined above. The alkynylene chain and the carbocyclyl radical is optionally substituted as defined above.

[0034] "Carbocyclylalkoxy" refers to a radical bonded through an oxygen atom of the formula –O-R^c-carbocyclyl where R^c is an alkylene chain as defined above. The alkylene chain and the carbocyclyl radical is optionally substituted as defined above.

[0035] "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo substituents.

[0036] "Fluoroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, as defined above, for example, trifluoromethyl, difluoromethyl, fluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. In some embodiments, the alkyl part of the fluoroalkyl radical is optionally substituted as defined above for an alkyl group.

[0037] "Heterocyclyl" refers to a stable 3- to 18-membered non-aromatic ring radical that comprises two to twelve carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. Unless stated otherwise specifically in the specification, the heterocyclyl radical is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which optionally includes fused or bridged ring systems. The heteroatoms in the heterocyclyl radical are optionally oxidized. One

or more nitrogen atoms, if present, are optionally quaternized. The heterocyclyl radical is partially or fully saturated. The heterocyclyl is attached to the rest of the molecule through any atom of the ring(s). Examples of such heterocyclyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification, the term "heterocyclyl" is meant to include heterocyclyl radicals as defined above that are optionally substituted by one or more substituents selected from optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, -R^b-OR^a, -R^b-OC(O)-R^a, -R^b-OC(O)-OR^a, -R^b-OC(O)-$N(R^a)_2$, -R^b-$N(R^a)_2$, -R^b-C(O)R^a, -R^b-C(O)OR^a, -R^b-C(O)$N(R^a)_2$, -R^b-O-R^c-C(O)$N(R^a)_2$, -R^b-$N(R^a)$C(O)OR^a, -R^b-$N(R^a)$C(O)R^a, -R^b-$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -R^b-$S(O)_tR^a$ (where t is 1 or 2), -R^b-$S(O)_tOR^a$ (where t is 1 or 2) and -R^b-$S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, cycloalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), cycloalkylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the R^a, R^b, or R^c substituents is unsubstituted unless otherwise indicated.

[0038] "*N*-heterocyclyl" or "N-attached heterocyclyl" refers to a heterocyclyl radical as defined above containing at least one nitrogen and where the point of attachment of the heterocyclyl radical to the rest of the molecule is through a nitrogen atom in the heterocyclyl radical. An *N*-heterocyclyl radical is optionally substituted as described above for heterocyclyl radicals. Examples of such *N*-heterocyclyl radicals include, but are not limited to, 1-morpholinyl, 1-piperidinyl, 1-piperazinyl, 1-pyrrolidinyl, pyrazolidinyl, imidazolinyl, and imidazolidinyl.

[0039] "*C*-heterocyclyl" or "C-attached heterocyclyl" refers to a heterocyclyl radical as defined above containing at least one heteroatom and where the point of attachment of the heterocyclyl radical to the rest of the molecule is through a carbon atom in the heterocyclyl radical. A *C*-heterocyclyl radical is optionally substituted as described above for heterocyclyl radicals. Examples of such *C*-heterocyclyl radicals include, but are not limited to, 2-morpholinyl, 2- or 3- or 4-piperidinyl, 2-piperazinyl, 2- or 3-pyrrolidinyl, and the like.

[0040] "Heterocyclylalkyl" refers to a radical of the formula $-R^c$-heterocyclyl where R^c is an alkylene chain as defined above. If the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heterocyclylalkyl radical is optionally substituted as defined above for an alkylene chain. The heterocyclyl part of the heterocyclylalkyl radical is optionally substituted as defined above for a heterocyclyl group.

[0041] "Heterocyclylalkoxy" refers to a radical bonded through an oxygen atom of the formula $-O-R^c$-heterocyclyl where R^c is an alkylene chain as defined above. If the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heterocyclylalkoxy radical is optionally substituted as defined above for an alkylene chain. The heterocyclyl part of the heterocyclylalkoxy radical is optionally substituted as defined above for a heterocyclyl group.

[0042] "Heteroaryl" refers to a radical derived from a 3- to 18-membered aromatic ring radical that comprises two to seventeen carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen, and sulfur. As used herein, the heteroaryl radical is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, wherein at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. Heteroaryl includes fused or bridged ring systems. The heteroatom(s) in the heteroaryl radical is optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl is attached to the rest of the molecule through any atom of the ring(s). Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[d]thiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, benzo[b][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzothieno[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5,6-dihydrobenzo[h]cinnolinyl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl,

furo[3,2-c]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridinyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno[2,3-d]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-c]pyridazinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, thieno[2,3-c]pridinyl, and thiophenyl (*i.e.* thienyl). Unless stated otherwise specifically in the specification, the term "heteroaryl" is meant to include heteroaryl radicals as defined above which are optionally substituted by one or more substituents selected from optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, halo, optionally substituted fluoroalkyl, optionally substituted haloalkenyl, optionally substituted haloalkynyl, oxo, thioxo, cyano, nitro, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, cycloalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), cycloalkylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the R^a, R^b, or R^c substituents is unsubstituted unless otherwise indicated.

[0043] "*N*-heteroaryl" refers to a heteroaryl radical as defined above containing at least one nitrogen and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a nitrogen atom in the heteroaryl radical. An *N*-heteroaryl radical is optionally substituted as described above for heteroaryl radicals.

[0044] "*C*-heteroaryl" refers to a heteroaryl radical as defined above and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a carbon atom in the heteroaryl radical. A *C*-heteroaryl radical is optionally substituted as described above for heteroaryl radicals.

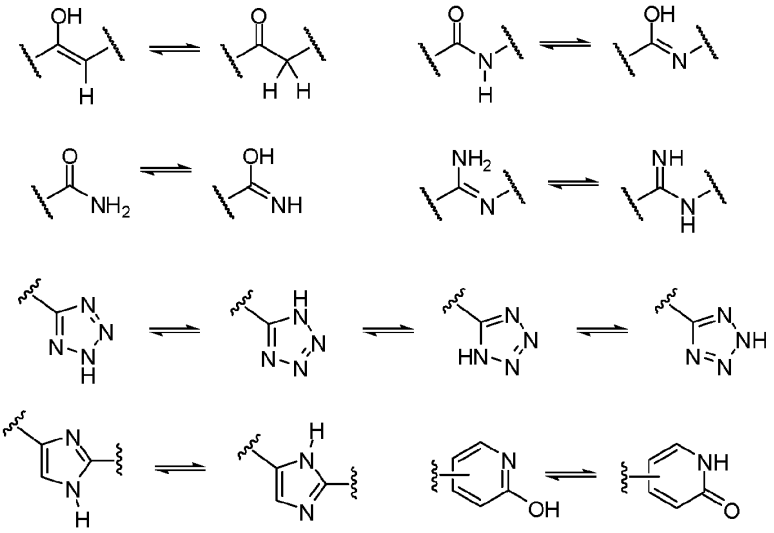
[0045] "Heteroarylalkyl" refers to a radical of the formula $-R^c$-heteroaryl, where R^c is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkyl radical is optionally substituted as defined above for an alkylene chain. The heteroaryl part of the heteroarylalkyl radical is optionally substituted as defined above for a heteroaryl group.

[0046] "Heteroarylalkoxy" refers to a radical bonded through an oxygen atom of the formula $-O-R^c$-heteroaryl, where R^c is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkoxy radical is optionally substituted as defined above for an alkylene chain. The heteroaryl part of the heteroarylalkoxy radical is optionally substituted as defined above for a heteroaryl group.

[0047] The compounds disclosed herein, in some embodiments, contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that are defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-. Unless stated otherwise, it is intended that all stereoisomeric forms of the compounds disclosed herein are contemplated by this disclosure. When the compounds described herein contain alkene double bonds, and unless specified otherwise, it is intended that this disclosure includes both *E* and Z geometric isomers (*e.g., cis* or *trans*.) Likewise, all possible isomers, as well as their racemic and optically pure forms, and all tautomeric forms are also intended to be included. The term "geometric isomer" refers to *E* or Z geometric isomers (*e.g., cis* or *trans*) of an alkene double bond. The term "positional isomer" refers to structural isomers around a central ring, such as *ortho*-, *meta*-, and *para*- isomers around a benzene ring.

[0048] A "tautomer" refers to a molecule wherein a proton shift from one atom of a molecule to another atom of the same molecule is possible. The compounds presented herein, in certain embodiments, exist as tautomers. In circumstances where tautomerization is possible, a chemical equilibrium of the tautomers will exist. The exact ratio of the tautomers depends on several

factors, including physical state, temperature, solvent, and pH. Some examples of tautomeric equilibrium include:



[0049] The compounds disclosed herein, in some embodiments, are used in different enriched isotopic forms, e.g., enriched in the content of ^{2}H, ^{3}H, ^{11}C, ^{13}C and/or ^{14}C. In one particular embodiment, the compound is deuterated in at least one position. Such deuterated forms can be made by the procedure described in U.S. Patent Nos. 5,846,514 and 6,334,997. As described in U.S. Patent Nos. 5,846,514 and 6,334,997, deuteration can improve the metabolic stability and or efficacy, thus increasing the duration of action of drugs.

[0050] Unless otherwise stated, structures depicted herein are intended to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of the present disclosure.

[0051] The compounds of the present disclosure optionally contain unnatural proportions of atomic isotopes at one or more atoms that constitute such compounds. For example, the compounds may be labeled with isotopes, such as for example, deuterium (^{2}H), tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). Isotopic substitution with ^{2}H, ^{11}C, ^{13}C, ^{14}C, ^{15}C, ^{12}N, ^{13}N, ^{15}N, ^{16}N, ^{16}O, ^{17}O, ^{14}F, ^{15}F, ^{16}F, ^{17}F, ^{18}F, ^{33}S, ^{34}S, ^{35}S, ^{36}S, ^{35}Cl, ^{37}Cl, ^{79}Br, ^{81}Br, ^{125}I are all contemplated. In some embodiments, isotopic substitution with ^{18}F is contemplated. All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

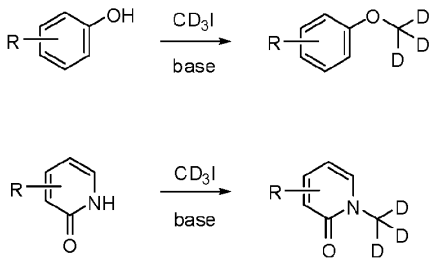
[0052] In certain embodiments, the compounds disclosed herein have some or all of the ^{1}H atoms replaced with ^{2}H atoms. The methods of synthesis for deuterium-containing compounds are

known in the art and include, by way of non-limiting example only, the following synthetic methods.

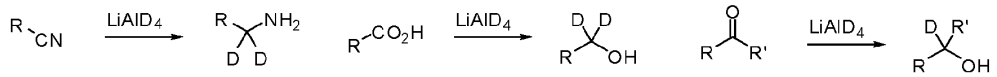
[0053] Deuterium substituted compounds are synthesized using various methods such as described in: Dean, Dennis C.; Editor. Recent Advances in the Synthesis and Applications of Radiolabeled Compounds for Drug Discovery and Development. [Curr., Pharm. Des., 2000; 6(10)] **2000**, 110 pp; George W.; Varma, Rajender S. The Synthesis of Radiolabeled Compounds via Organometallic Intermediates, Tetrahedron, **1989**, 45(21), 6601-21; and Evans, E. Anthony. Synthesis of radiolabeled compounds, J. Radioanal. Chem., **1981**, 64(1-2), 9-32.

[0054] Deuterated starting materials are readily available and are subjected to the synthetic methods described herein to provide for the synthesis of deuterium-containing compounds. Large numbers of deuterium-containing reagents and building blocks are available commercially from chemical vendors, such as Aldrich Chemical Co.

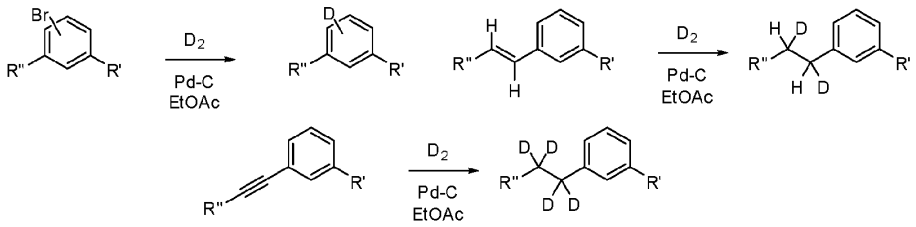
[0055] Deuterium-transfer reagents suitable for use in nucleophilic substitution reactions, such as iodomethane-d_3 (CD_3I), are readily available and may be employed to transfer a deuterium-substituted carbon atom under nucleophilic substitution reaction conditions to the reaction substrate. The use of CD_3I is illustrated, by way of example only, in the reaction schemes below.



[0056] Deuterium-transfer reagents, such as lithium aluminum deuteride ($LiAlD_4$), are employed to transfer deuterium under reducing conditions to the reaction substrate. The use of $LiAlD_4$ is illustrated, by way of example only, in the reaction schemes below.



[0057] Deuterium gas and palladium catalyst are employed to reduce unsaturated carbon-carbon linkages and to perform a reductive substitution of aryl carbon-halogen bonds as illustrated, by way of example only, in the reaction schemes below.



[0058] In one embodiment, the compounds disclosed herein contain one deuterium atom. In another embodiment, the compounds disclosed herein contain two deuterium atoms. In another embodiment, the compounds disclosed herein contain three deuterium atoms. In another embodiment, the compounds disclosed herein contain four deuterium atoms. In another embodiment, the compounds disclosed herein contain five deuterium atoms. In another embodiment, the compounds disclosed herein contain six deuterium atoms. In another embodiment, the compounds disclosed herein contain more than six deuterium atoms. In another embodiment, the compound disclosed herein is fully substituted with deuterium atoms and contains no non-exchangeable ^{1}H hydrogen atoms. In one embodiment, the level of deuterium incorporation is determined by synthetic methods in which a deuterated synthetic building block is used as a starting material.

[0059] "Pharmaceutically acceptable salt" includes both acid and base addition salts. A pharmaceutically acceptable salt of any one of the CDK2/4/6 kinase inhibitory compounds described herein is intended to encompass any and all pharmaceutically suitable salt forms. Preferred pharmaceutically acceptable salts of the compounds described herein are pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts.

[0060] "Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, hydroiodic acid, hydrofluoric acid, phosphorous acid, and the like. Also included are salts that are formed with organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and. aromatic sulfonic acids, etc. and include, for example, acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Exemplary salts thus include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, nitrates, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, trifluoroacetates, propionates, caprylates,

isobutyrates, oxalates, malonates, succinate suberates, sebacates, fumarates, maleates, mandelates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, phthalates, benzenesulfonates, toluenesulfonates, phenylacetates, citrates, lactates, malates, tartrates, methanesulfonates, and the like. Also contemplated are salts of amino acids, such as arginates, gluconates, and galacturonates (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Science,* 66:1-19 (1997)). Acid addition salts of basic compounds are, in some embodiments, prepared by contacting the free base forms with a sufficient amount of the desired acid to produce the salt according to methods and techniques with which a skilled artisan is familiar.

[0061] "Pharmaceutically acceptable base addition salt" refers to those salts that retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Pharmaceutically acceptable base addition salts are, in some embodiments, formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Salts derived from inorganic bases include, but are not limited to, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, for example, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, *N,N*-dibenzylethylenediamine, chloroprocaine, hydrabamine, choline, betaine, ethylenediamine, ethylenedianiline, *N*-methylglucamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. See Berge et al., supra.

[0062] "Pharmaceutically acceptable solvate" refers to a composition of matter that is the solvent addition form. In some embodiments, solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are formed during the process of making with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of compounds described herein are conveniently prepared or formed during the processes described herein. The compounds provided herein exist in either unsolvated or solvated forms.

[0063] The term "subject" or "patient" encompasses mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. In one aspect, the mammal is a human.

[0064] As used herein, "treatment" or "treating," or "palliating" or "ameliorating" are used interchangeably. These terms refer to an approach for obtaining beneficial or desired results including but not limited to therapeutic benefit and/or a prophylactic benefit. By "therapeutic benefit" is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient is still afflicted with the underlying disorder. For prophylactic benefit, the compositions are, in some embodiments, administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease has not been made.

CDK2/4/6 Kinase

[0065] Cyclin-dependent kinases (CDKs) are a conserved family of proline-directed serine/threonine kinases that perform critical roles in the regulation of cell division and proliferation. CDKs are members of the CMGC kinase family, which encompasses 63 family members including mitogen-activated protein kinase (MAPK), glycogen synthase kinase (GSK) and CDC-like kinase (CLK). The activity of CDKs is regulated through phosphorylation by interaction with cyclin proteins and other upstream kinases such as CDK-activating kinases (CAKs). At least 21 CDKs have been identified to date, including CDK1, 2, 4, and 6 (which regulate the transition of the cell cycle steps), CDK7, 8, 9, 12 and 13 (which regulate gene transcription through phosphorylation of the heptad repeats that comprise the C-terminal tail of RNA polymerase II), and CDK3 (which regulates the transition from G0 (quiescence) into G1 phase of cell division). CDKs regulate the transition between the four distinct phases of the eukaryotic cell cycle, i.e., the G1, S (DNA synthesis), G2 and M phases. Furthermore, CDKs are implicated in the progression of many different types of cancer. In particular, dysregulation of CDK2, CDK4 and CDK6 (CDK2/4/6) has been demonstrated to be a key driver of many cancers, and inhibition of CDK2/4/6 has become a validated treatment modality in some disease, such as breast cancer.

[0066] Structurally, CDK4 and 6 have a bilobal structure typically seen in other kinases, comprising a 5-stranded β-sheet on the N-terminal side of the protein and a predominantly helical C-terminal domain The ATP binding site is located in the cleft between the domains. Although a structure for a CDK6 with its primary cyclin partner (cyclin D) has not yet been determined, the crystal structure of CDK6 bound to a viral cyclin has been solved and provides some structural insight to the function of CDK6. Furthermore, the structures of non-phosphorylated and phosphorylated CDK4 bound to cyclin D3 or cyclin D1 have been solved. The kinase binding sites of CDK4 and 6 are highly conserved and the structural similarity between these kinases is

likely the reason that highly selective ATP-competitive inhibitors of both CDK4 and CDK6 (CDK4/6 inhibitors) have been developed.

[0067] CDK4 and CDK6 associate with the D-type cyclins, activating the CDK4/6 and causing them to phosphorylate and inactivate the retinoblastoma (Rb) protein family members. Cyclin D possesses a tertiary structure that is common to other cyclins, known as the cyclin fold. The cyclin fold contains a core of two compact domains, with each domain having five alpha helices. The first five-helix bundle is a conserved cyclin box, a region of about 100 amino acid residues shared by all cyclins. The cyclin box functions by binding to and activating CDKs. The second five-helix bundle is composed of the same arrangement of helices but comprises several differences in the primary sequence. All three D-type cyclins (D1, D2, D3) share a common alpha 1 helix hydrophobic patch, and each of these D-type cyclins bind to and activate CDK4 and 6, leading to cell cycle progression.

Cell Cycle

[0068] The eukaryotic cell division cycle is divided into two basic parts: mitosis and interphase. Mitosis (nuclear division) corresponds to the separation of daughter chromosomes and usually ends with cell division (cytokinesis). The period between mitoses is interphase, which generally accounts for approximately 95% of the cell cycle time (e.g., 23 hours of a 24-hour cycle). During interphase, the chromosomes are decondensed and distributed throughout the nucleus, and the cell prepares itself for mitosis by regulating both cell growth and DNA replication. The cell grows at a steady rate throughout interphase, with most dividing cells doubling in size between mitosis cycles. In contrast, DNA is synthesized during only a relatively short portion of interphase.

[0069] The timing of the cycle of eukaryotic cells into four discrete phases based on DNA synthesis and cell division. The M phase of the cycle corresponds to mitosis, which is usually followed by cytokinesis (cell division). This phase is followed by the G1 phase (gap 1), which corresponds to the interval between mitosis and initiation of DNA synthesis. During G1, the cell is metabolically active and continuously grows but does not replicate its DNA. Following G1, the cell enters the S phase (synthesis phase), during which DNA replication takes place. After completion of DNA synthesis, the cell contains two identical chromosome sets and enters the G2 phase (gap 2) of cell division. During the G2 phase, the cell continues to grow, and proteins are synthesized in preparation for the next round of mitosis (i.e., the next M cycle).

[0070] In some cell types, including many embryonic cells, cell division is perpetual and the cells continuously cycle between the M, G1, S, and G2 phases. In contrast, many cells in adult animals either cease division altogether (e.g., nerve cells) and or divide only as needed to replace cells that have been lost due to injury. Such intermittently dividing cells include skin

fibroblasts and cells of many internal organs, including the liver, kidney, and lung. Such cells exit G1 to enter a quiescent stage of the cycle called G0, where they remain metabolically active but no longer proliferate unless called on to do so by appropriate extracellular signals, such as those resulting from an injury to the local tissue. However, in cancer, a relatively large subpopulation of the cells remain cycling through the four phases of cell division, driving tumor proliferation and disease progression.

[0071] To enter the cell cycle, a cell must progress from G1 to S phase via a restriction point, and most cells will only do so in the presence of the appropriate growth factors. Once the cell has passed through the restriction point, the cell is committed to proceed through S phase and the rest of the cell cycle, even in the absence of further growth factor stimulation. However, if appropriate growth factors are not available in G1, progression through the cell cycle generally stops at the restriction point, and the cell will enter G0 (the quiescent stage) until a signal is received to resume cell division. The transition from G1 to S phase is mediated in part by the retinoblastoma protein (RB), which is usually regulated through a delicate balance of pro- and anti-mitotic signals. In healthy cells, the balance of pro- and anti-mitotic signals is tightly regulated, and specific mitogenic signals (e.g., growth factors) are necessary for normal cells to enter the cell division cycle.

Cell Signaling Networks

[0072] CDK2, 4 and 6 are directly involved with mediating the transition from the G1 to S phase, with activated CDK2/4/6 initiating a downstream pathway that advances the cell into the S phase of cell division. According to the "classical" cell cycle model, the G1/S transition begins in early G1 when the balance between mitogenic stimulation (via growth factor receptor activation) and inhibition tips in favor of the former, triggering an increase in the levels of D-type cyclins (Dl, D2, and D3). The expression level of the D type cyclins is controlled by growth factor signaling, with transcription, turnover and nuclear transport of D type cyclins all dependent on this signaling. D-type cyclins bind to CDK4 or CDK6, and the cyclin-CDK complexes subsequently enter the nucleus where the cyclin-CDK complexes are phosphorylated by the CDK-activating kinase (CAK) complex.

[0073] Once activated, CDK4/6 complexes phosphorylate the retinoblastoma (RB) tumor suppressor protein, as well as the related p107 and p130 proteins. RB phosphorylation by CDK4/6 partially inhibits activity of the E2F family of transcription factors, which, in turn, increases the expression of E2F target genes including those for the E-type cyclins (cyclins E1 and E2). Cyclin E then binds to and activates CDK2, which hyper-phosphorylates RB. Hyper-phosphorylation of RB further increases the expression of E2F target genes, which are critical for initiation of DNA synthesis and entry into S-phase. This creates a positive feedback loop, as

the E2Fs promote transcription of the E type cyclins, activating CDK2 and other proteins important for initiation of S phase and DNA synthesis.

[0074] Regulation of CDK4/6 is primarily achieved by two families of endogenous inhibitory proteins. The first is the INK4 family, comprising the p16INK4A, p15INK4B, p18INK4C, and p19INK4D proteins, which bind to CDKs 4 and 6, forming binary complexes that lack kinase activity. The second is the CIP/KIP family, which includes p27KIP1, p21CIP1, and p57KIP2. These proteins bind to a variety of CDKs having more diverse functions, potently inhibiting a number of CDKs (including CDK4/6, CDK2, and CDK1). However, in some circumstances, these proteins bind to and stabilize the cyclin D-CDK4/6 holoenzyme. These divergent functions may be regulated by the extent of phosphorylation of the CIP/KIP proteins.

Prior Art CDK2/4/6 Kinase Inhibitors

[0075] Several CDK inhibitors have been developed and tested in many different types of cancer. The first generation of CDK inhibitors, including flavopiridol (inhibitor of at least CDKs 1, 2, 4, and 9 inhibitor) and roscovitine (inhibitor of at least CDKs 1, 2, 5, 7, and 9), were pan inhibitors that acted on several kinases. These first-generation CDK inhibitors has limited clinical success due to an inadequate balance between efficacy and toxicity. The second generation of inhibitors, such as dinaciclib (inhibitor of CDKs 1, 2, 5, and 9) were developed with the aim to increase potency and selectivity for CDKs over other kinases. However, these compounds demonstrated limited efficacy and considerable toxicity in clinical studies. The toxicity of these compounds results from their broad-spectrum activity against numerous CDK isoforms, including CDK1 and CDK9, which are required for the proliferation (CDK1) and survival (CDK9) of normal cells. More recently, selective CDK2/4/6 inhibitors have been developed, which exhibit more targeted action on tumor cells and reduced toxicity. This third generation of CDK inhibitors selectively inhibit CDK4 and CDK6 with potent efficacy and reduced toxicity, selectively binding to the CDK4/6 ATP-binding pockets.

[0076] To date, three CDK4/6 inhibitors have received FDA approval: palbociclib, ribociclib, and abemaciclib. Palbociclib (Ibrance®) received accelerated FDA approval in 2015 in combination with letrozole for the treatment of estrogen receptor positive (ER+) advanced breast cancer. In 2017, palbociclib in combination with an aromatase inhibitor received full FDA approval for use in hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer. Ribociclib (Kisqali ®) was approved in 2017 for use in combination with an aromatase inhibitor (such as letrozole) to treat HR-positive, HER2-negative advanced or metastatic breast cancers. Abemaciclib (Verzenio®) was FDA approved in 2017 for use as a monotherapy or in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-

negative advanced or metastatic breast cancer with disease progression following endocrine therapy. In 2018 abemaciclib received a second approval for use in combination with an aromatase inhibitor as an initial endocrine based therapy for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. More recently, in 2021, abemaciclib was approved in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer.

[0077] The development of selective CDK4/6 inhibitor agents has radically changed the approach to managing this disease hormone receptor-positive, HER2-negative advanced breast cancer, approximately doubling the progression-free survival (PFS) for most patients. However, resistance to CDK4/6 inhibitors is considered to be nearly inevitable in most patients. Although mechanisms of resistance to these agents are multifactorial and research in this field is ongoing, several mechanisms of resistance to CDK 4/6 inhibitors have been identified to date.

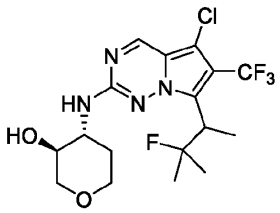
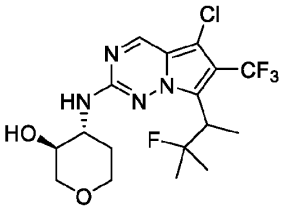
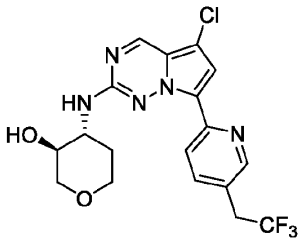
[0078] First, overexpression of CDK6 (and potentially CDK4) is a major mechanism of resistance to CDK4/6 inhibitors. Studies in human cell lines have shown that increased expression of CDK6 reduced the response of CDK4/6 inhibitors, and subsequent knockdown of CDK6 rescued the therapy sensitivity, indicating that CDK6-mediated drug resistance may be independent of CDK4 expression. However, both increased and decreased expression of CDK4 has been detected in CDK4/6 inhibitor–resistant breast cancer cells, indicating that the role of CDK4 expression in CDK4/6 inhibitor resistance requires further investigation. Second, loss of Rb has been implicated as a driver of resistance to CDK4/6 inhibitors in several preclinical studies. Without the inhibitory influence of Rb, transcription factors of the E2F family continue unchecked, thus facilitating unregulated cellular progression to S-phase entry independently of CDK4/6 activity. Acquired CDK4/6 inhibitor resistance due to RB1 mutations has been identified in several patients treated with CDK 4/6 inhibitors. Third, decrease in cyclin D1 expression can lead to CDK4/6 inhibitor resistance. Cyclin D1 expression is regulated by the estrogen receptor (ER), and decreased ER expression results in reduced expression of cyclin D1. In preclinical trials, resistance to abemaciclib was associated with the loss of cyclin D1 and concomitant loss of ER/PR expression. Resistance in these patients may be related to the decrease in cyclin D1 due to the loss of ER. Additional possible mechanisms of action include overexpression of Brk (breast tumor-related kinase), overexpression of the E2F2 transcription factor, and overexpression of cyclins E1 or E2. Thus, there exists a need for a new generation of CDK inhibitors that are not susceptible to one or more of these resistance mechanisms and provide longer progression-free survival.

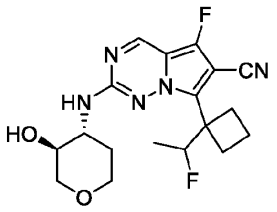
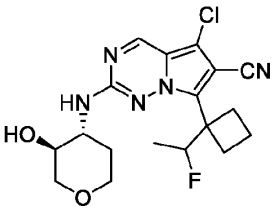
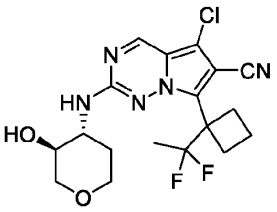
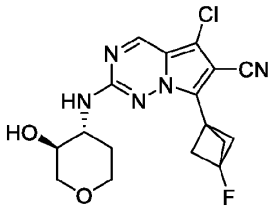
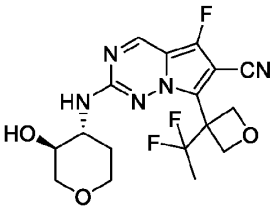
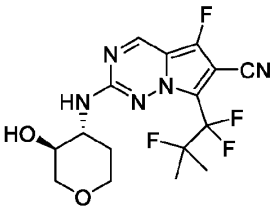
CDK2/4/6 Kinase Inhibitory Compounds

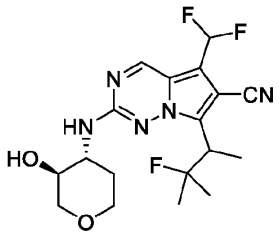
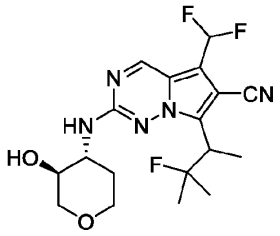
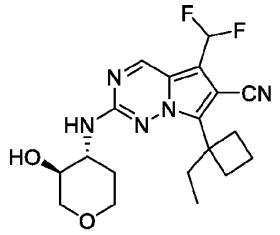
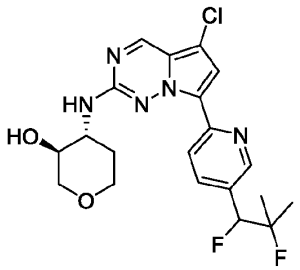
[0079] In one aspect, provided herein is a CDK2/4/6 kinase inhibitory compound.

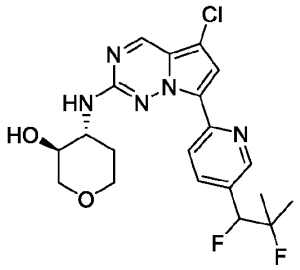
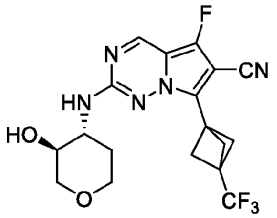
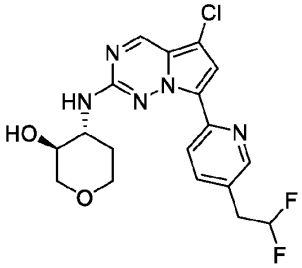
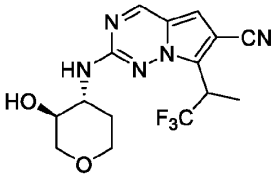
[0080] One embodiment provides a CDK2/4/6 kinase inhibitory compound, or a pharmaceutically acceptable salt or solvate thereof, having a structure presented in Table 1.

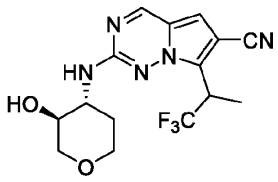
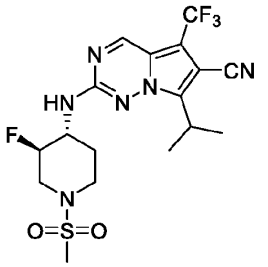
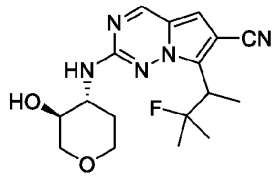
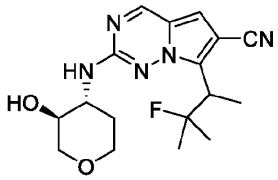
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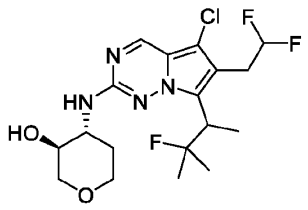
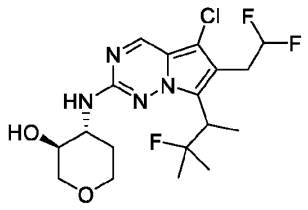
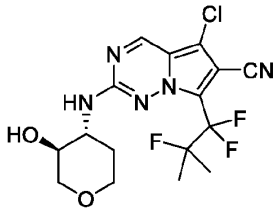
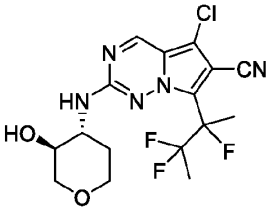
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
1		(3*S*,4*R*)-4-((5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK ID, Hexane/^{n}PrOH = 93/7, 1st peak)	425.15
2		(3*S*,4*R*)-4-((5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK ID, Hexane/^{n}PrOH = 93/7, 2nd peak)	425.15
3		(3*S*,4*R*)-4-({5-chloro-7-[5-(2,2,2-trifluoroethyl)pyridin-2-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol	428.10

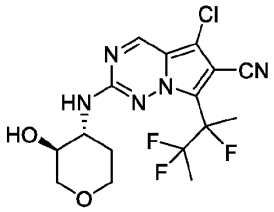
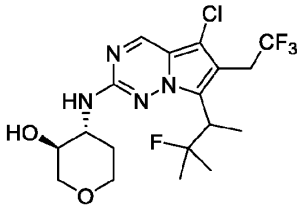
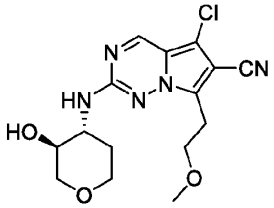
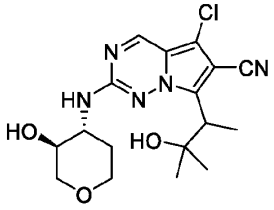
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
4		5-fluoro-7-[1-(1-fluoroethyl)cyclobutyl]-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	378.20
5		5-chloro-7-[1-(1-fluoroethyl)cyclobutyl]-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	394.15
6		5-chloro-7-[1-(1,1-difluoroethyl)cyclobutyl]-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	411.95
7		5-chloro-7-{3-fluorobicyclo[1.1.1]pentan-1-yl}-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	377.95
8		7-[3-(1,1-difluoroethyl)oxetan-3-yl]-5-fluoro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	398.05
9		5-fluoro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	387.90

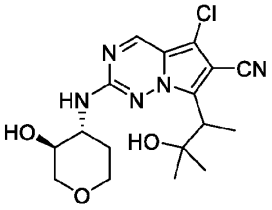
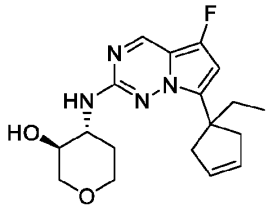
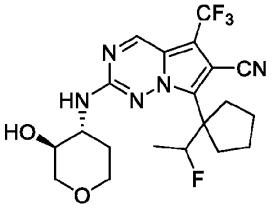
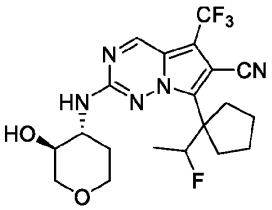
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
10		5-(difluoromethyl)-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH = 70/30, 1st peak)	398.20
11		5-(difluoromethyl)-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH = 70/30, 2nd peak)	398.20
12		5-(difluoromethyl)-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	392.20
13		(3*S*,4*R*)-4-((5-chloro-7-(5-(1,2-difluoro-2-methylpropyl)pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 1,2-difluoro-2-methylpropyl was not determined) (CHIRALPAK IG, Hexane/EtOH = 50/50, 1st peak)	438.00

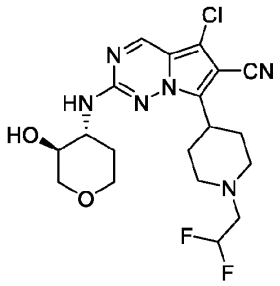
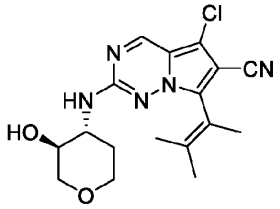
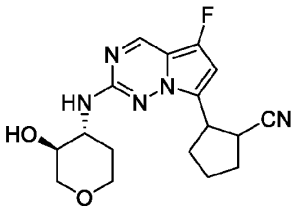
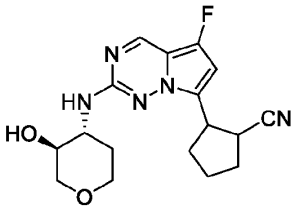
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
14		(3*S*,4*R*)-4-((5-chloro-7-(5-(1,2-difluoro-2-methylpropyl)pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 1,2-difluoro-2-methylpropyl was not determined) (CHIRALPAK IG, Hexane/EtOH = 50/50, 2nd peak)	438.05
15		5-fluoro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	412.10
16		(3*S*,4*R*)-4-({5-chloro-7-[5-(2,2-difluoroethyl)pyridin-2-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol	410.20
17		2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1,1,1-trifluoropropan-2-yl was not determined) (CHIRALPAK IG, Hexane/EtOH = 70/30, 1st peak)	356.15

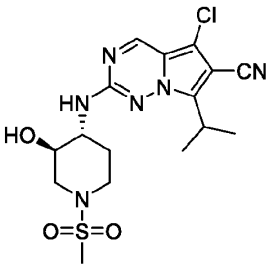
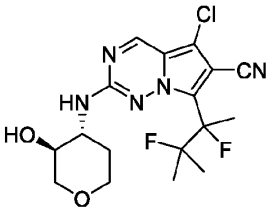
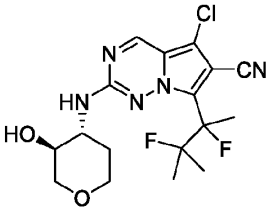
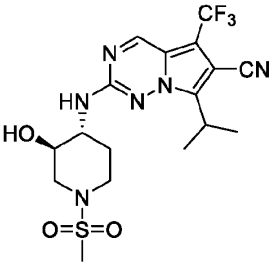
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
18		2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1,1,1-trifluoropropan-2-yl was not determined) (CHIRALPAK IG, Hexane/EtOH = 70/30, 2nd peak)	356.10
19		2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-isopropyl-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	449.15
20		7-(3-fluoro-3-methylbutan-2-yl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH/DCM = 80/10/10, 1st peak)	348.05
21		7-(3-fluoro-3-methylbutan-2-yl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH/DCM = 80/10/10, 2nd peak)	348.20

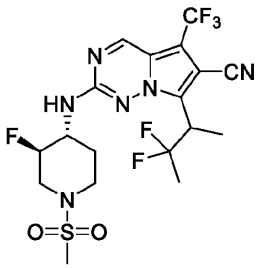
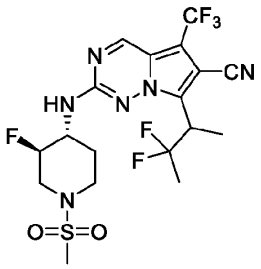
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
22		(3*S*,4*R*)-4-((5-chloro-6-(2,2-difluoroethyl)-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IF, Hexane/EtOH = 90/10, 1st peak)	421.30
23		(3*S*,4*R*)-4-((5-chloro-6-(2,2-difluoroethyl)-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IF, Hexane/EtOH = 90/10, 2nd peak)	421.20
24		5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	404.10
25		5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(2,3,3-trifluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 2,3,3-trifluorobutan-2-yl was not determined) (DAICEL DCpak® P4VP, CO_2/MeOH = 66/34, 1st peak)	403.95

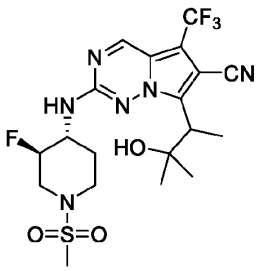
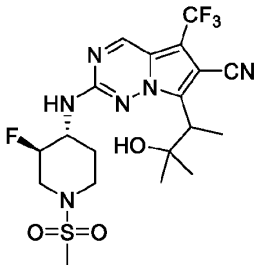
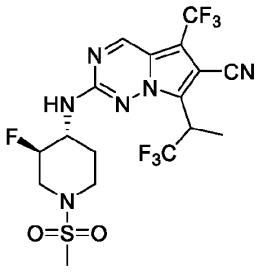
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
26		5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(2,3,3-trifluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 2,3,3-trifluorobutan-2-yl was not determined) (DAICEL DCpak® P4VP, CO_2/MeOH = 66/34, 2nd peak)	403.90
27		(3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-(2,2,2-trifluoroethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol	439.05
28		5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(2-methoxyethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	352.20
29		5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-hydroxy-3-methylbutan-2-yl was not determined) (CHIRALPAK IG, CO_2/MeOH = 54/46, 1st peak)	380.15

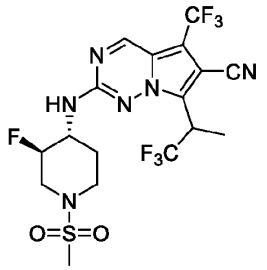
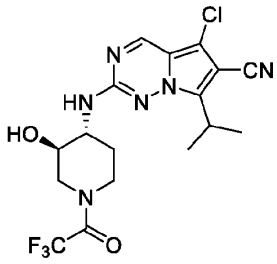
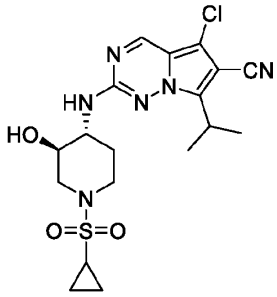
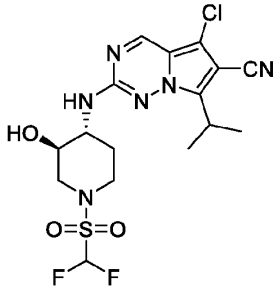
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
30		5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-hydroxy-3-methylbutan-2-yl was not determined) (CHIRALPAK IG, CO_2/MeOH = 54/46, 2nd peak)	380.15
31		(3*S*,4*R*)-4-{[7-(1-ethylcyclopent-3-en-1-yl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol	347.20
32		7-(1-(1-fluoroethyl)cyclopentyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1-fluoroethyl)cyclopentyl was not determined) (CHIRALPAK IG, Hexane/EtOH/DCM = 87/6.5/6.5, 1st peak)	442.35
33		7-(1-(1-fluoroethyl)cyclopentyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1-fluoroethyl)cyclopentyl was not determined) (CHIRALPAK IG, Hexane/EtOH/DCM = 87/6.5/6.5, 2nd peak)	442.30

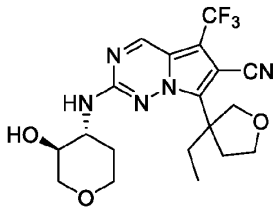
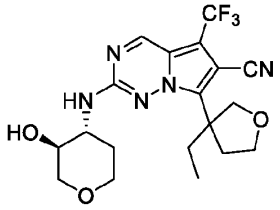
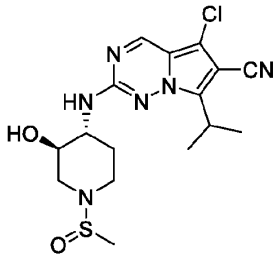
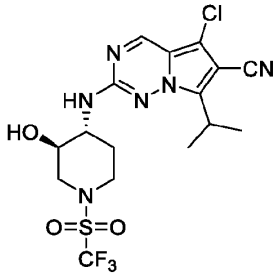
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
34		5-chloro-7-[1-(2,2-difluoroethyl)piperidin-4-yl]-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	441.30
35		5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(3-methylbut-2-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	362.15
36		2-(5-fluoro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)cyclopentane-1-carbonitrile (single diastereoisomer, absolute chiral configuration of cyclopentane-1-carbonitrile was not determined) (CHIRALPAK IG, Hexane/EtOH/DCM = 50/25/25, 1st peak)	346.10
37		2-(5-fluoro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)cyclopentane-1-carbonitrile (single diastereoisomer, absolute chiral configuration of cyclopentane-1-carbonitrile was not determined) (CHIRALPAK IG, Hexane/EtOH/DCM = 50/25/25, 2nd peak)	346.10

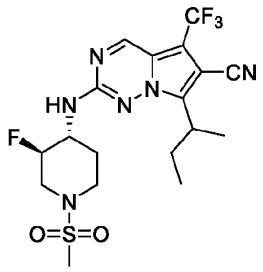
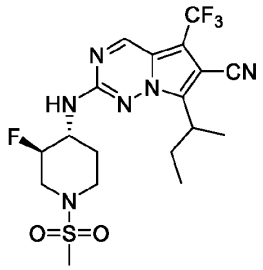
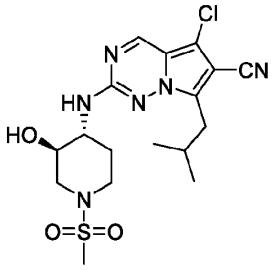
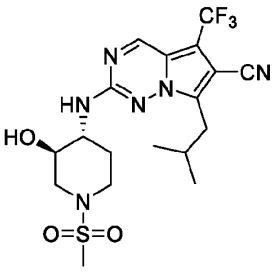
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
38		5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	413.15
39		5-chloro-7-(2,3-difluoro-3-methylbutan-2-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 2,3-difluoro-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH/DCM = 70/15/15, 1st peak)	400.20
40		5-chloro-7-(2,3-difluoro-3-methylbutan-2-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 2,3-difluoro-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH/DCM = 70/15/15, 2nd peak)	400.25
41		2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-isopropyl-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	447.15

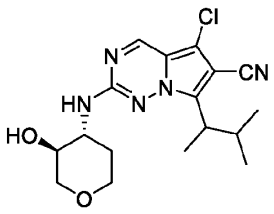
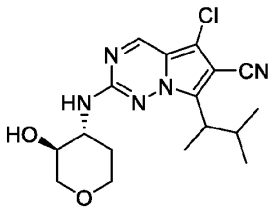
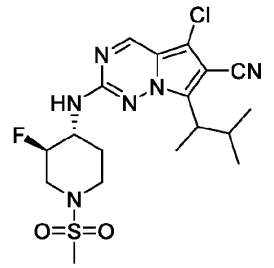
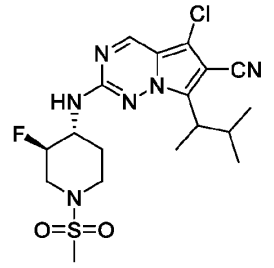
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
42		7-(3,3-difluorobutan-2-yl)-2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3,3-difluorobutan-2-yl was not determined) (CHIRALPAK IE, Hexane/EtOH = 80/20, 1st peak)	499.10
43		7-(3,3-difluorobutan-2-yl)-2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3,3-difluorobutan-2-yl was not determined) (CHIRALPAK IE, Hexane/EtOH = 80/20, 2nd peak)	499.10

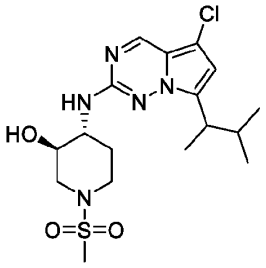
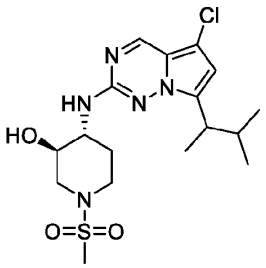
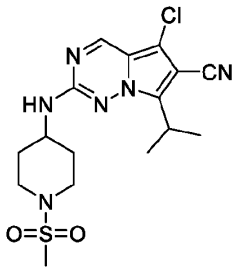
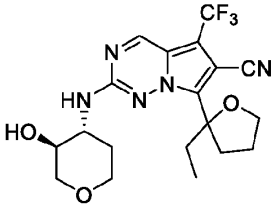
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
44		2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-hydroxy-3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-hydroxy-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/MeOH/EtOH = 85/7.5/7.5, 1st peak)	493.15
45		2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-hydroxy-3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-hydroxy-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/MeOH/EtOH = 85/7.5/7.5, 2nd peak)	493.20
46		2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1,1,1-trifluoropropan-2-yl was not determined) (CHIRAL ART Cellulose-SC, Hexane/^{i}PrOH = 75/25, 1st peak)	503.15

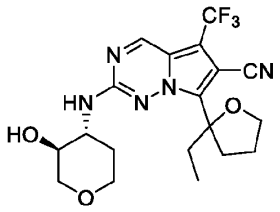
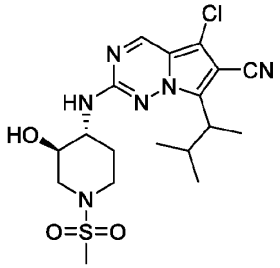
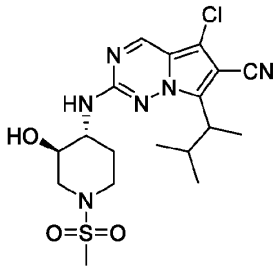
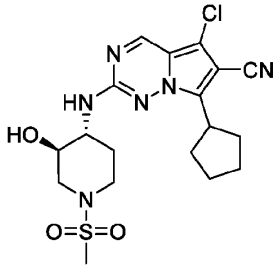
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
47		2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1,1,1-trifluoropropan-2-yl was not determined) (CHIRAL ART Cellulose-SC, Hexane/^{i}PrOH = 75/25, 2nd peak)	503.10
48		5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	431.10
49		5-chloro-2-{[(3*R*,4*R*)-1-(cyclopropanesulfonyl)-3-hydroxypiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	439.25
50		5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	449.10

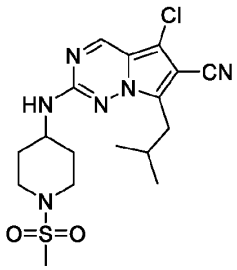
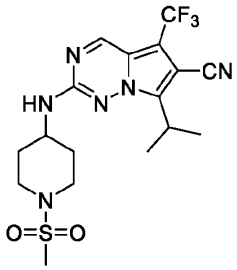
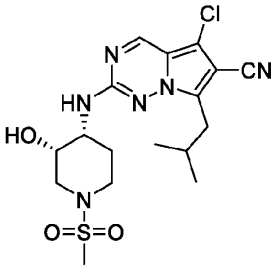
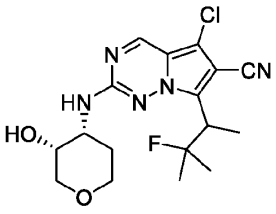
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
51		7-(3-ethyltetrahydrofuran-3-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-ethyltetrahydrofuran-3-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH/DCM = 70/15/15, 1st peak)	426.20
52		7-(3-ethyltetrahydrofuran-3-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-ethyltetrahydrofuran-3-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH/DCM = 70/15/15, 2nd peak)	426.15
53		5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfinylpiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	397.20
54		5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-trifluoromethanesulfonylpiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	467.30

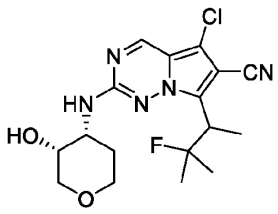
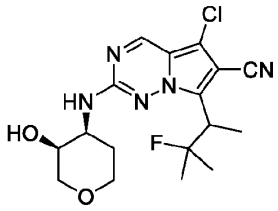
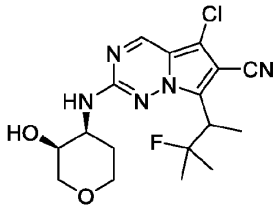
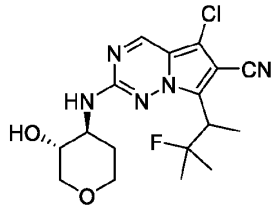
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
55		7-(*sec*-butyl)-2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (Lux 5um Cellulose-3, Hexane/MeOH/EtOH = 90/5/5, 1st peak)	463.35
56		7-(*sec*-butyl)-2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (Lux 5um Cellulose-3, Hexane/MeOH/EtOH = 90/5/5, 2nd peak)	463.30
57		5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	427.20
58		2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(2-methylpropyl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	461.30

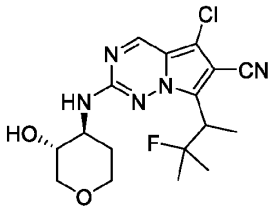
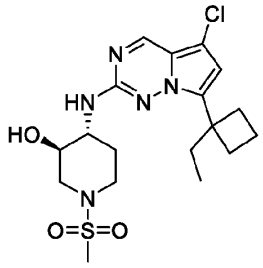
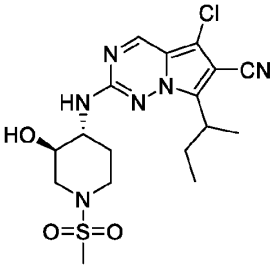
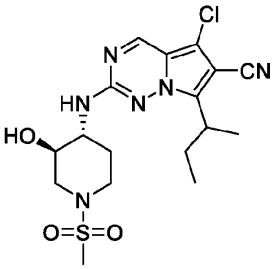
Example	Compound Structure	Compound Name	Observed [M + H]$^+$
59		5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) ((*R*,*R*)-WHELK-O1-Kromasil, Hexane/EtOH/DCM = 90/5/5, 1st peak)	364.20
60		5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) ((*R*,*R*)-WHELK-O1-Kromasil, Hexane/EtOH/DCM = 90/5/5, 2nd peak)	364.25
61		5-chloro-2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 85/15, 2nd peak)	443.20
62		5-chloro-2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 85/15, 1st peak)	443.20

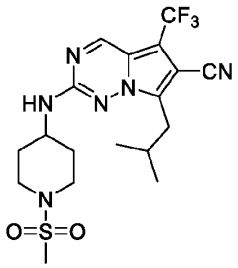
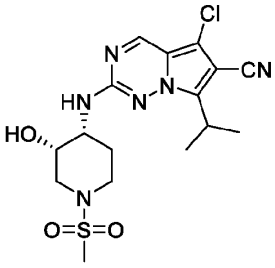
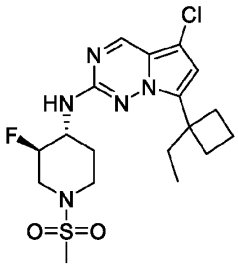
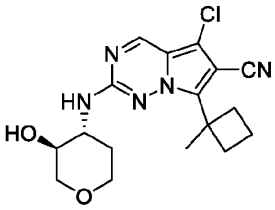
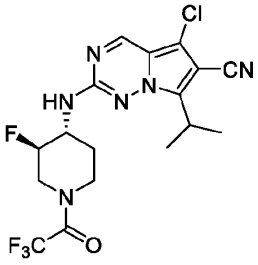
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
63		(3*R*,4*R*)-4-((5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)-1-(methylsulfonyl)piperidin-3-ol (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/MeOH/EtOH = 85/7.5/7.5, 2nd peak)	416.25
64		(3*R*,4*R*)-4-((5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)-1-(methylsulfonyl)piperidin-3-ol (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/MeOH/EtOH = 85/7.5/7.5, 1st peak)	416.25
66		5-chloro-7-isopropyl-2-[(1-methanesulfonylpiperidin-4-yl)amino]pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	397.20
67		(3*S*,4*R*)-4-{[6-cyano-7-(2-ethyloxolan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (single diastereoisomer, absolute chiral configuration of 2-ethyltetrahydrofuran-2-yl was not determined) (CHIRALPAK IG, CO_2/EtOH = 80/20, 1st peak)	426.35

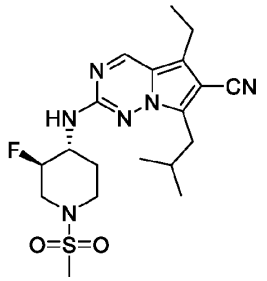
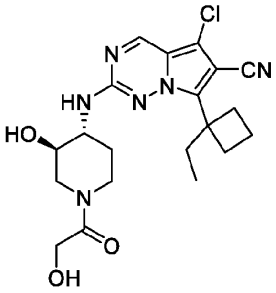
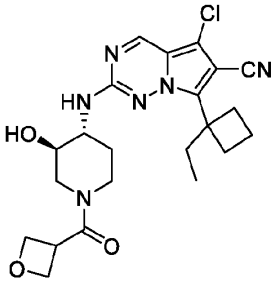
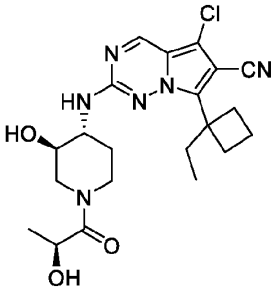
Example	Compound Structure	Compound Name	Observed [M + H]$^+$
68		(3*S*,4*R*)-4-{[6-cyano-7-(2-ethyloxolan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (single diastereoisomer, absolute chiral configuration of 2-ethyltetrahydrofuran-2-yl was not determined) (CHIRALPAK IG, CO2/EtOH = 80/20, 2nd peak)	426.35
69		5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/MeOH/EtOH = 80/10/10, 1st peak)	441.25
70		5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/MeOH/EtOH = 80/10/10, 2nd peak)	441.30
71		5-chloro-7-cyclopentyl-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	439.15

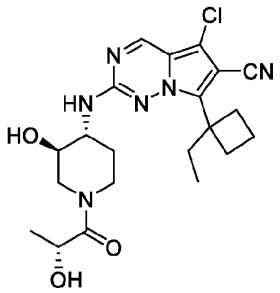
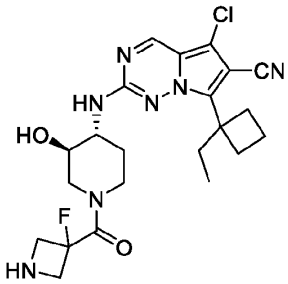
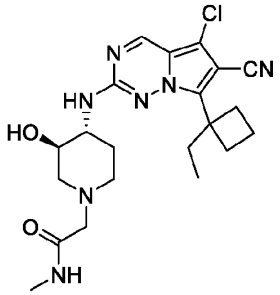
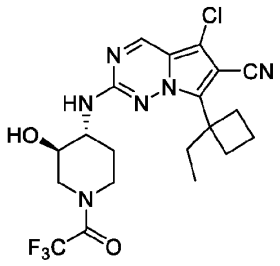
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
75		5-chloro-2-[(1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	411.25
76		7-isopropyl-2-[(1-methanesulfonylpiperidin-4-yl)amino]-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	431.30
77		5-chloro-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	427.30
78		5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*R*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IG, Hexane/EtOH/DCM = 70/15/15, 2nd peak)	382.20

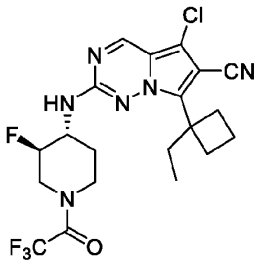
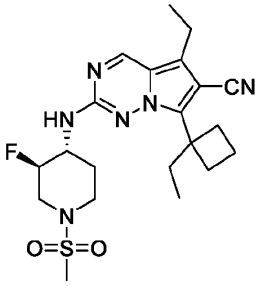
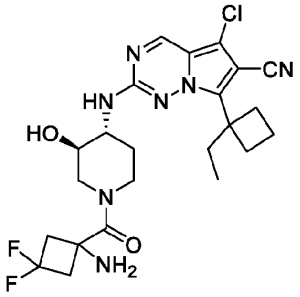
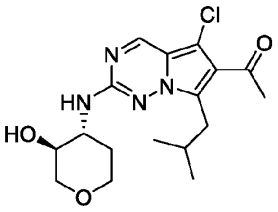
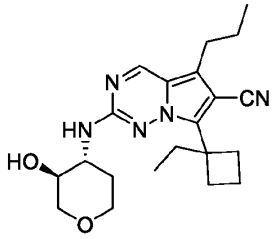
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
79		5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*R*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IG, Hexane/EtOH/DCM = 70/15/15, 1st peak)	382.15
80		5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*S*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IH, Hexane/EtOH = 85/15, 2nd peak)	382.25
81		5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*S*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IH, Hexane/EtOH = 85/15, 1st peak)	382.25
82		5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*R*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IF, Hexane/EtOH/DCM = 80/10/10, 2nd peak)	382.25

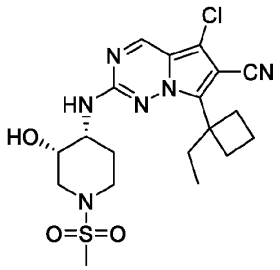
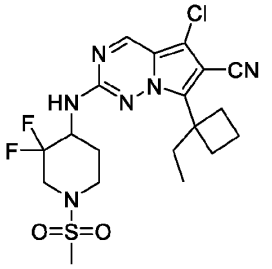
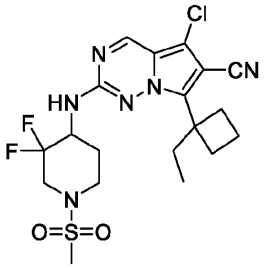
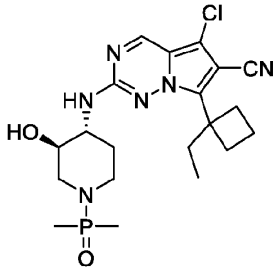
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
83		5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*R*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IF, Hexane/EtOH/DCM = 80/10/10, 1st peak)	382.25
84		(3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-ol	428.30
85		7-(*sec*-butyl)-5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (chiral resolution of 6-I intermediate, CHIRALPAK IG, CO_2/MeOH = 65/35, 1st peak)	427.20
86		7-(*sec*-butyl)-5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (chiral resolution of 6-I intermediate, CHIRALPAK IG, CO_2/MeOH = 65/35, 2nd peak)	427.30

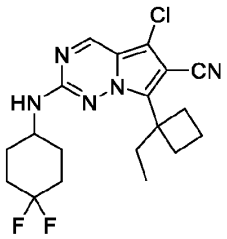
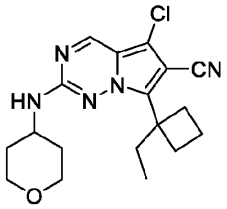
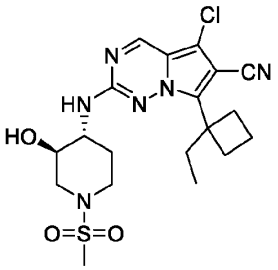
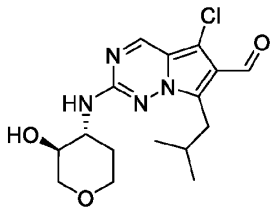
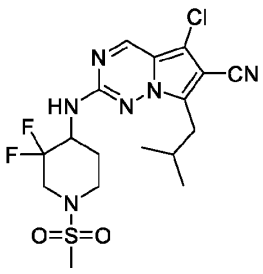
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
87		2-[(1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	445.30
88		5-chloro-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	413.30
89		(3*R*,4*R*)-*N*-[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]-3-fluoro-1-methanesulfonylpiperidin-4-amine	430.30
90		5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	362.20
91		5-chloro-2-{[(3*R*,4*R*)-3-fluoro-1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	433.10

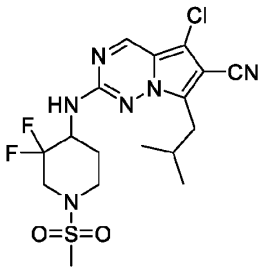
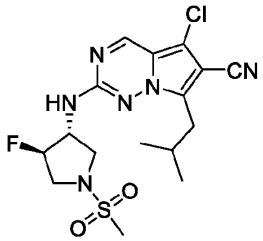
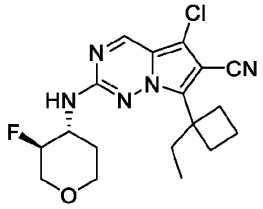
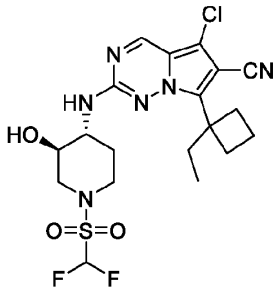
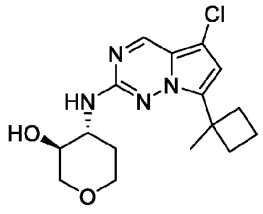
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
92		5-ethyl-2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	423.30
93		5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-(2-hydroxyacetyl)piperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	433.15
94		5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-(oxetane-3-carbonyl)piperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	459.10
95		5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-[(2*S*)-2-hydroxypropanoyl]piperidin-4-yl]amino}pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile	447.20

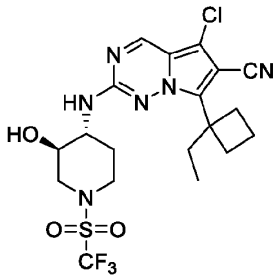
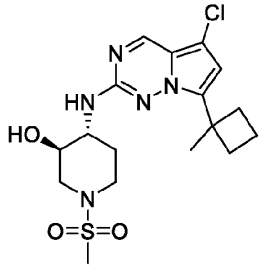
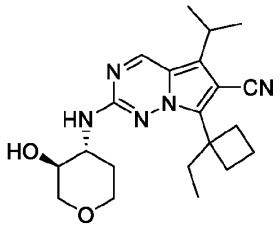
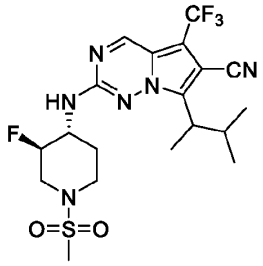
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
96		5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-[(2*R*)-2-hydroxypropanoyl]piperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	447.20
97		5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-1-(3-fluoroazetidine-3-carbonyl)-3-hydroxypiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	476.25
98		2-[(3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidin-1-yl]-*N*-methylacetamide	446.20
99		5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	471.15

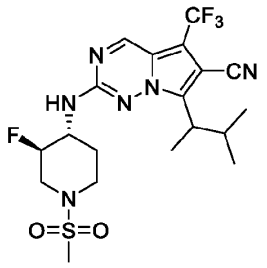
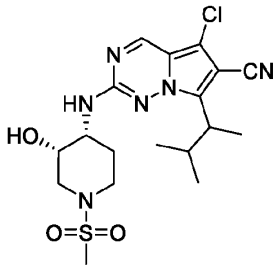
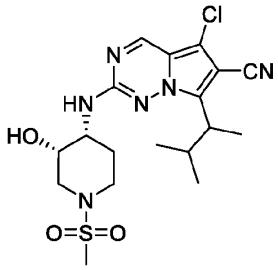
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
100		5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-fluoro-1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	473.15
101		5-ethyl-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo [2,1-*f*][1,2,4]triazine-6-carbonitrile	449.35
102		2-{[(3*R*,4*R*)-1-(1-amino-3,3-difluorocyclobutanecarbonyl)-3-hydroxypiperidin-4-yl]amino}-5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	508.25
103		1-(5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-6-yl)ethanone	367.20
104		7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-5-propylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	384.30

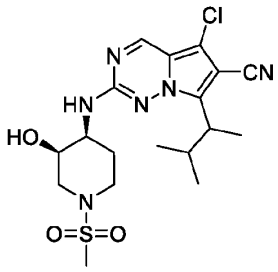
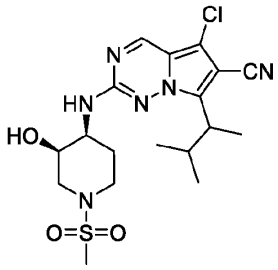
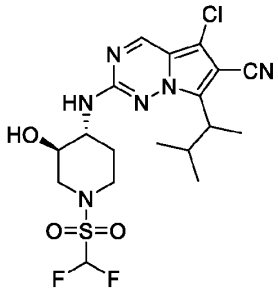
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
106		5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	453.20
107		5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl was not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 70/15/15, 2nd peak)	473.20
108		5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl was not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 70/15/15, 1st peak)	473.15
109		5-chloro-2-{[(3*R*,4*R*)-1-(dimethylphosphoryl)-3-hydroxypiperidin-4-yl]amino}-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	451.30

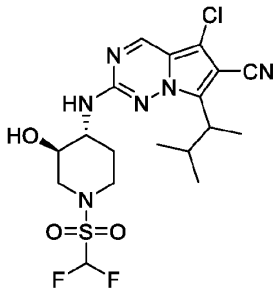
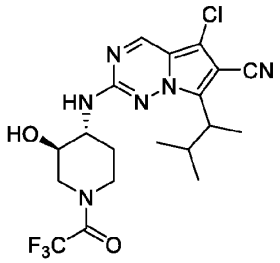
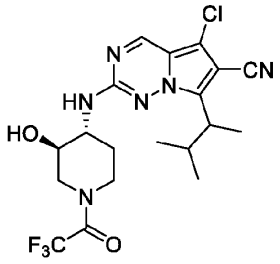
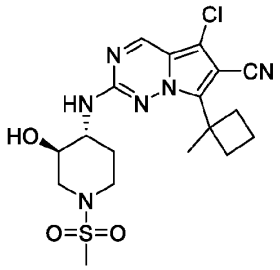
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
110		5-chloro-2-[(4,4-difluorocyclohexyl)amino]-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	394.15
111		5-chloro-7-(1-ethylcyclobutyl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	360.20
112		5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	453.25
113		5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbaldehyde	353.05
114		5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl was not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 65/17.5/17.5, 2nd peak)	447.25

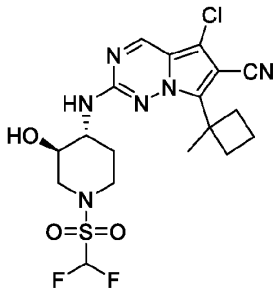
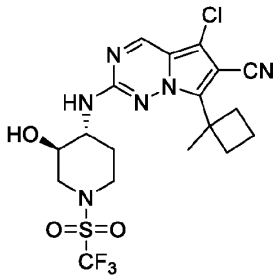
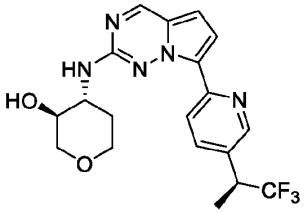
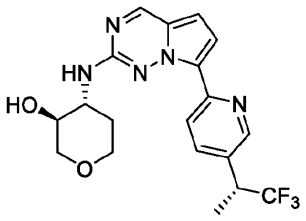
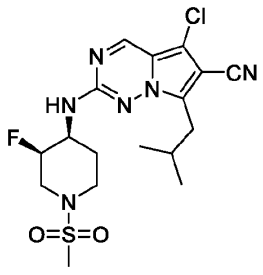
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
115		5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl was not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 65/17.5/17.5, 1st peak)	447.25
116		5-chloro-2-{[(3*R*,4*R*)-4-fluoro-1-methanesulfonylpyrrolidin-3-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	415.20
117		5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	378.20
118		5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	489.10
119		(3*S*,4*R*)-4-((5-chloro-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol	337.15

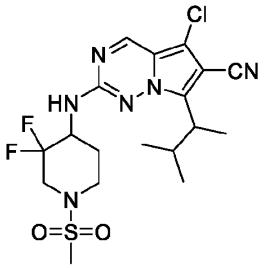
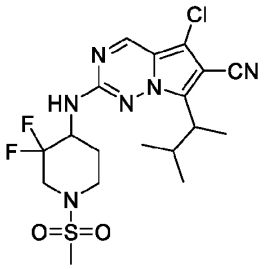
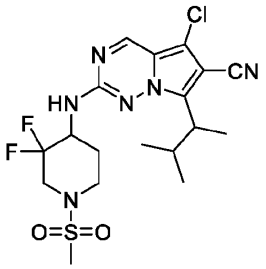
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
120		5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-trifluoromethanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	507.15
121		(3*R*,4*R*)-4-((5-chloro-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)-1-(methylsulfonyl)piperidin-3-ol	414.25
122		7-(1-Ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-5-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	384.20
123		2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/^{i}PrOH = 90/10, 1st peak)	477.25

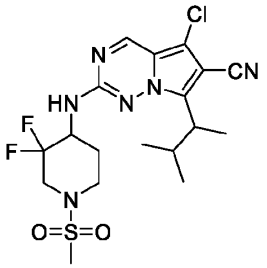
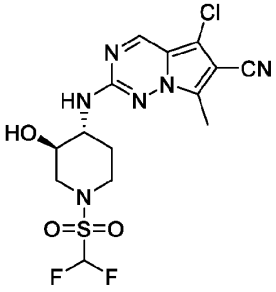
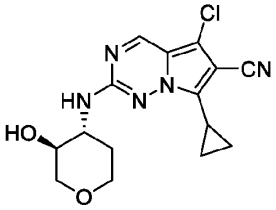
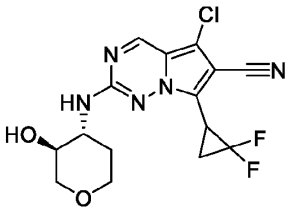
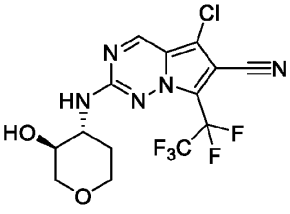
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
124		2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/^{i}PrOH = 90/10, 2nd peak)	477.35
125		5-chloro-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IE, Hexane/MeOH/EtOH = 50/25/25, 2nd peak)	441.30
126		5-chloro-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IE, Hexane/MeOH/EtOH = 50/25/25, 1st peak)	441.35

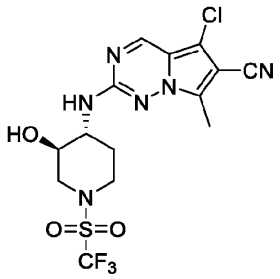
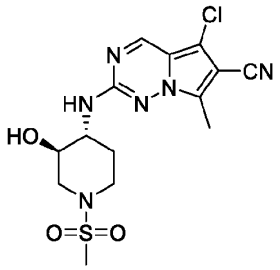
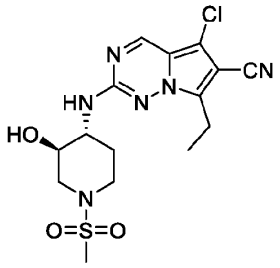
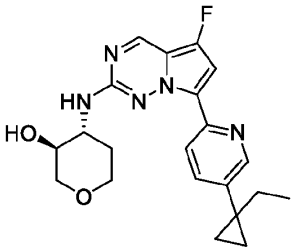
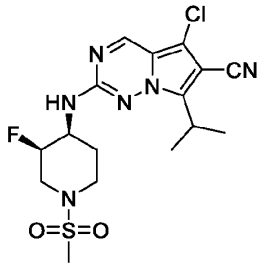
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
127		5-chloro-2-{[(3*R*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IF, Hexane/MeOH/DCM = 60/20/20, 1st peak)	441.10
128		5-chloro-2-{[(3*R*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IF, Hexane/MeOH/DCM = 60/20/20, 2nd peak)	441.10
129		5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IE, Hexane/EtOH/DCM = 85/7.5/7.5, 1st peak)	477.35

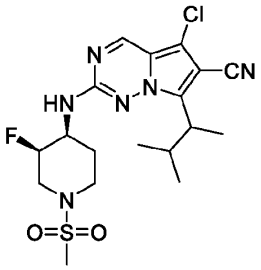
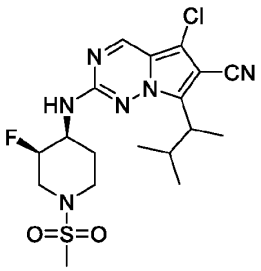
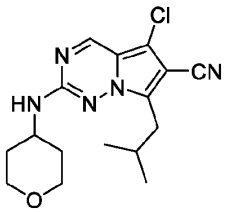
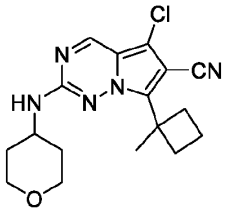
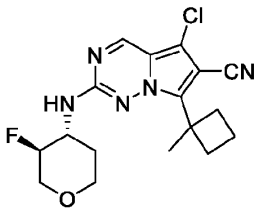
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
130		5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IE, Hexane/EtOH/DCM = 85/7.5/7.5, 2nd peak)	477.35
131		5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 95/5, 1st peak)	459.35
132		5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 95/5, 2nd peak)	459.30
133		5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	439.25

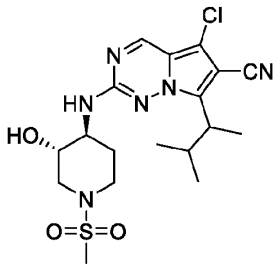
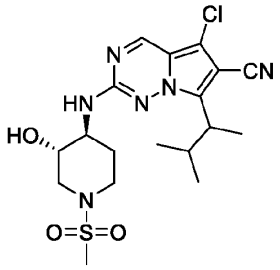
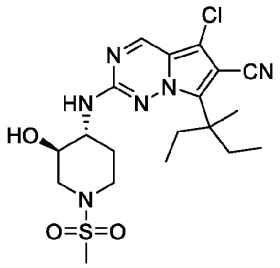
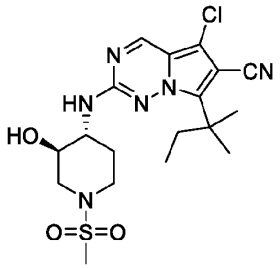
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
134		5-chloro-2-(((3*R*,4*R*)-1-((difluoromethyl)sulfonyl)-3-hydroxypiperidin-4-yl)amino)-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	475.30
135		5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-((trifluoromethyl)sulfonyl)piperidin-4-yl)amino)-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	493.30
136		(3*S*,4*R*)-4-[(7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol	408.15
137		(3*S*,4*R*)-4-[(7-{5-[(2*R*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol	408.25
138		5-chloro-2-{[(3*R*,4*S*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	429.25

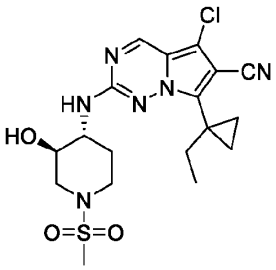
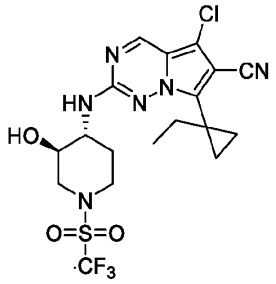
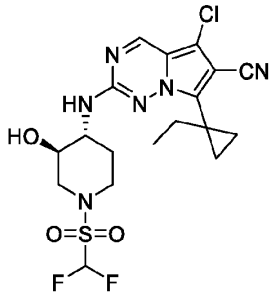
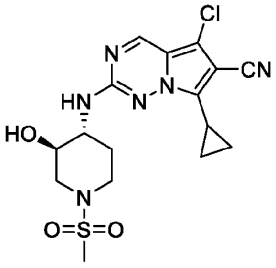
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
139		5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl and 3-methylbutan-2-yl were not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 70/15/15, 1st peak, then CHIRALPAK ID, Hexane/EtOH/DCM = 80/10/10, 1st peak)	461.20
140		5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl and 3-methylbutan-2-yl were not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 70/15/15, 1st peak, then CHIRALPAK ID, Hexane/EtOH/DCM = 80/10/10, 2nd peak)	461.20
141		5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl and 3-methylbutan-2-yl were not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 70/15/15, 2nd peak, then CHIRALPAK AD-H, Hexane/EtOH = 85/15, 1st peak)	461.15

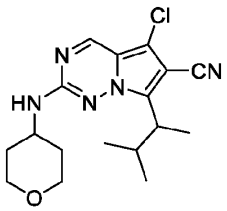
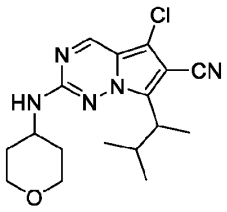
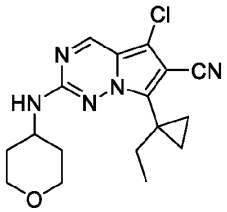
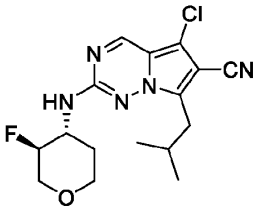
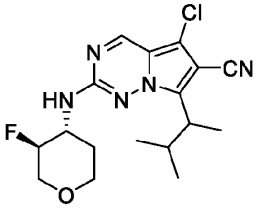
Example	Compound Structure	Compound Name	Observed [M + H]$^+$
142		5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl and 3-methylbutan-2-yl were not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 70/15/15, 2nd peak, then CHIRALPAK AD-H, Hexane/EtOH = 85/15, 2nd peak)	461.20
143		5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	421.10
144		5-chloro-7-cyclopropyl-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	334.15
145		5-chloro-7-(2,2-difluorocyclopropyl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	370.10
146		5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(1,1,2,2,2-pentafluoroethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	412.10

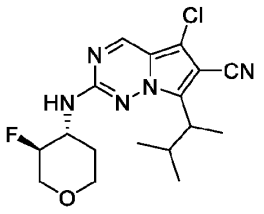
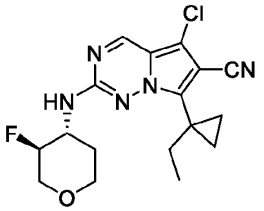
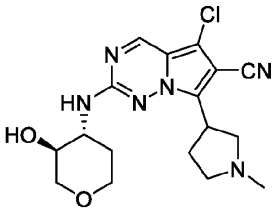
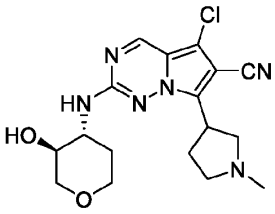
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
147		5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-trifluoromethanesulfonylpiperidin-4-yl]amino}-7-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	439.00
148		5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	385.05
149		5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-ethylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	399.10
150		(3*S*,4*R*)-4-({7-[5-(1-ethylcyclopropyl)pyridin-2-yl]-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol	398.15
153		5-chloro-2-{[(3*R*,4*S*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	415.10

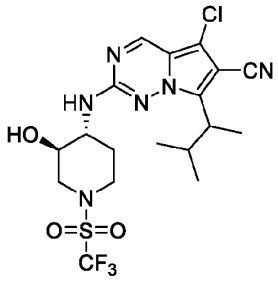
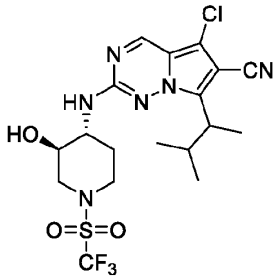
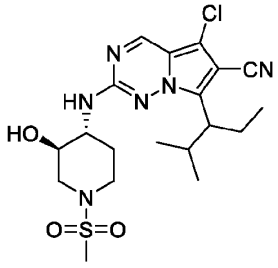
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
154		5-chloro-2-{[(3*R*,4*S*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/^{i}PrOH = 70/30, 1st peak)	443.25
155		5-chloro-2-{[(3*R*,4*S*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/^{i}PrOH = 70/30, 1st peak)	443.25
156		5-chloro-7-(2-methylpropyl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	334.10
157		5-chloro-7-(1-methylcyclobutyl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	346.20
158		5-chloro-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	364.10

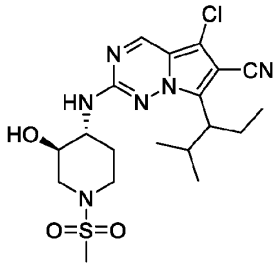
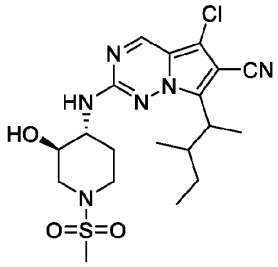
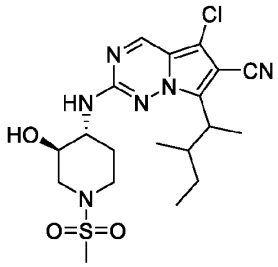
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
159		5-chloro-2-{[(3*S*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (Lux 5um Cellulose-4, Hexane/EtOH = 60/40, 1st peak)	441.25
160		5-chloro-2-{[(3*S*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (Lux 5um Cellulose-4, Hexane/EtOH = 60/40, 2nd peak)	441.25
161		5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	455.25
162		5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	441.30

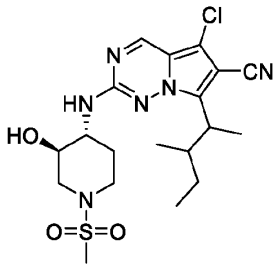
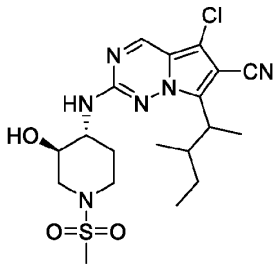
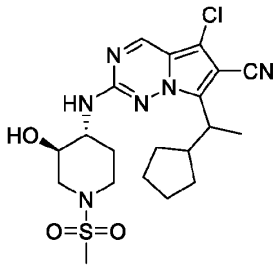
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
163		5-chloro-7-(1-ethylcyclopropyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	439.25
164		5-chloro-7-(1-ethylcyclopropyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-trifluoromethanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	493.30
165		5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	475.25
166		5-chloro-7-cyclopropyl-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	411.10

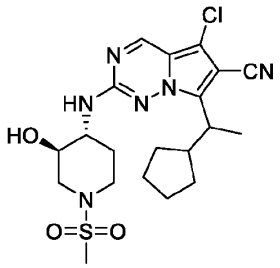
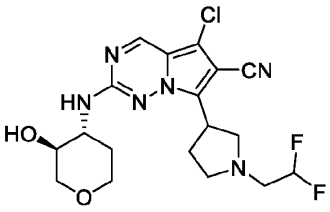
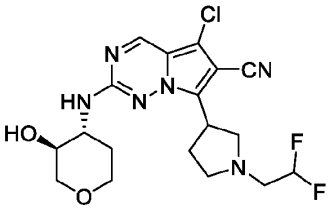
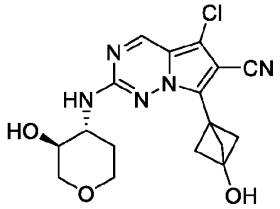
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
167		5-chloro-7-(3-methylbutan-2-yl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/^{i}PrOH = 97/3, 1st peak)	348.20
168		5-chloro-7-(3-methylbutan-2-yl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/^{i}PrOH = 97/3, 2nd peak)	348.20
169		5-chloro-7-(1-ethylcyclopropyl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	346.20
170		5-chloro-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	352.20
171		5-chloro-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 95/5, 1st peak)	366.15

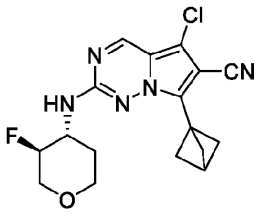
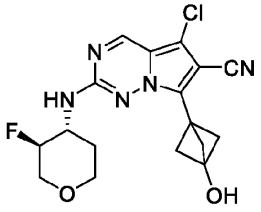
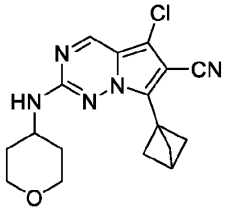
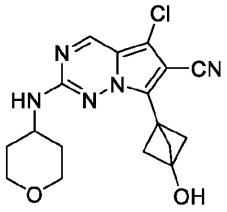
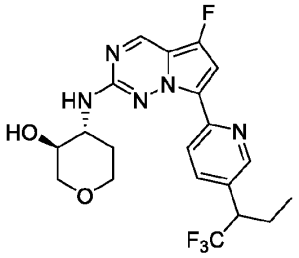
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
172		5-chloro-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 95/5, 2nd peak)	366.20
173		5-chloro-7-(1-ethylcyclopropyl)-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	364.10
174		5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(1-methylpyrrolidin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1-methylpyrrolidin-3-yl was not determined) (CHIRALPAK IG, CO_2/MeOH = 55/45, 1st peak)	377.15
175		5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(1-methylpyrrolidin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1-methylpyrrolidin-3-yl was not determined) (CHIRALPAK IG, CO_2/MeOH = 55/45, 2nd peak)	377.20

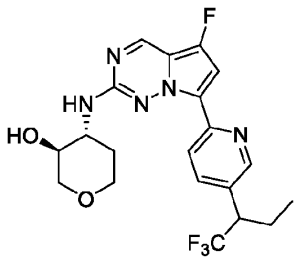
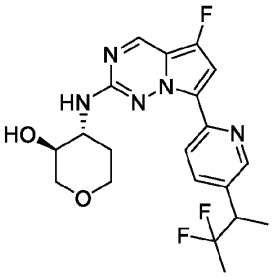
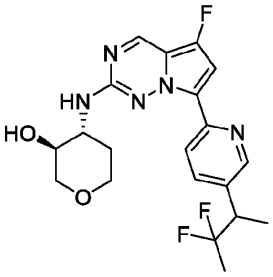
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
176		5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-trifluoromethanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IE, Hexane/EtOH/DCM = 87/2/11, 1st peak)	495.35
177		5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-trifluoromethanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IE, Hexane/EtOH/DCM = 87/2/11, 2nd peak)	495.35
178		5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(2-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 2-methylpentan-3-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 90/10, 2nd peak)	455.25

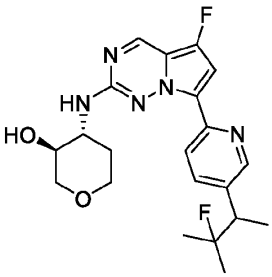
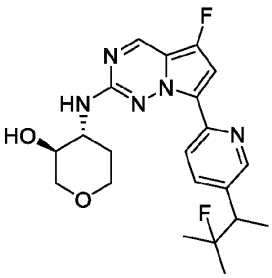
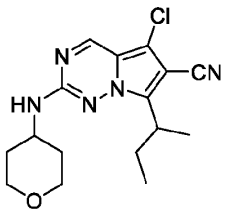
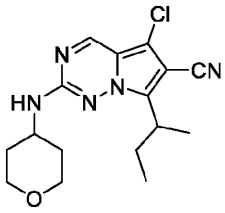
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
179		5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(2-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 2-methylpentan-3-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 90/10, 1st peak)	455.25
180		5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-methylpentan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylpentan-2-yl was not determined) (CHIRAL ART Amylose-C NEO, CO_2/EtOH = 80/20, 1st peak)	455.15
181		5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-methylpentan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylpentan-2-yl was not determined) (CHIRAL ART Amylose-C NEO, CO_2/EtOH = 80/20, 2nd peak)	455.15

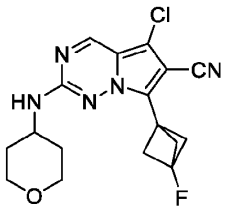
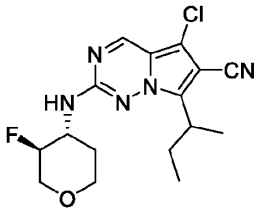
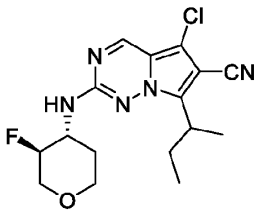
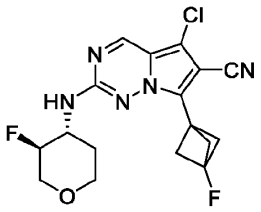
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
182		5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-methylpentan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylpentan-2-yl was not determined) (CHIRAL ART Amylose-C NEO, CO_2/EtOH = 80/20, 4th peak)	455.15
183		5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-methylpentan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylpentan-2-yl was not determined) (CHIRAL ART Amylose-C NEO, CO_2/EtOH = 80/20, 3rd peak)	455.15
184		5-chloro-7-(1-cyclopentylethyl)-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1-cyclopentylethyl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 80/20, 1st peak)	467.10

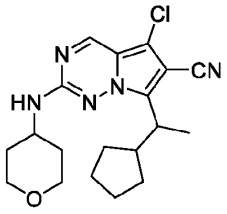
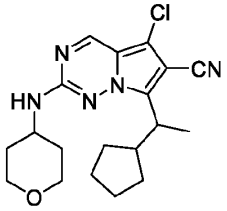
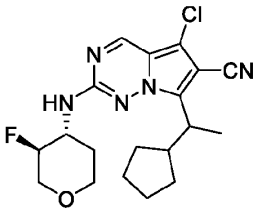
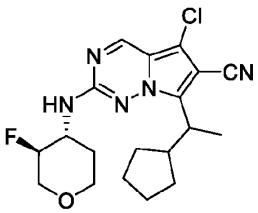
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
185		5-chloro-7-(1-cyclopentylethyl)-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1-cyclopentylethyl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 80/20, 2nd peak)	467.10
186		5-chloro-7-(1-(2,2-difluoroethyl)pyrrolidin-3-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1-(2,2-difluoroethyl)pyrrolidin-3-yl was not determined) (CHIRALPAK IG, CO_2/MeOH = 60/40, 1st peak)	427.20
187		5-chloro-7-(1-(2,2-difluoroethyl)pyrrolidin-3-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1-(2,2-difluoroethyl)pyrrolidin-3-yl was not determined) (CHIRALPAK IG, CO_2/MeOH = 60/40, 2nd peak)	427.20
188		5-chloro-7-(3-hydroxybicyclo[1.1.1]pentan-1-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	376.10

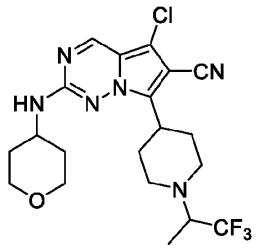
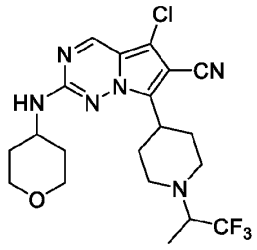
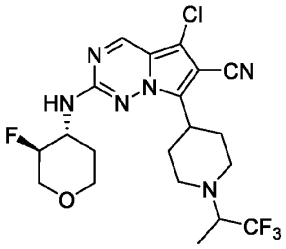
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
189		7-(bicyclo[1.1.1]pentan-1-yl)-5-chloro-2-(((3*S*,4*R*)-3-fluorotetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	362.15
190		5-chloro-2-(((3*S*,4*R*)-3-fluorotetrahydro-2*H*-pyran-4-yl)amino)-7-(3-hydroxybicyclo[1.1.1]pentan-1-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	378.15
191		7-(bicyclo[1.1.1]pentan-1-yl)-5-chloro-2-((tetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	344.20
192		5-chloro-7-(3-hydroxybicyclo[1.1.1]pentan-1-yl)-2-((tetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	360.05
193		(3*S*,4*R*)-4-((5-fluoro-7-(5-(1,1,1-trifluorobutan-2-yl)pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 5-(1,1,1-trifluorobutan-2-yl was not determined((CHIRALPAK IE, Hexane/EtOH = 80/20, 1st peak)	440.35

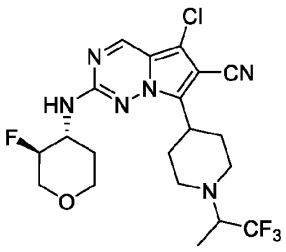
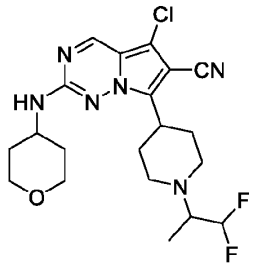
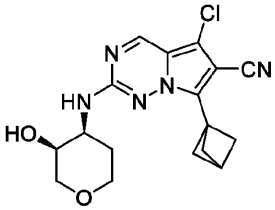
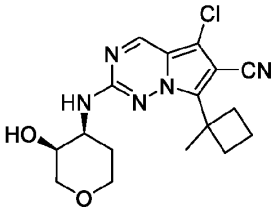
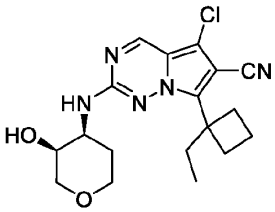
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
194		(3*S*,4*R*)-4-((5-fluoro-7-(5-(1,1,1-trifluorobutan-2-yl)pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 5-(1,1,1-trifluorobutan-2-yl was not determined((CHIRALPAK IE, Hexane/EtOH = 80/20, 2nd peak)	440.35
195		(3*S*,4*R*)-4-((7-(5-(3,3-difluorobutan-2-yl)pyridin-2-yl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 5-(3,3-difluorobutan-2-yl)pyridin-2-yl was not determined) (CHIRALPAK IE, Hexane/EtOH = 80/20, 1st peak)	422.15
196		(3*S*,4*R*)-4-((7-(5-(3,3-difluorobutan-2-yl)pyridin-2-yl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 5-(3,3-difluorobutan-2-yl)pyridin-2-yl was not determined) (CHIRALPAK IE, Hexane/EtOH = 80/20, 2nd peak)	422.15

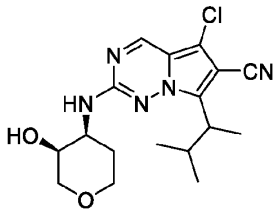
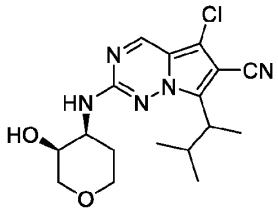
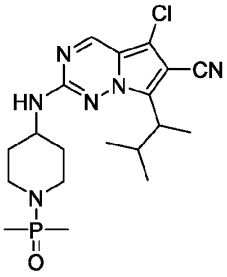
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
197		(3*S*,4*R*)-4-((5-fluoro-7-(5-(3-fluoro-3-methylbutan-2-yl)pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 5-(3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH/MeOH = 88/4/8, 1st peak)	418.25
198		(3*S*,4*R*)-4-((5-fluoro-7-(5-(3-fluoro-3-methylbutan-2-yl)pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 5-(3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH/MeOH = 88/4/8, 2nd peak)	418.25
199		7-(*sec*-butyl)-5-chloro-2-((tetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single enantiomer, absolute chiral configuration of *sec*-butyl was not determined) (CHIRALPAK AY, Hexane/^{i}PrOH = 95/5, 1st peak)	334.15
200		7-(*sec*-butyl)-5-chloro-2-((tetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single enantiomer, absolute chiral configuration of *sec*-butyl was not determined) (CHIRALPAK AY, Hexane/^{i}PrOH = 95/5, 2nd peak)	334.15

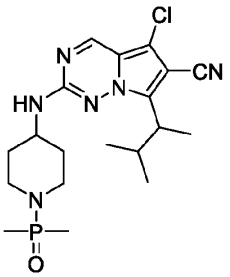
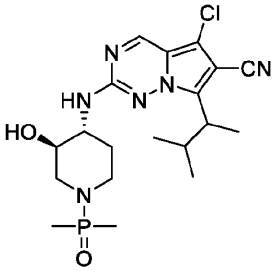
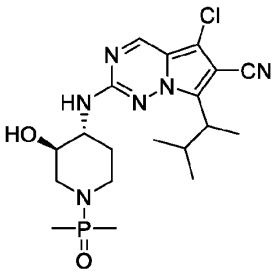
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
201		5-chloro-7-(3-fluorobicyclo[1.1.1]pentan-1-yl)-2-((tetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	362.15
202		7-(*sec*-butyl)-5-chloro-2-(((3*S*,4*R*)-3-fluorotetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (CHIRALPAK AD, Hexane/^{i}PrOH = 95/5, 1st peak)	352.15
203		7-(*sec*-butyl)-5-chloro-2-(((3*S*,4*R*)-3-fluorotetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (CHIRALPAK AD, Hexane/^{i}PrOH = 95/5, 2nd peak)	352.15
204		5-chloro-7-(3-fluorobicyclo[1.1.1]pentan-1-yl)-2-(((3*S*,4*R*)-3-fluorotetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	380.20

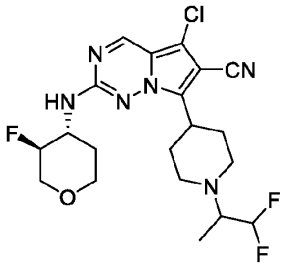
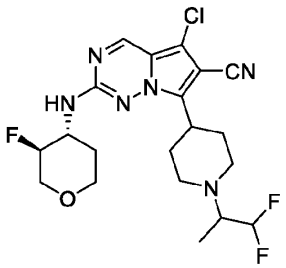
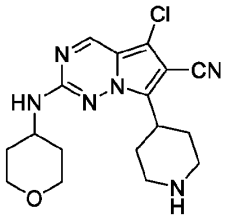
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
205		5-chloro-7-(1-cyclopentylethyl)-2-((tetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single enantiomer, absolute chiral configuration of 1-cyclopentylethyl was not determined) (Lux Cellulose, Hexane/^{i}PrOH = 95/5, 1st peak)	374.20
206		5-chloro-7-(1-cyclopentylethyl)-2-((tetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single enantiomer, absolute chiral configuration of 1-cyclopentylethyl was not determined) (Lux Cellulose, Hexane/^{i}PrOH = 95/5, 2nd peak)	374.20
207		5-chloro-7-(1-cyclopentylethyl)-2-(((3*S*,4*R*)-3-fluorotetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1-cyclopentylethyl was not determined) (CHIRALPAK IF, Hexane/EtOH = 98/2, 1st peak)	392.10
208		5-chloro-7-(1-cyclopentylethyl)-2-(((3*S*,4*R*)-3-fluorotetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1-cyclopentylethyl was not determined) (CHIRALPAK IF, Hexane/EtOH = 98/2, 2nd peak)	392.15

Example	Compound Structure	Compound Name	Observed $[M + H]^+$
209		5-chloro-2-((tetrahydro-2*H*-pyran-4-yl)amino)-7-(1-(1,1,1-trifluoropropan-2-yl)piperidin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single enantiomer, absolute chiral configuration of 1-(1,1,1-trifluoropropan-2-yl was not determined) (CHIRAL ART Amylose-C NEO, CO_2/^{i}PrOH = 82/18, 1st peak)	457.15
210		5-chloro-2-((tetrahydro-2*H*-pyran-4-yl)amino)-7-(1-(1,1,1-trifluoropropan-2-yl)piperidin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single enantiomer, absolute chiral configuration of 1-(1,1,1-trifluoropropan-2-yl was not determined) (CHIRAL ART Amylose-C NEO, CO_2/^{i}PrOH = 82/18, 2nd peak)	457.20
211		5-chloro-2-(((3*S*,4*R*)-3-fluorotetrahydro-2*H*-pyran-4-yl)amino)-7-(1-(1,1,1-trifluoropropan-2-yl)piperidin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1-(1,1,1-trifluoropropan-2-yl was not determined) (CHIRALPAK AD, CO_2/^{i}PrOH = 90/10, 2nd peak)	475.15

Example	Compound Structure	Compound Name	Observed $[M + H]^+$
212		5-chloro-2-(((3*S*,4*R*)-3-fluorotetrahydro-2*H*-pyran-4-yl)amino)-7-(1-(1,1,1-trifluoropropan-2-yl)piperidin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1-(1,1,1-trifluoropropan-2-yl was not determined) (CHIRALPAK AD, CO_2/^{i}PrOH = 90/10, 1st peak)	475.15
213		5-chloro-7-(1-(1,1-difluoropropan-2-yl)piperidin-4-yl)-2-((tetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	439.20
214		7-(bicyclo[1.1.1]pentan-1-yl)-5-chloro-2-(((3*S*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	360.10
215		5-chloro-2-(((3*S*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	362.10
216		5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	376.20

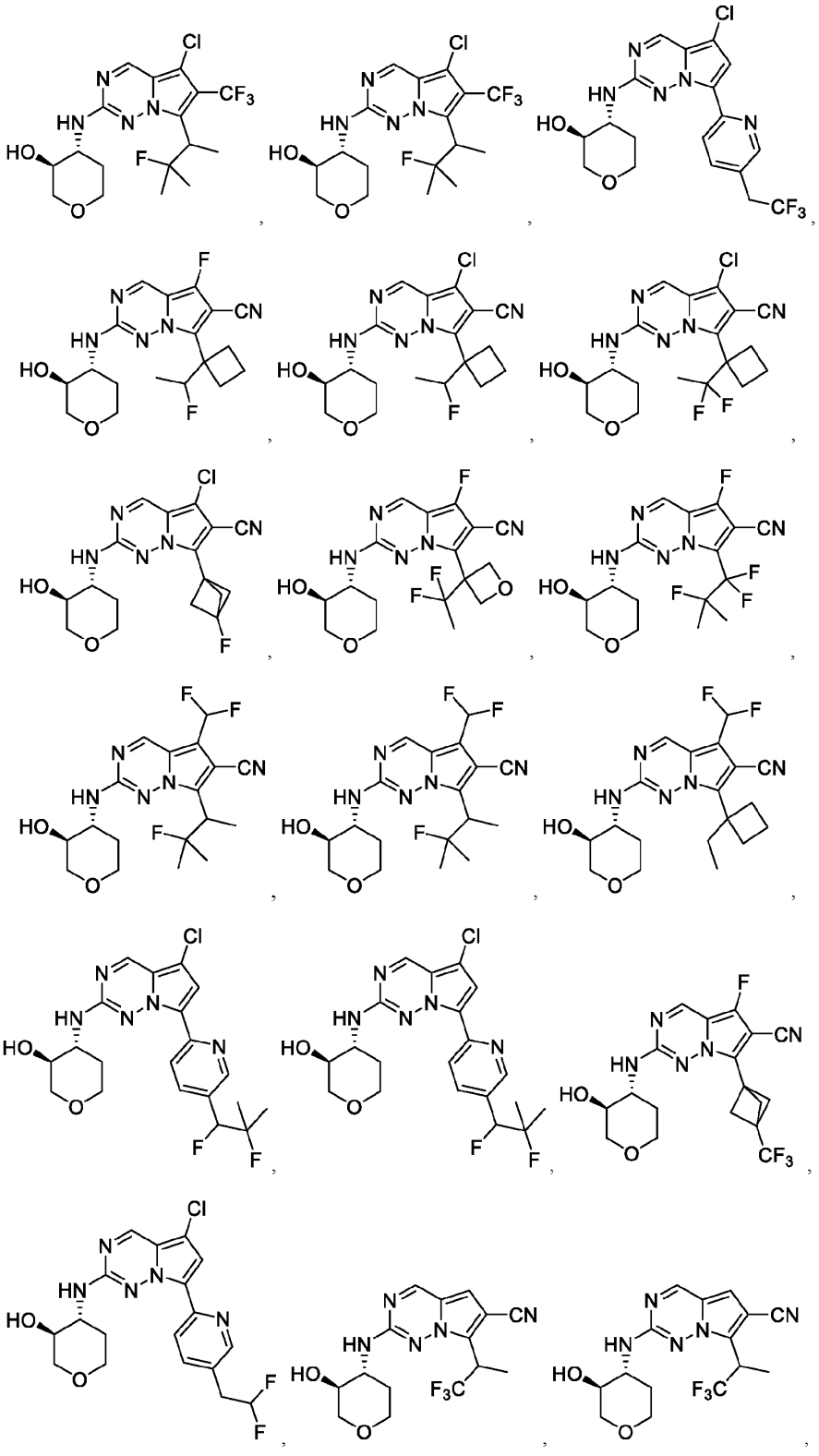
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
217		5-chloro-2-(((3*S*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IG, CO_2/MeOH = 74/26, 1st peak)	364.10
218		5-chloro-2-(((3*S*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IG, CO_2/MeOH = 74/26, 2nd peak)	364.10
219		5-chloro-2-((1-(dimethylphosphoryl)piperidin-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single enantiomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AS-10-CSP, CO_2/MeOH = 85/15, 1st peak)	423.25

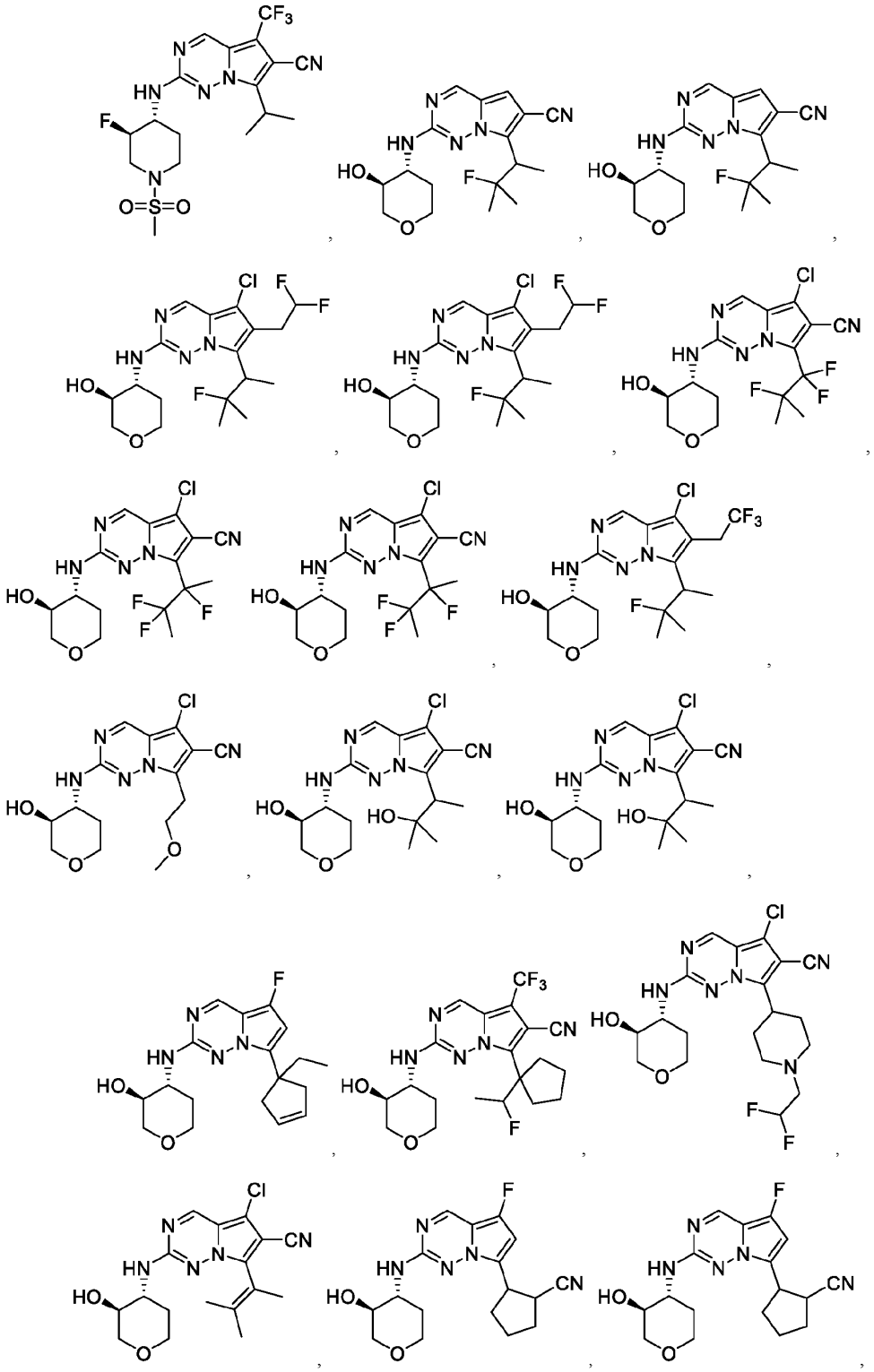
Example	Compound Structure	Compound Name	Observed $[M + H]^+$
220		5-chloro-2-((1-(dimethylphosphoryl)piperidin-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single enantiomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AS-10-CSP, CO_2/MeOH = 85/15, 2nd peak)	423.20
221		5-chloro-2-{[(3*R*,4*R*)-1-(dimethylphosphoryl)-3-hydroxypiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (YG-AS-10-CSP, CO_2/MeOH = 85/15, 1st peak)	439.15
222		5-chloro-2-{[(3*R*,4*R*)-1-(dimethylphosphoryl)-3-hydroxypiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (YG-AS-10-CSP, CO_2/MeOH = 85/15, 2nd peak)	439.25

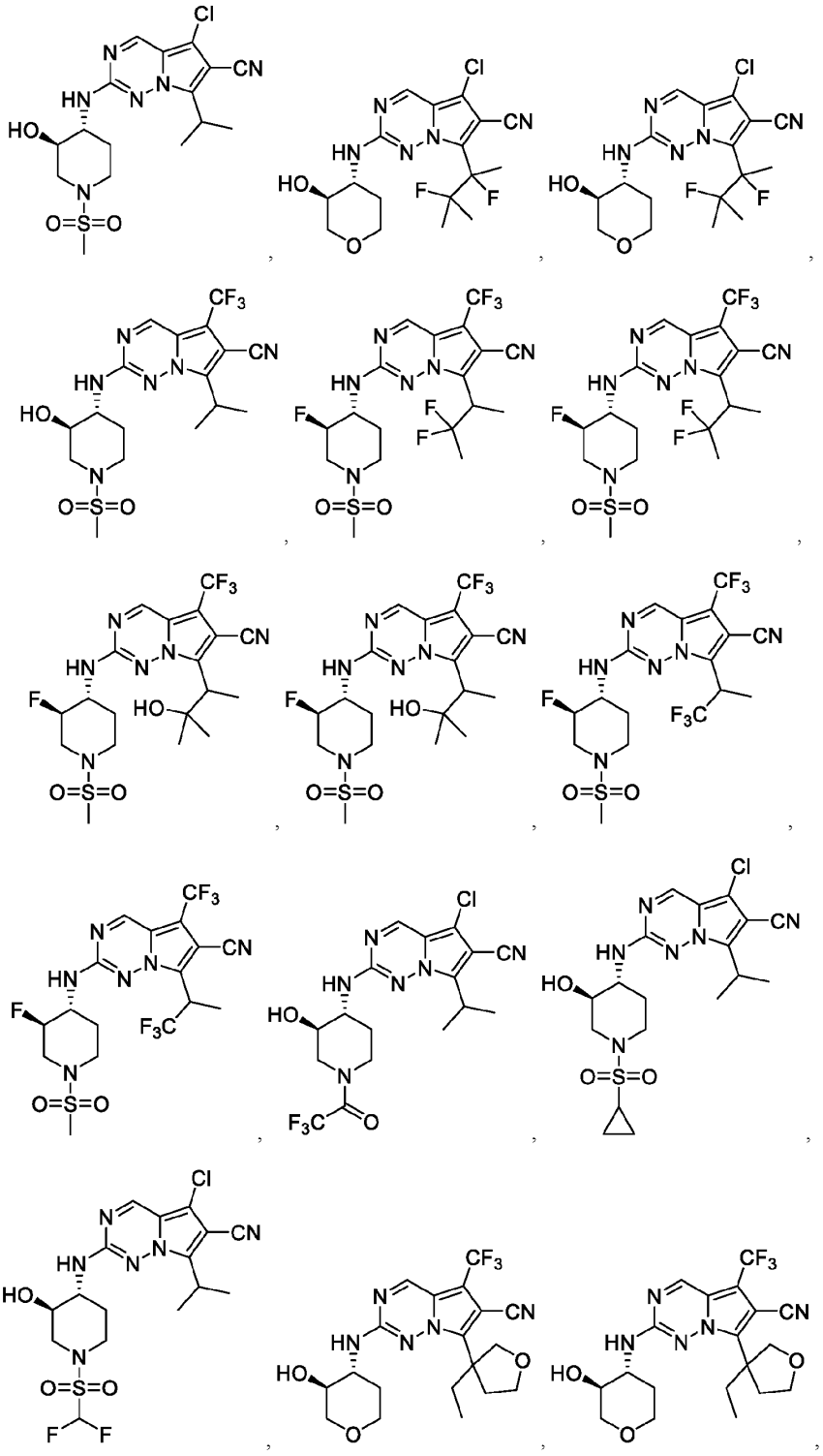
Example	Compound Structure	Compound Name	Observed [M + H]$^+$
223		5-chloro-7-(1-(1,1-difluoropropan-2-yl)piperidin-4-yl)-2-(((3*S*,4*R*)-3-fluorotetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1-(1,1-difluoropropan-2-yl was not determined) (CHIRALPAK IG, Hexane/EtOH = 90/10, 2nd peak)	457.15
224		5-chloro-7-(1-(1,1-difluoropropan-2-yl)piperidin-4-yl)-2-(((3*S*,4*R*)-3-fluorotetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1-(1,1-difluoropropan-2-yl was not determined) (CHIRALPAK IG, Hexane/EtOH = 90/10, 1st peak)	457.15
225		5-chloro-2-(oxan-4-ylamino)-7-(piperidin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile	361.15

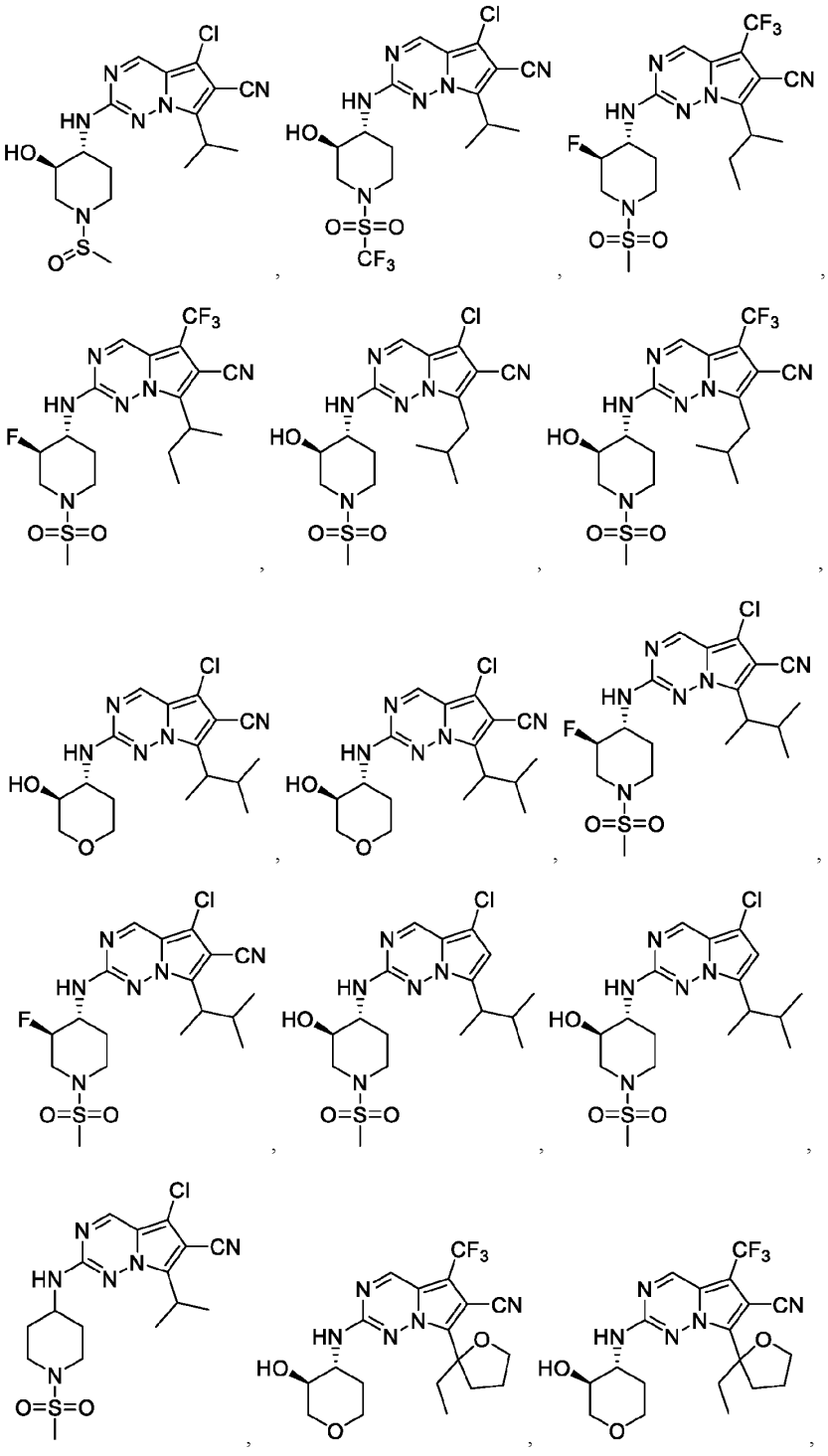
Numbered Embodiments

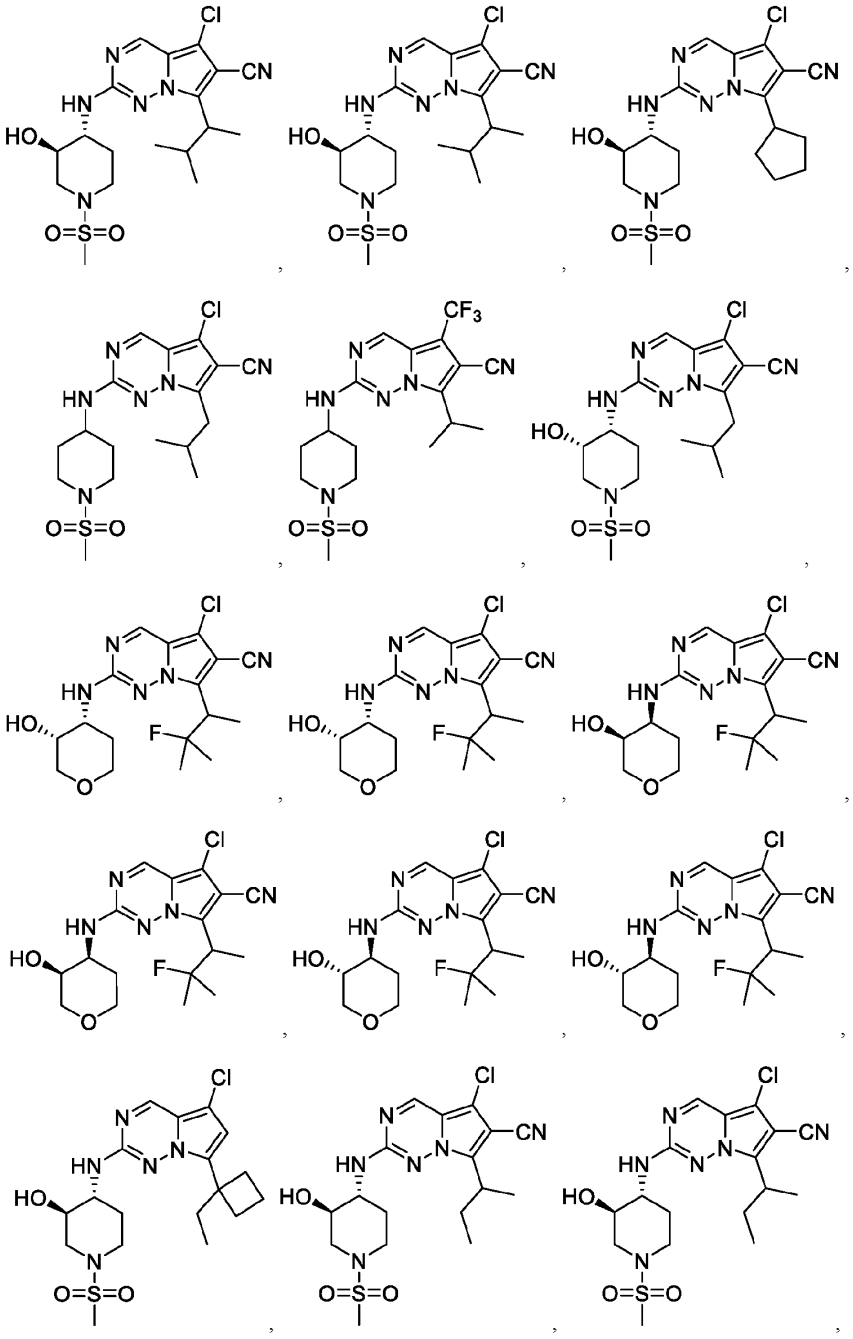
Embodiment 1. A compound, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, having a structure selected from the group consisting of:

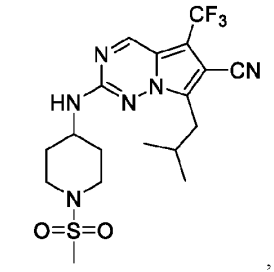
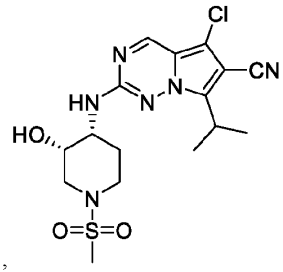
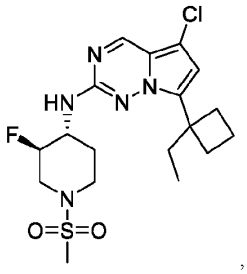
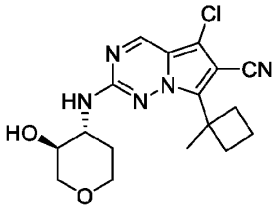
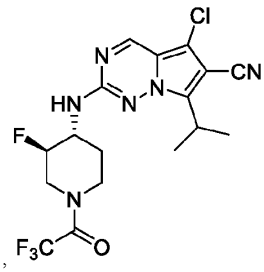
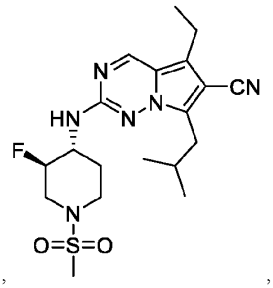
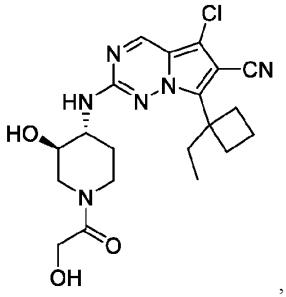
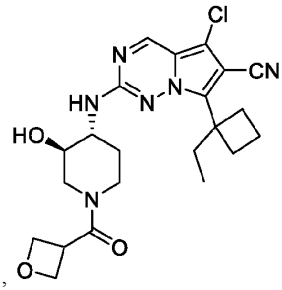
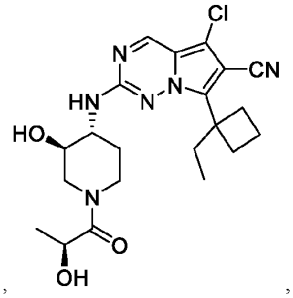
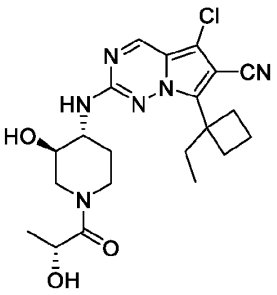
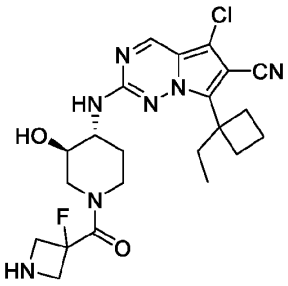
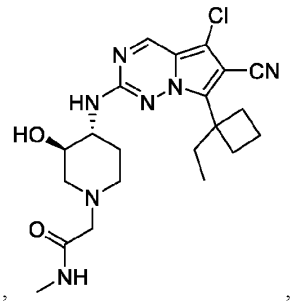
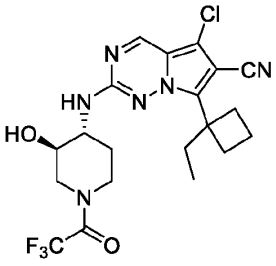
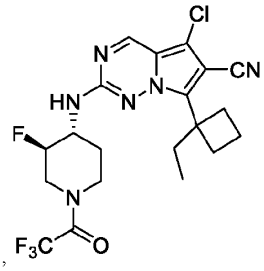
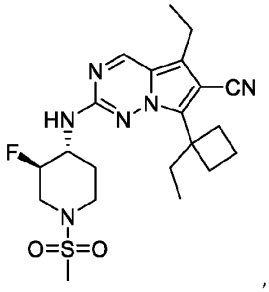


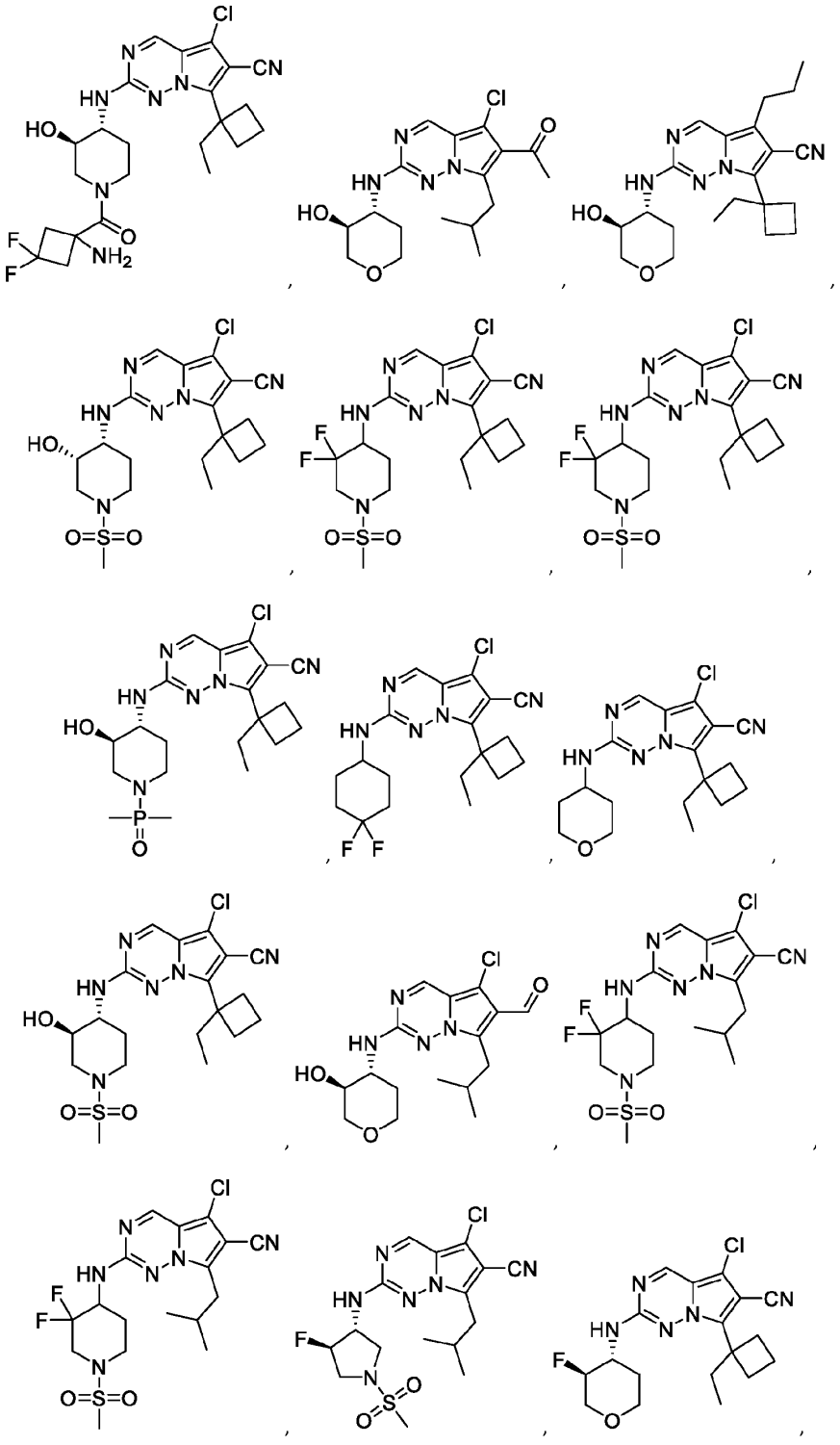


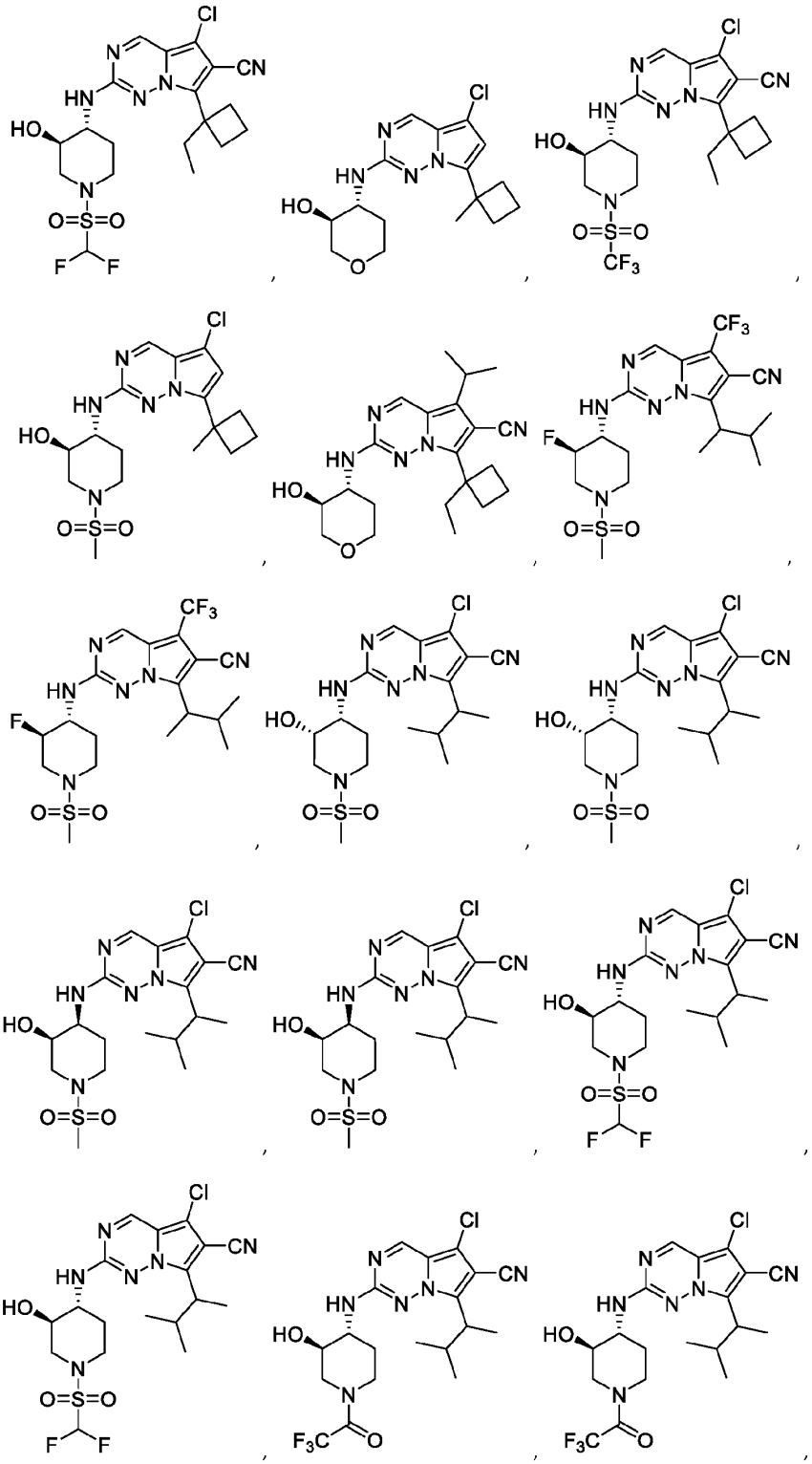


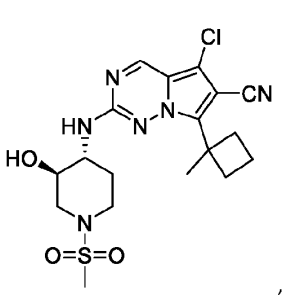
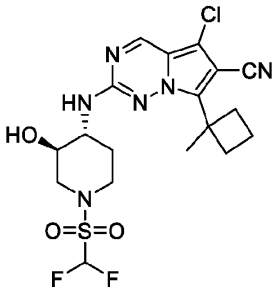
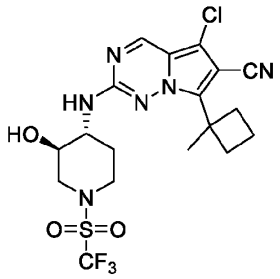
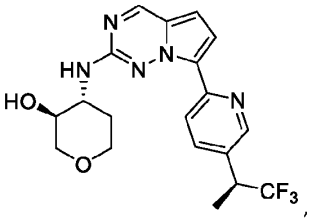
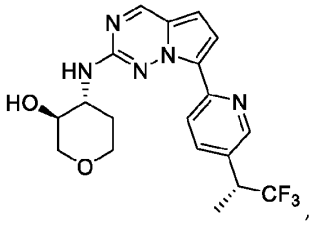
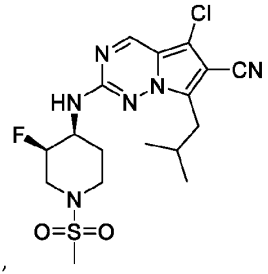
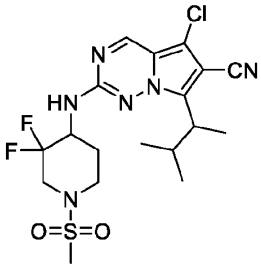
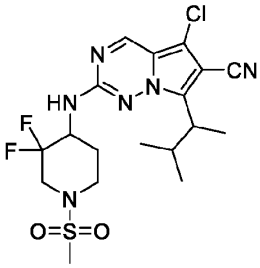
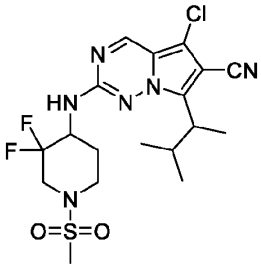
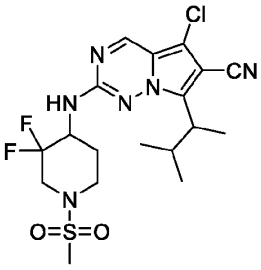
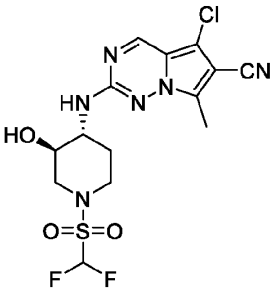
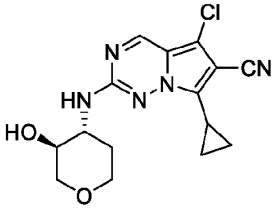
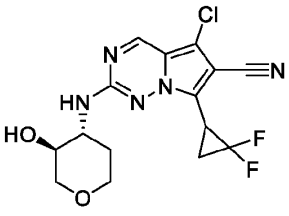
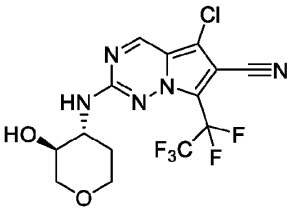
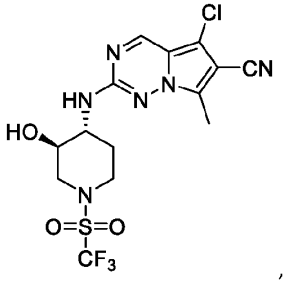


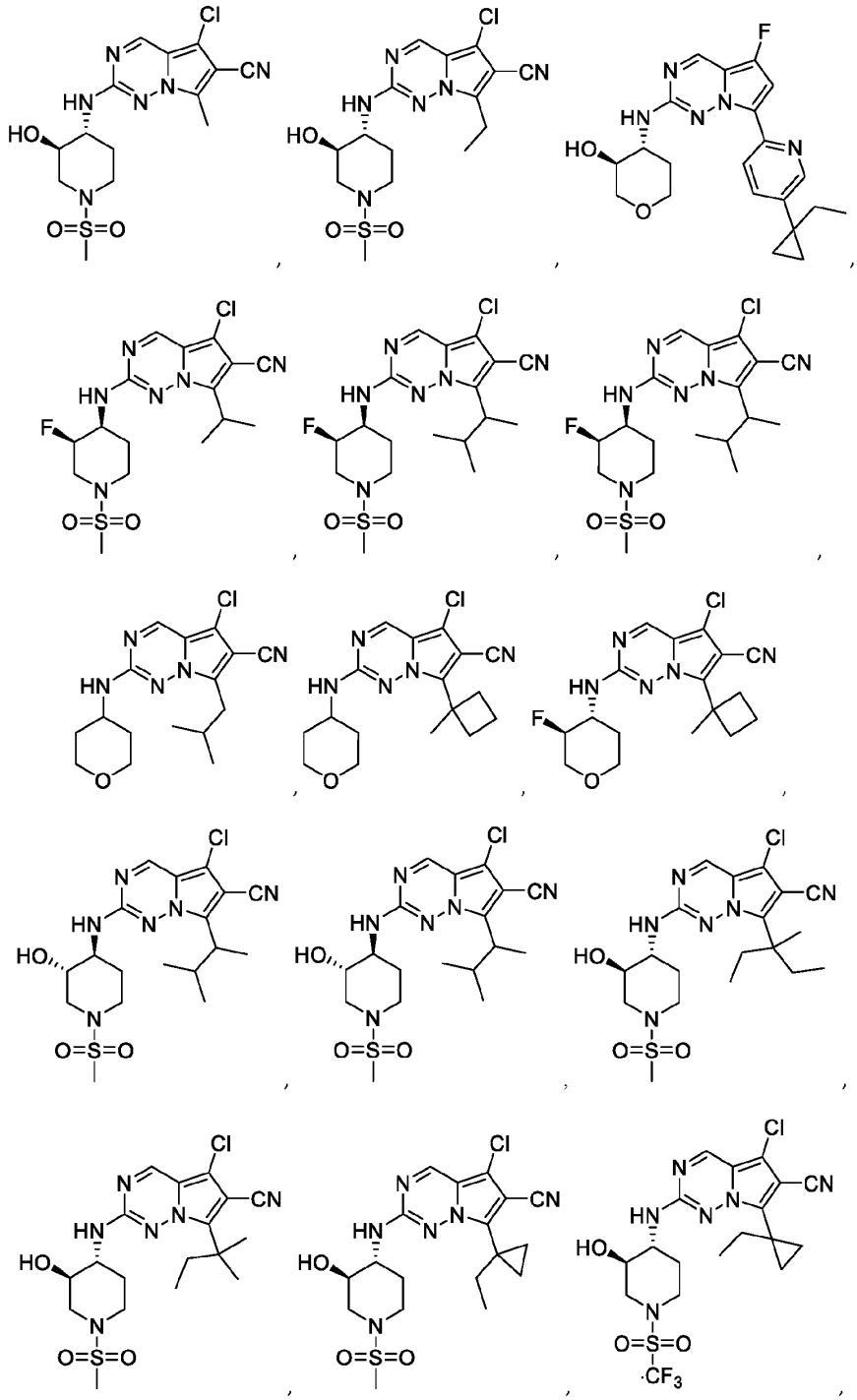


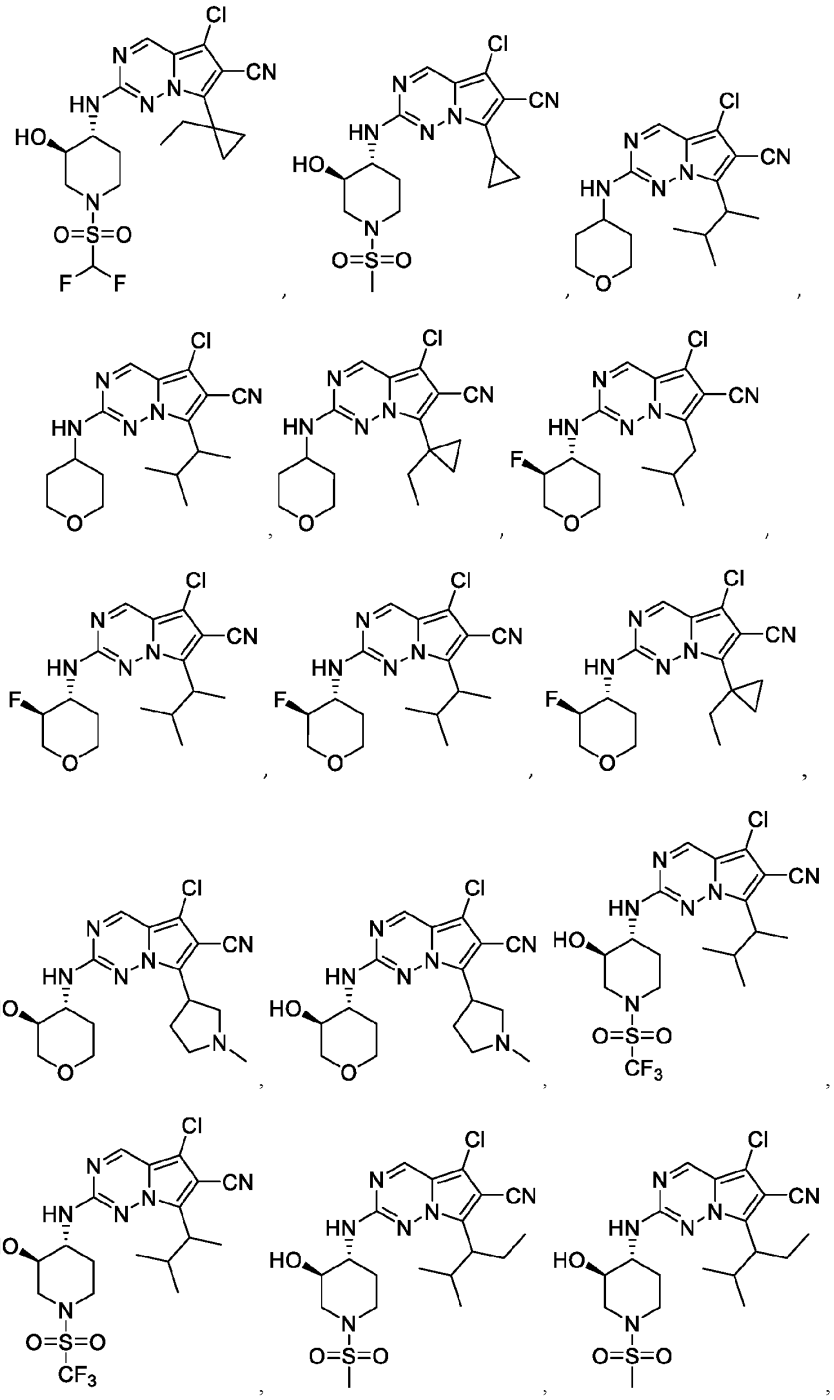
















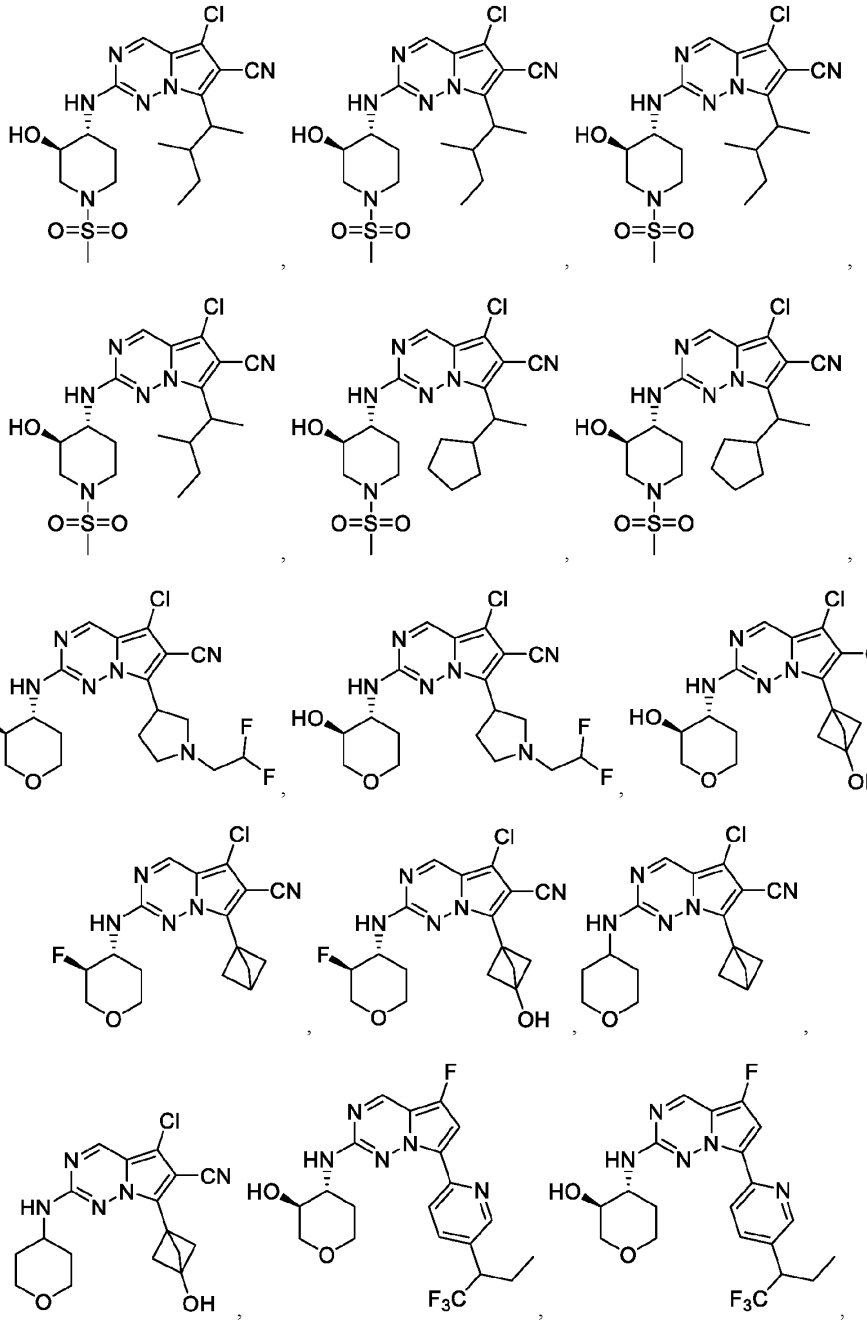


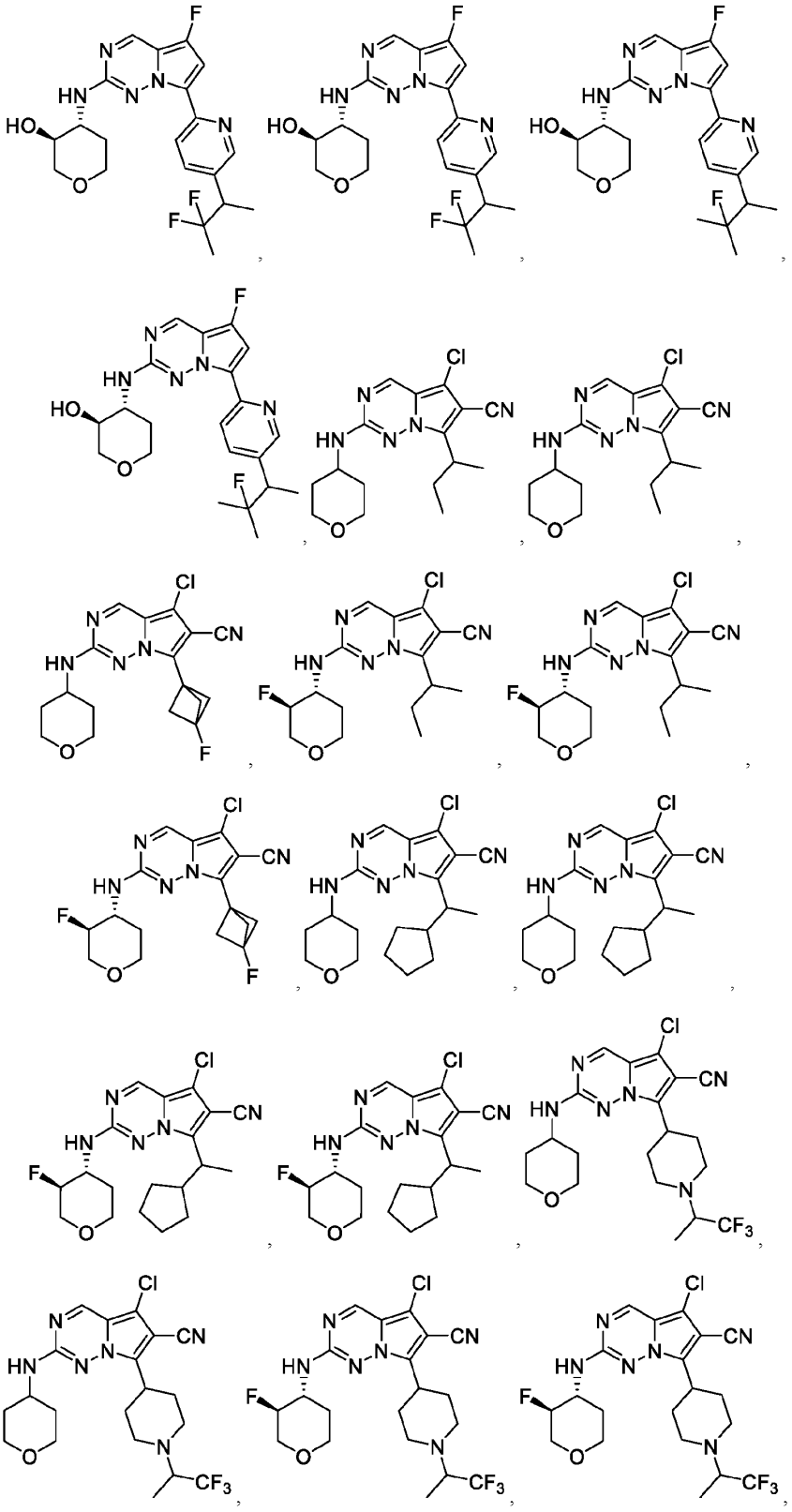


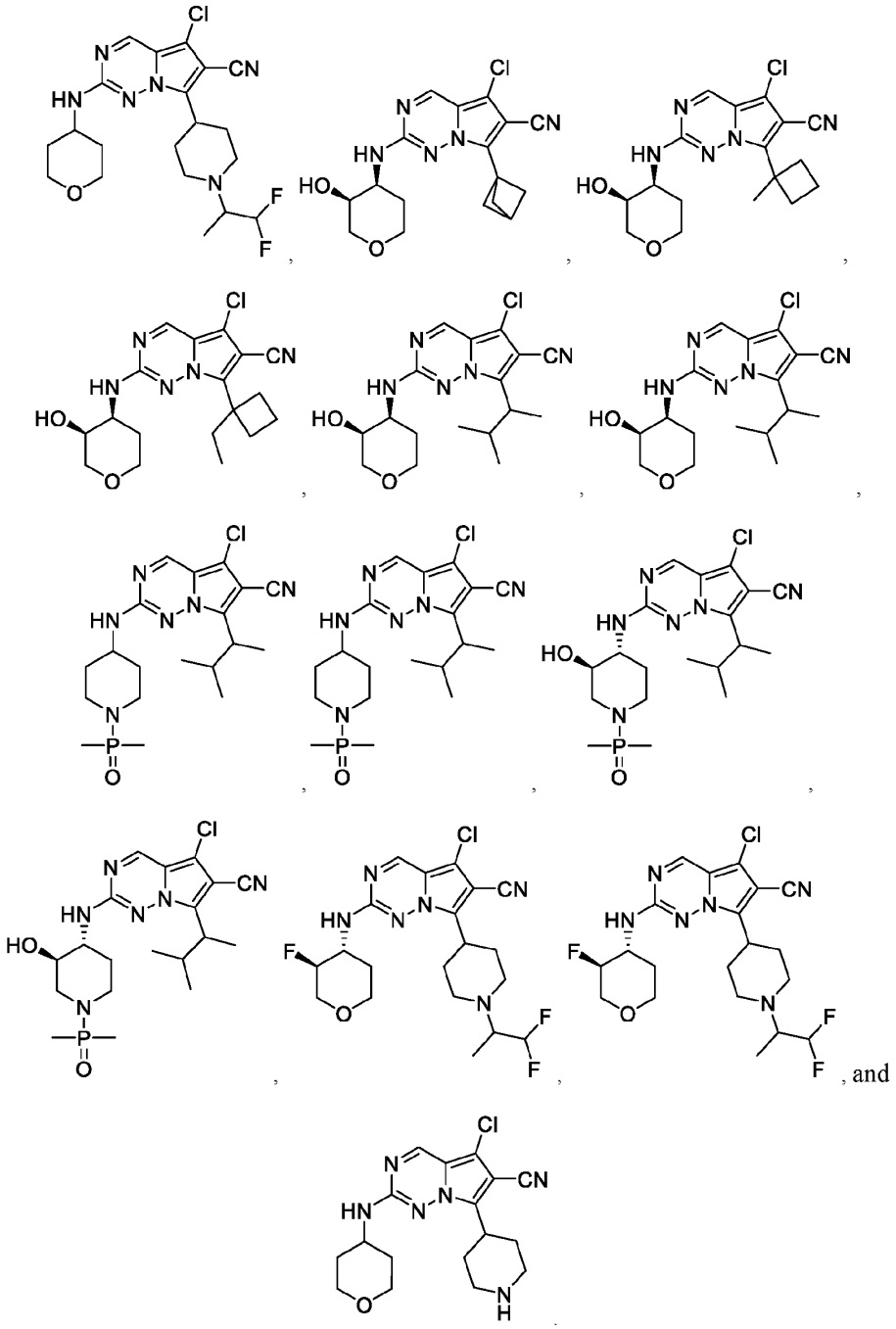


























Embodiment 2. A pharmaceutical composition comprising a compound, a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, as described in embodiment 1 and a pharmaceutically acceptable excipient.

Embodiment 3. A method of preparing a pharmaceutical composition comprising mixing a compound, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, of embodiment 1, and a pharmaceutically acceptable carrier.

Embodiment 4. A compound of embodiment 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, for use in a method of treatment of the human or animal body.

Embodiment 5. A compound of embodiment 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, for use in a method of treatment of cancer or neoplastic disease.

Embodiment 6. Use of a compound of embodiment 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, in the manufacture of a medicament for the treatment of cancer or neoplastic disease.

Embodiment 7. A method of treating cancer in a patient in need thereof, comprising administering to the patient a compound as described in embodiment 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof.

Embodiment 8. A method of treating cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising a compound as described in embodiment 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, and a pharmaceutically acceptable excipient.

Embodiment 9. The use of embodiment any one of embodiments 4 to 6, or the method of embodiment 7 or 8, wherein the cancer is selected from breast cancer, skin cancer, melanoma, or leukemia.

Embodiment 10. A method of inhibiting a CDK2, CDK4 or CDK6 kinase enzyme comprising contacting the enzyme with a compound of embodiment 1, or a stereoisomer thereof, wherein the CDK2, CDK4 or CDK6 kinase is contacted in an *in vitro* setting.

Embodiment 11. A method of inhibiting a CDK2, CDK4 or CDK6 kinase enzyme comprising contacting the enzyme with a compound of embodiment 1, or a stereoisomer thereof, wherein the CDK2, CDK4 or CDK6 kinase is contacted in an *in vivo* setting.

Preparation of Compounds

[0081] The compounds used in the synthetic chemistry reactions described herein are made according to organic synthesis techniques known to those skilled in this art, starting from commercially

available chemicals and/or from compounds described in the chemical literature. "Commercially available chemicals" are obtained from standard commercial sources including Acros Organics (Pittsburgh, PA), Aldrich Chemical (Milwaukee, WI, including Sigma Chemical and Fluka), Apin Chemicals Ltd. (Milton Park, UK), Avocado Research (Lancashire, U.K.), BDH Inc. (Toronto, Canada), Bionet (Cornwall, U.K.), Chemservice Inc. (West Chester, PA), Crescent Chemical Co. (Hauppauge, NY), Eastman Organic Chemicals, Eastman Kodak Company (Rochester, NY), Fisher Scientific Co. (Pittsburgh, PA), Fisons Chemicals (Leicestershire, UK), Frontier Scientific (Logan, UT), ICN Biomedicals, Inc. (Costa Mesa, CA), Key Organics (Cornwall, U.K.), Lancaster Synthesis (Windham, NH), Maybridge Chemical Co. Ltd. (Cornwall, U.K.), Parish Chemical Co. (Orem, UT), Pfaltz & Bauer, Inc. (Waterbury, CN), Polyorganix (Houston, TX), Pierce Chemical Co. (Rockford, IL), Riedel de Haen AG (Hanover, Germany), Spectrum Quality Product, Inc. (New Brunswick, NJ), TCI America (Portland, OR), Trans World Chemicals, Inc. (Rockville, MD), and Wako Chemicals USA, Inc. (Richmond, VA).

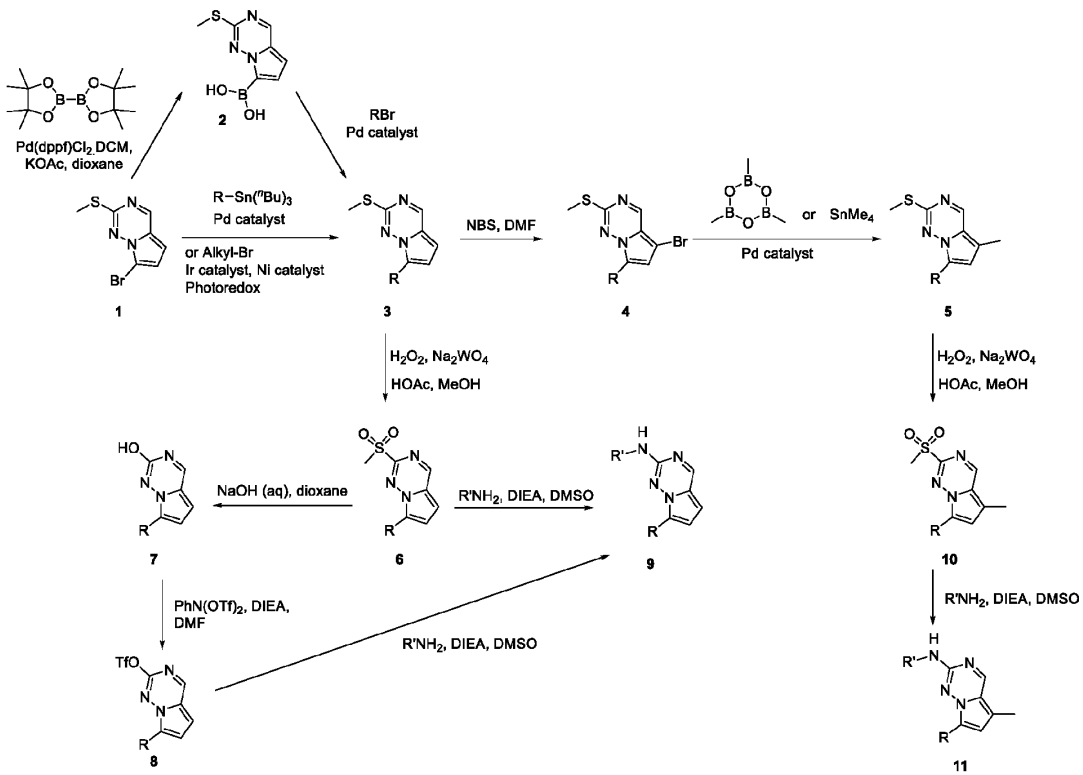
[0082] Suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, "Synthetic Organic Chemistry", John Wiley & Sons, Inc., New York; S. R. Sandler et al., "Organic Functional Group Preparations," 2nd Ed., Academic Press, New York, 1983; H. O. House, "Modern Synthetic Reactions", 2nd Ed., W. A. Benjamin, Inc. Menlo Park, Calif. 1972; T. L. Gilchrist, "Heterocyclic Chemistry", 2nd Ed., John Wiley & Sons, New York, 1992; J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th Ed., Wiley-Interscience, New York, 1992. Additional suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, Fuhrhop, J. and Penzlin G. "Organic Synthesis: Concepts, Methods, Starting Materials", Second, Revised and Enlarged Edition (1994) John Wiley & Sons ISBN: 3-527-29074-5; Hoffman, R.V. "Organic Chemistry, An Intermediate Text" (1996) Oxford University Press, ISBN 0-19-509618-5; Larock, R. C. "Comprehensive Organic Transformations: A Guide to Functional Group Preparations" 2nd Edition (1999) Wiley-VCH, ISBN: 0-471-19031-4; March, J. "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure" 4th Edition (1992) John Wiley & Sons, ISBN: 0-471-60180-2; Otera, J. (editor) "Modern Carbonyl Chemistry" (2000) Wiley-VCH, ISBN: 3-527-29871-1; Patai, S. "Patai's 1992 Guide to the Chemistry of Functional Groups" (1992) Interscience ISBN: 0-471-93022-9; Solomons, T. W. G. "Organic Chemistry" 7th Edition (2000) John Wiley & Sons, ISBN: 0-471-19095-0; Stowell, J.C., "Intermediate Organic Chemistry" 2nd Edition (1993) Wiley-Interscience, ISBN: 0-471-57456-2; "Industrial Organic Chemicals: Starting Materials and Intermediates: An Ullmann's

Encyclopedia" (1999) John Wiley & Sons, ISBN: 3-527-29645-X, in 8 volumes; "Organic Reactions" (1942-2000) John Wiley & Sons, in over 55 volumes; and "Chemistry of Functional Groups" John Wiley & Sons, in 73 volumes.

[0083] Specific and analogous reactants are optionally identified through the indices of known chemicals prepared by the Chemical Abstract Service of the American Chemical Society, which are available in most public and university libraries, as well as through on-line databases (contact the American Chemical Society, Washington, D.C. for more details). Chemicals that are known but not commercially available in catalogs are optionally prepared by custom chemical synthesis houses, where many of the standard chemical supply houses (*e.g.*, those listed above) provide custom synthesis services. A reference useful for the preparation and selection of pharmaceutical salts of the compounds described herein is P. H. Stahl & C. G. Wermuth "Handbook of Pharmaceutical Salts", Verlag Helvetica Chimica Acta, Zurich, 2002.

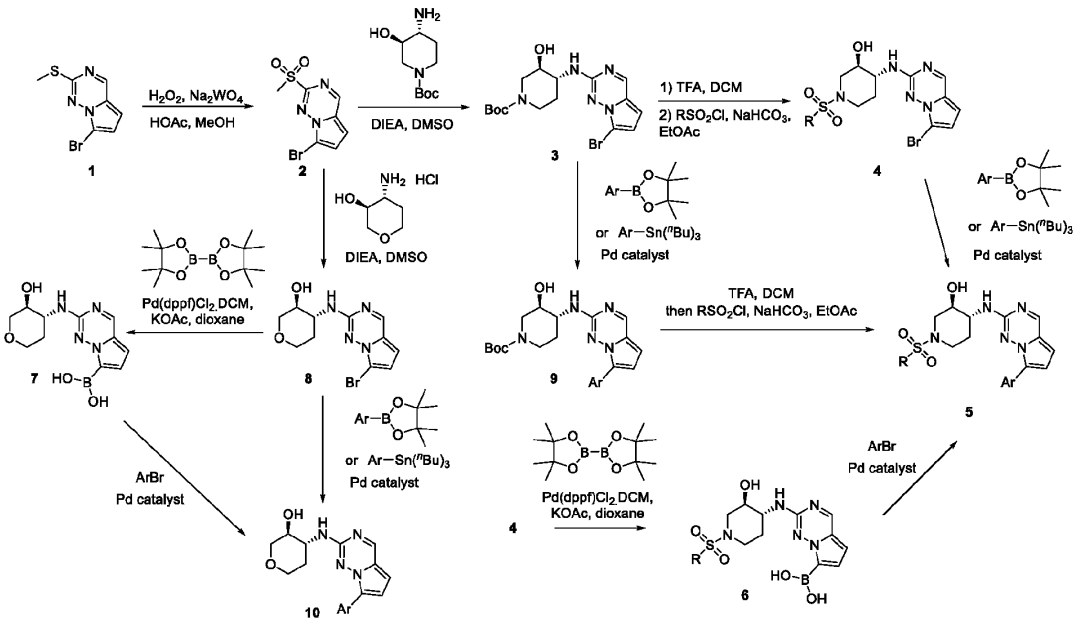
General Synthetic Schemes

SCHEME 1



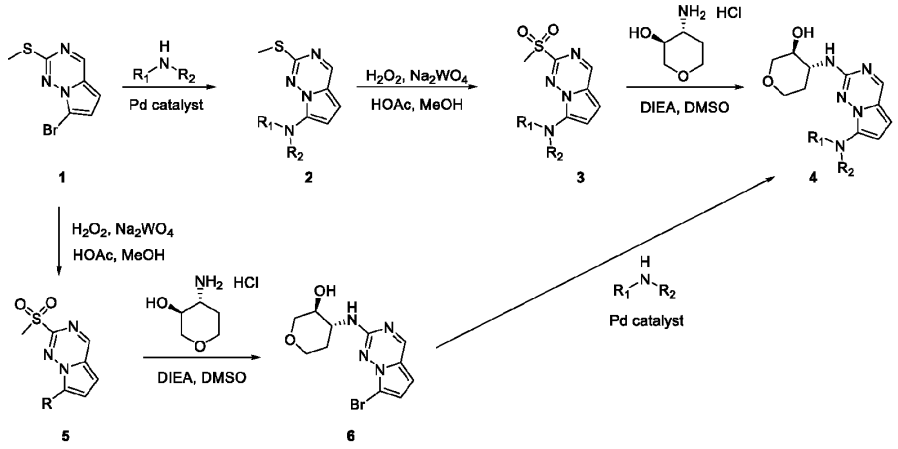
[0084] One common route is illustrated in Scheme 1. Treatment of bromide **1** with 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) in the presence of a palladium catalyst generated boronic acid **2,** which was further converted to intermediate **3** by treatment with an appropriate substituted bromide in the presence of a palladium catalyst. Alternatively, bromide **1** could be treated with a substituted tin reagent in the presence of a palladium catalyst, or an alkyl bromide under metal catalyzed photo-redox conditions, to generate intermediate **3** directly. Intermediate **3** can be brominated, such as with NBS, to generate bromide **4**, which can then be converted to intermediate **5** by the treatment with a methylating agent, such as tetramethylstannane or 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane. Sulfone **10** is then made by the treatment of intermediate **5** with an oxidizing agent, such as hydrogen peroxide and sodium tungstate. Sulfone **10** is reacted with a substituted amine and a base, such as DIEA, to make compound **11**. Alternatively, intermediate **3** can be oxidized to sulfone **6**, such as with hydrogen peroxide and sodium tungstate, and sulfone **6** is reacted directly with a substituted amine and a base, such as DIEA, to generate compound **9**. Alternatively, hydrolysis with aqueous sodium base to form intermediate 7 followed by conversion to triflate **8** and reaction with a substituted amine and a base such as DIEA provides compound **9**.

SCHEME 2



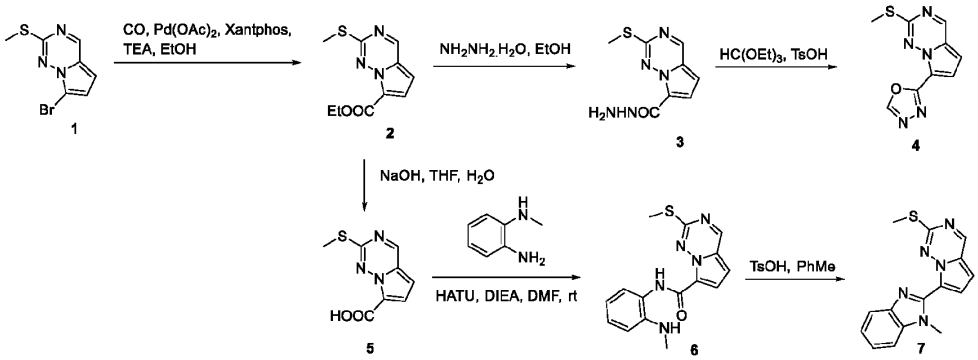
[0085] Another common route is illustrated in Scheme 2. Bromide **1** is oxidized, such as with hydrogen peroxide and sodium tungstate, to form sulfone **2**, which is treated with an appropriate amine, such as tert-butyl (3R,4R)-4-amino-3-hydroxypiperidine-1-carboxylate, in the presence of a base such as DIEA, to afford intermediate **3**. Removal of the Boc group is accomplished with TFA in DCM. Subsequent sulfonylation with a substituted sulfonyl chloride in the presence of a base, such as sodium bicarbonate, affords bromide **4**. Conversion of bromide **4** to boronic acid **6**, followed by palladium-mediated cross-coupling with a suitably substituted aryl bromide generates compound **5**. Bromide **4** can be converted to compound **5** by direct palladium-mediated cross-coupling with an appropriately substituted aryl boronic acid ester or substituted aryl tin reagent. Compound **5** can also be generated through palladium-mediated cross-coupling of intermediate **3** with an appropriately substituted aryl boron reagent or substituted aryl tin reagent to form intermediate **9**. Removal of the Boc group of intermediate 9 is accomplished with TFA in DCM. Subsequent sulfonylation with a suitably substituted sulfonyl chloride in the presence of a base, such as sodium bicarbonate, would afford compound **5**. Alternatively, sulfone **2** could be treated with an amine, such as (3S,4R)-4-aminotetrahydro-2H-pyran-3-ol, in the presence of a base, such as DIEA, to afford bromide **8**. Conversion of bromide **8** to boronic acid **7** followed by palladium-mediated cross-coupling with a suitably substituted aryl bromide generates compound **10**. Bromide **8** can also be converted to compound **10** by direct coupling with an appropriately substituted aryl boronic acid ester or substituted aryl tin reagent.

SCHEME 3



[0086] Another common route is illustrated in Scheme 3. Bromide **1** is treated with a suitably substituted amine in the presence of a palladium catalyst to afford intermediate **2**, which is oxidized, such as with hydrogen peroxide and sodium tungstate, to form sulfone **3**. Treatment of sulfone **3** with an appropriate amine, such as (3S,4R)-4-aminotetrahydro-2H-pyran-3-ol, in the presence of an appropriate base, such as DIEA, would then generate compound **4**. Alternatively, bromide **1** can be oxidized, such as with hydrogen peroxide and sodium tungstate, to form sulfone **5** which can be reacted with a suitable amine, such as (3S,4R)-4-aminotetrahydro-2H-pyran-3-ol, in the presence of an appropriate base, such as DIEA, to afford intermediate **6**. Treatment of compound **6** with a suitably substituted amine in the presence of a palladium catalyst would then generate compound **4**.

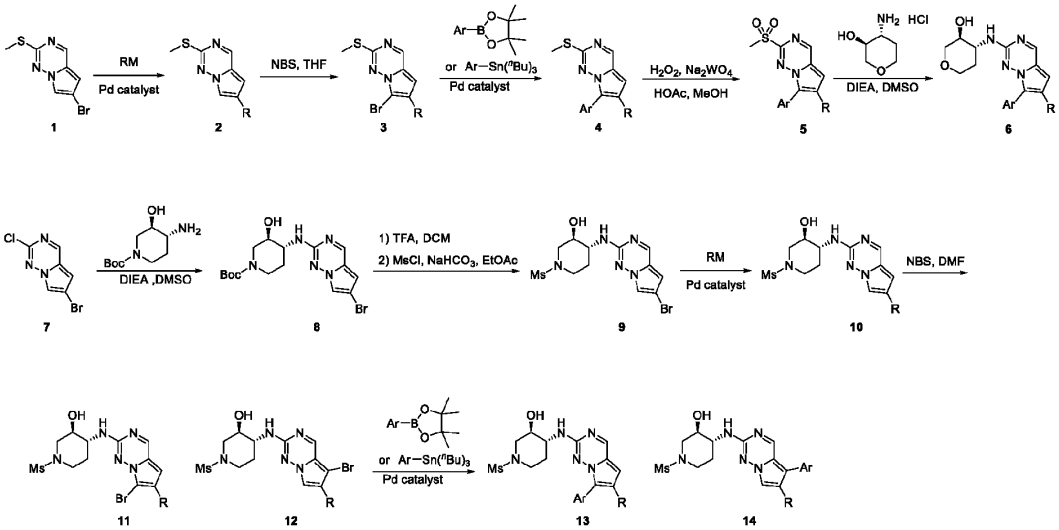
SCHEME 4



[0087] Another common route is illustrated in Scheme 4. Bromide **1** is esterified, such as with carbon monoxide under palladium-catalyzed conditions to afford ester **2**, which could then be treated with hydrazine in an appropriate solvent, e.g., ethanol, to generate intermediate **3**. Treatment of intermediate **3** with triethyl orthoformate and toluene sulfonic acid produced compound **4**. Ester **2** can also be hydrolyzed, such as with aqueous sodium hydroxide, to acid **5**. This is followed by amide bond formation, such as via HATU mediated amide coupling, to afford intermediate **6**.

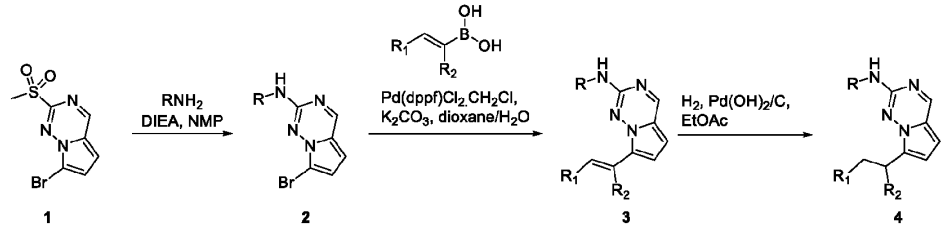
Compound 7 can be generated from intermediate **6** by cyclizing under acidic conditions, such as toluene sulfonic acid in a solvent such as toluene.

SCHEME 5



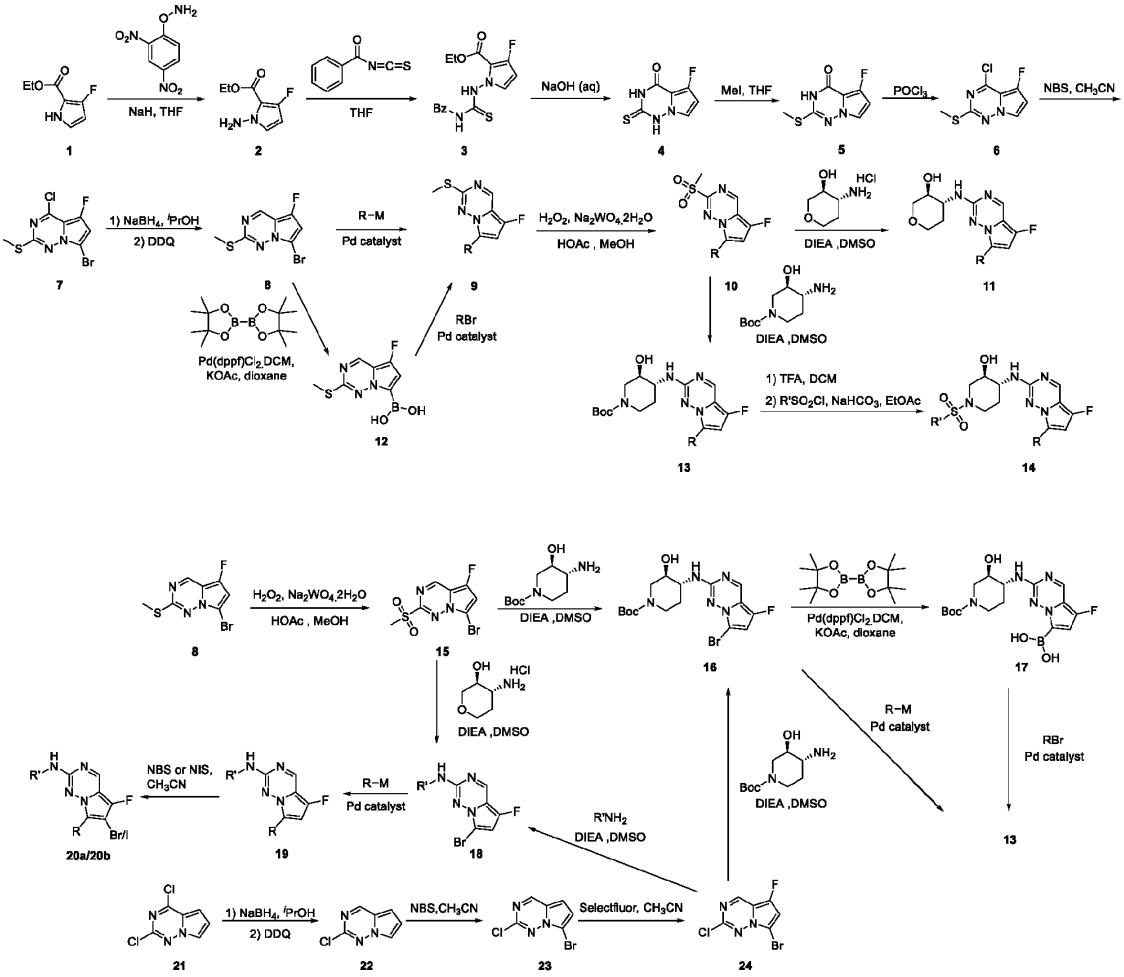
[0088] One common route is illustrated in Scheme 5. Bromide **1** is reacted under palladium-catalyzed conditions with a suitably substituted metal reagent to afford intermediate **2** which can be subsequently brominated, such as with NBS, to generate bromide **3**. Palladium-mediated cross-coupling of bromide **3** with an appropriately substituted aryl boronic acid ester or substituted aryl tin reagent forms intermediate **4,** which is then oxidized to sulfone **5,** such as with hydrogen peroxide and sodium tungstate. Compound **6** is then generated by the addition of an appropriate amine, such as (3S,4R)-4-aminotetrahydro-2H-pyran-3-ol, with an appropriate base, such as DIEA. Bromide **7** is reacted with an appropriate amine, such as tert-butyl (3R,4R)-4-amino-3-hydroxypiperidine-1-carboxylate, using an appropriate base, such as DIEA, to afford bromide **8**. Removal of the Boc group under acidic conditions, such as with TFA, in dichloromethane followed by mesylation with methanesulfonyl chloride then generates bromide **9**, which is reacted under palladium-catalyzed conditions with a substituted metal reagent to afford intermediate **10**. Bromination of intermediate **10**, such as with NBS, afforded two regioisomers which could be directly coupled to a suitably substituted aryl boron reagent or substituted aryl tin reagent under palladium mediated cross-coupling conditions to afford compound **13** and compound **14**.

SCHEME 6



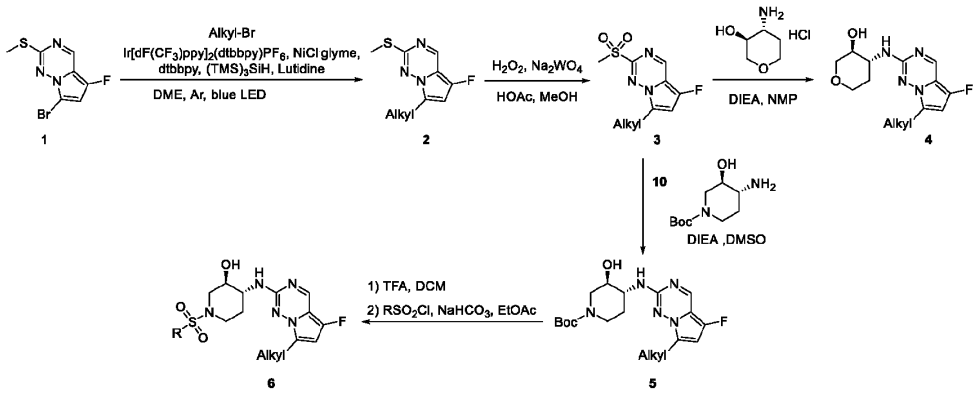
[0089] One common route is illustrated in Scheme 6. Sulfone **1** can be treated with a suitably substituted amine using an appropriate base, such as DIEA, to afford bromide **2**. Palladium-mediated cross-coupling with a suitably substituted vinyl boronic acid is then carried out to generate intermediate **3**. Reduction of the intermediate **3** olefin is carried out with a catalyst such as palladium hydroxide on carbon to afford compound **4**.

SCHEME 7



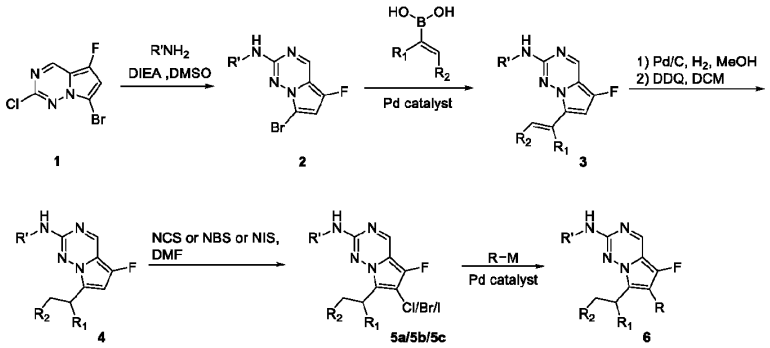
[0090] Another common route is illustrated in Scheme 7. Pyrrole **1** is deprotonated with base, such as sodium hydride, followed by the addition of O-(2,4-dinitrophenyl)hydroxylamine to afford intermediate **2**, which is then treated with benzoyl isothiocyanate in THF to afford intermediate **3**. Treatment of intermediate **3** with base, such as aqueous sodium hydroxide, followed by methylation with iodomethane generated intermediate **5**. Treatment of intermediate **5** with phosphorus oxychloride followed by bromination, such as with NBS, would afford chloride **7**. Removal of the chlorine group could be accomplished by the treatment with sodium borohydride followed by oxidation with DDQ to afford bromide **8**. Bromide **8** is converted to intermediate **9** via boron intermediate **12** by the palladium-catalyzed coupling with suitably substituted bromide, or by a palladium-catalyzed coupling with a suitably substituted metal reagent. Oxidation of intermediate **9** is carried out using hydrogen peroxide and sodium tungstate to form sulfone **10** which is reacted with an appropriate amine, such as (3S,4R)-4-aminotetrahydro-2H-pyran-3-ol, using an appropriate base, such as DIEA, to afford compound **11**. Alternatively, sulfone **10** could be reacted with an appropriate amine, such as tert-butyl (3R,4R)-4-amino-3-hydroxypiperidine-1-carboxylate, to generate key intermediate **13**. Compound **14** is generated by removing the Boc group of intermediate **13** followed by sulfonylation with a suitably substituted sulfonyl chloride in the presence of a base, such as sodium bicarbonate. An alternative route to key intermediate **13** is also provided. Bromide **8** is oxidized to sulfone **15,** such as by using hydrogen peroxide and sodium tungstate, followed by treatment with an appropriate amine, such as tert-butyl (3R,4R)-4-amino-3-hydroxypiperidine-1-carboxylate, using an appropriate base, such as DIEA, to afford intermediate **16**. Intermediate **13** could also be generated either by direct treatment of compound **16** with a suitably substituted metal reagent under palladium catalyzed conditions, or via a boron reagent **17** and a suitably substituted bromide under palladium-catalyzed conditions. Dichloride **21** can be converted to the monochloride through a reduction and oxidation sequence, such as treatment with sodium borohydride, followed by oxidation with DDQ to afford chloride **22** which is brominated, such as with NBS, to generate bromide **23**. Fluorination with Selectfluor produces intermediate **24** which is reacted with an appropriate amine, such as tert-butyl (3R,4R)-4-amino-3-hydroxypiperidine-1-carboxylate, using an appropriate base, such as DIEA, to afford intermediate **16,** or reacted with a suitably substituted amine using an appropriate base, such as DIEA, to generate intermediate **18**. Intermediate **18** can also be made by treating sulfone **15** with a suitable amine, such as (3S,4R)-4-aminotetrahydro-2H-pyran-3-ol, using an appropriate base, such as DIEA. Intermediate **19** is made from intermediate **18** by palladium-catalyzed coupling conditions using a suitably substituted metal reagent. Halogenation, such as with either NBS or NIS, affords compound **20a** or **20b**.

SCHEME 8



[0091] One common route is illustrated in Scheme 8. Bromide **1** is reacted under photo-redox conditions using an iridium catalyst to afford alkyl substituted intermediate **2** which is oxidized to sulfone **3**, such as with hydrogen peroxide and sodium tungstate. Treatment of sulfone **3** with an appropriate amine, such as (3S,4R)-4-aminotetrahydro-2H-pyran-3-ol, using a base, such as DIEA, would generate compound **4**. Alternatively, sulfone **3** could be treated with an appropriate amine, such as tert-butyl (3R,4R)-4-amino-3-hydroxypiperidine-1-carboxylate, using a base, such as DIEA, to generate intermediate **5**. Removal of the Boc group under acidic conditions, such as TFA in dichloromethane, followed by sulfonylation with a suitably substituted sulfonyl chloride using a base, such as sodium bicarbonate, generates compound **6**.

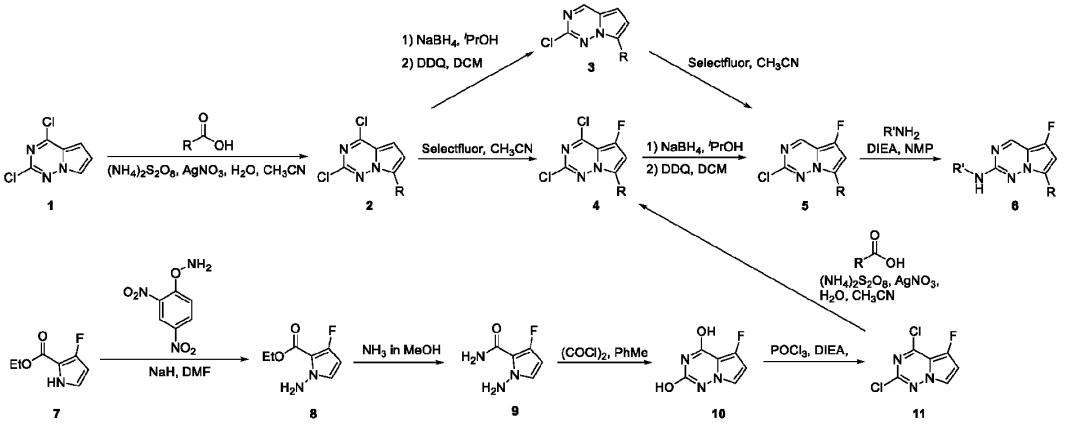
SCHEME 9



[0092] One common route is illustrated in Scheme 9. Chloride **1** is treated with a suitably substituted amine using a base, such as DIEA, to afford bromide **2**. Palladium-mediated cross-coupling with a suitably substituted vinyl boron reagent is carried out to generate intermediate **3**. Hydrogenation of intermediate **3** is carried out with a catalyst, such as palladium-on-carbon, followed by subsequent oxidation with DDQ to afford intermediate **4**. Halogenation of intermediate **4**, such as with either NCS, NBS, or NIS, produces compounds **5a**, **5b**, or **5c**.

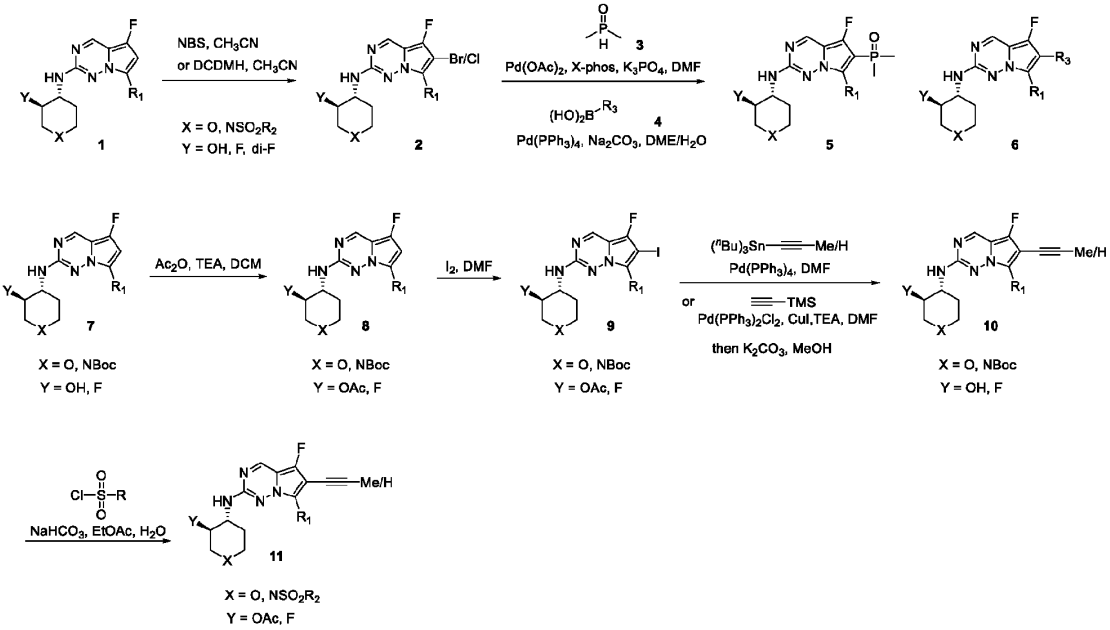
Palladium-catalyzed coupling with a suitably substituted metal reagent is carried out to afford compound **6**.

SCHEME 10



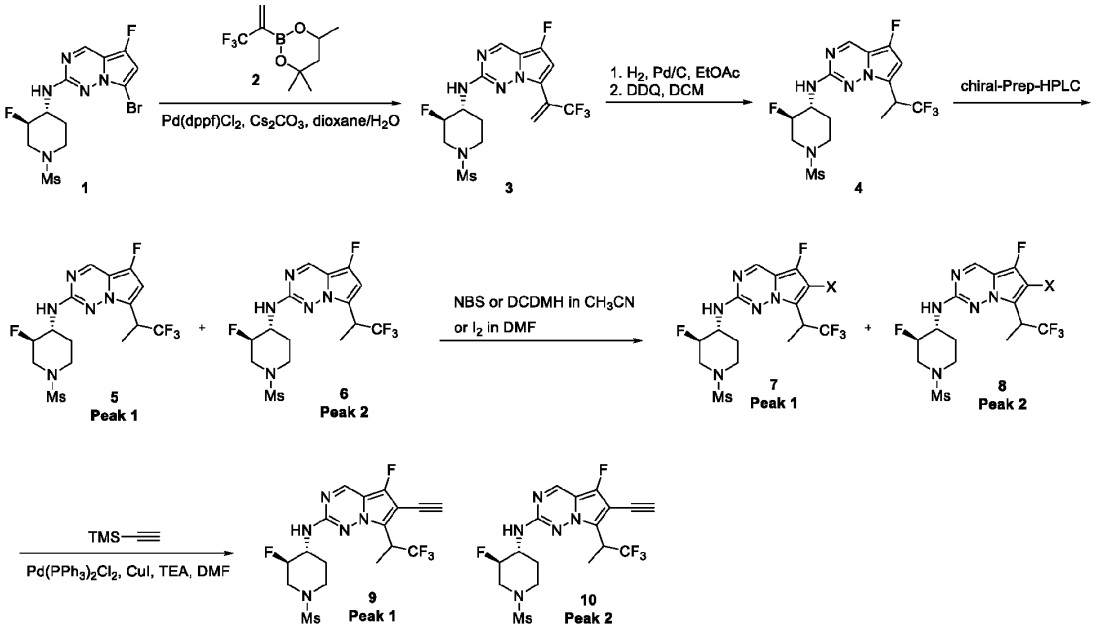
[0093] One common route is illustrated in Scheme 10. Dichloride **1** is treated with a suitably substituted carboxylic acid in the presence of a silver salt, such as silver nitrate, to afford intermediate **2,** which is subsequently fluorinated with a reagent, such as Selectfluor to generate fluoride **4**. Removal of a chloride from compound **4** is accomplished by treatment with sodium borohydride followed by oxidation with DDQ to generate intermediate **5**. Alternatively, removal of a chloride from intermediate **2** is accomplished by treatment with sodium borohydride followed by oxidation with DDQ to produce intermediate **3** which is fluorinated with a reagent like Selectfluor to generate intermediate **5**. Intermediate **5** is converted to compound **6** by the addition of a suitably substituted amine and using a base, such as DIEA. Pyrrole **7** is treated with a base, like sodium hydride, followed by the addition of O-(2,4-dinitrophenyl)hydroxylamine to afford intermediate **8** which is treated with ammonia in methanol to afford primary amide **9**. Cyclization of primary amide **9** is accomplished by treatment with oxalyl chloride in a suitable solvent, such as toluene, affords intermediate **10** which is chlorinated, such as by using phosphorus oxychloride and a base such as DIEA, to afford dichloride **11**. Fluoride **4** is made from dichloride **11** by treatment with a suitably substituted carboxylic acid in the presence of a silver salt, such as silver nitrate.

SCHEME 11



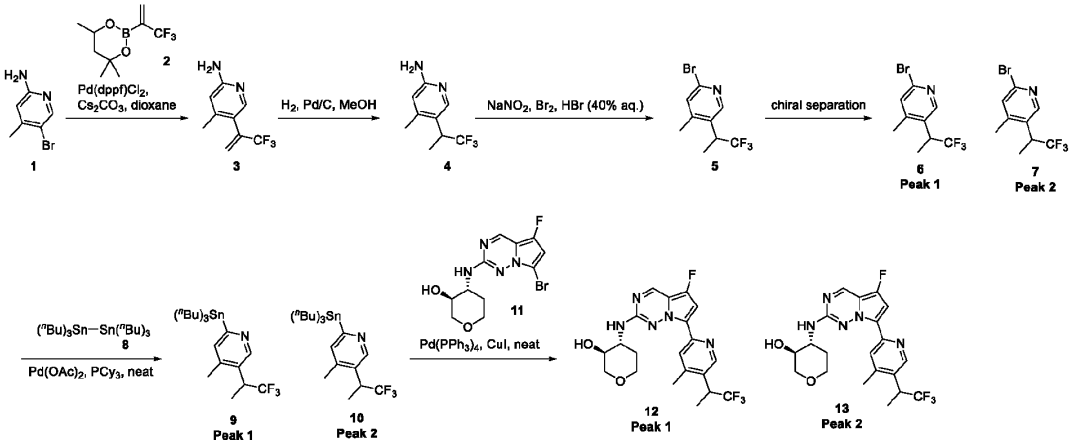
[0094] One common route is illustrated in Scheme 11. Intermediate 1 can be treated with NBS or 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione to afford compound 2. Dimethylphosphoryl compound 5 can be generated through palladium mediated cross-coupling of bromide 2 with dimethylphosphine oxide 3. Bromide 2 could also be converted to compound 6 by direct coupling with an appropriately substituted aryl boronic acid ester or substituted aryl tin reagent. Protection of hydroxy intermediate 7 could be accomplished with acetic anhydride and TEA in DCM. Intermediate 8 could be treated with iodine in DMF to generate iodide 9, followed by palladium mediated cross-coupling with alkynyl tin reagent or ethynyltrimethylsilane, and deprotection of Ac or TMS group in the presence of K_2CO_3 in MeOH to afford compound 10. Removal of the Boc group of compound 10 can be accomplished with TFA in DCM. Subsequent sulfonylation with a suitably substituted sulfonyl chloride in the presence of a base such as sodium bicarbonate would afford compound 11.

SCHEME 12



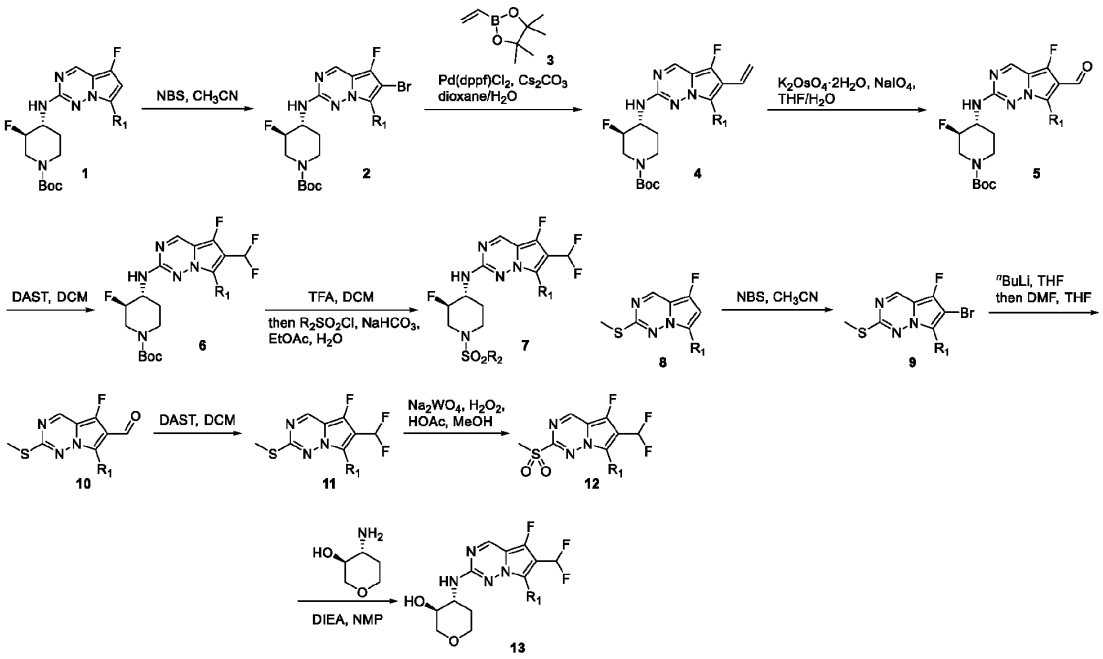
[0095] One common route is illustrated in Scheme 12. Bromide 1 can be converted to olefin 3 by direct palladium mediated cross-coupling with borate ester 2. The catalytic hydrogenation followed by oxidation with DDQ generated trifluoroisopropyl intermediate 4. Chiral separation (column: CHIRAL ART Cellulose-SB, Hexane/EtOH/DCM = 8/1/1) of intermediate 4 afforded diastereoisomers 5 (Peak1) and 6 (Peak 2), which could be halogenated in the presence of NBS and 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione or iodinated with iodine to generate intermediate 7 (Peak 1) and 8 (Peak 2). Subsequent palladium-copper mediated cross-coupling with ethynyltrimethylsilane, followed by removal of the TMS group would generate ethynyl compound 9 (Peak 1) and 10 (Peak 2).

SCHEME 13



[0096] One common route is illustrated in Scheme 13. Bromide 1 could convert to olefin 3 by direct palladium mediated cross-coupling with borate ester 2, followed by catalytic hydrogenation to generate trifluoroisopropyl intermediate 4, which could be then treated with sodium nitrite and bromine in the presence of HBr to afford bromide 5. Chiral separation (column: CHIRAL ART Cellulose-SB, CO_2/^{i}PrOH = 8/2) of 5 would afford enantiomers 6 (Peak 1) and 7 (Peak 2). Conversion of bromide 6 (Peak 1) and 7 (Peak 2) to tin reagent 9 (Peak 1) and 10 (Peak 2) through palladium mediated cross-coupling with hexabutyldistannane 8, followed by palladium-copper mediated cross-coupling with bromide 11 would generate compound 12 (Peak 1) and 13 (Peak 2).

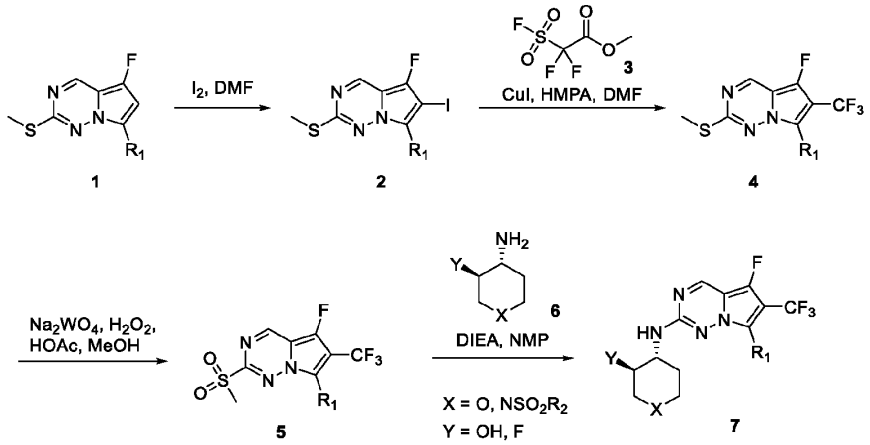
SCHEME 14



[0097] One common route is illustrated in Scheme 14. Corresponding intermediate 1 can be treated with NBS to afford bromide 2, which could be converted to olefin compound 4 by direct coupling with vinyl borate ester. Compound 4 could be treated with potassium osmate and sodium periodate to generate aldehyde 5, followed by fluoronation with DAST in DCM to afford compound 6. Removal of the Boc group of compound 6 can be accomplished with TFA in DCM, subsequent sulfonylation with a suitably substituted sulfonyl chloride in the presence of a base such as sodium bicarbonate would afford compound 7. Alternatively, methylthio intermediate 8 can be treated with NBS to afford bromide 9. Conversion of intermediate 9 to aldehyde 10 can be accomplished with butyl lithium in THF and DMF. *Di*-fluoromethyl 11 could be generated through fluoronation of intermediate 10 with DAST in DCM. Oxidation of

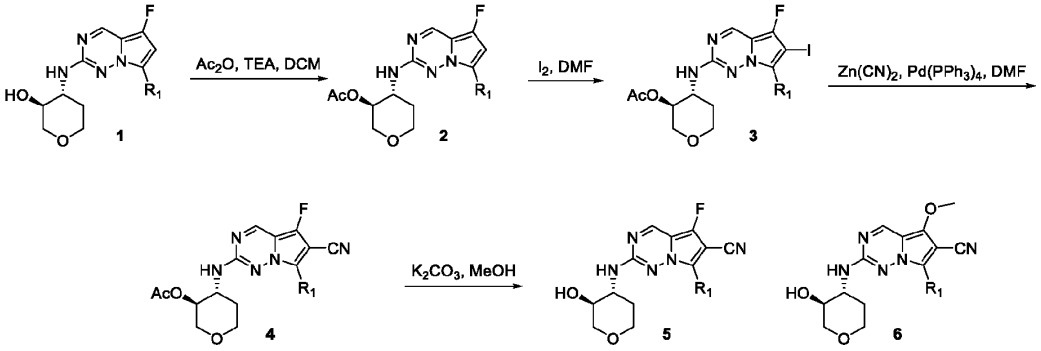
methylthio such as with hydrogen peroxide and sodium tungstate forms sulfone 12, which could be then treated with an appropriate amine like (3*S*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol in the presence of a base such as DIEA to afford compound 13.

SCHEME 15



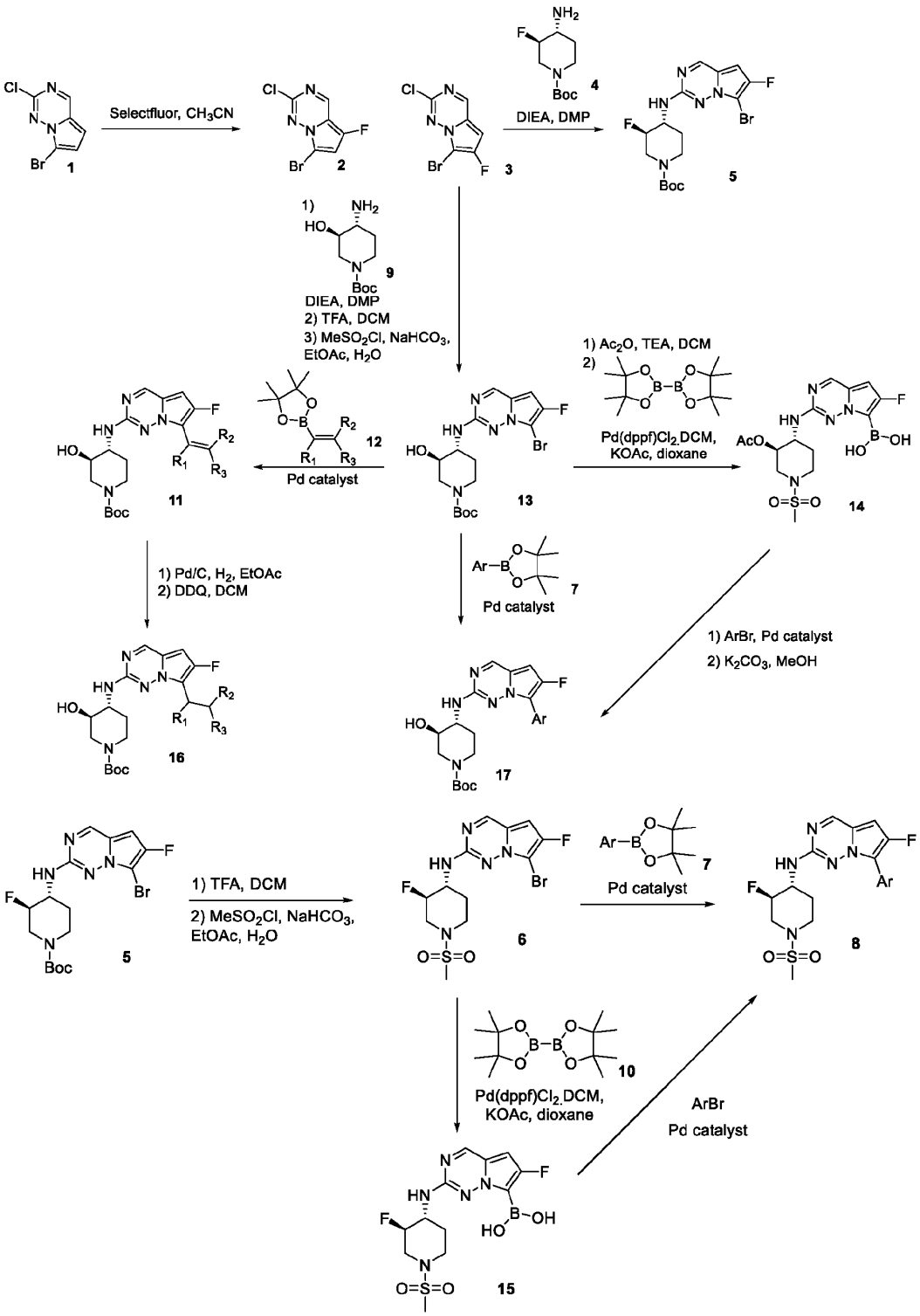
[0098] One common route is illustrated in Scheme 15. Methylthio intermediate 1 can be treated with iodine in DMF to afford iodide 2. Subsequent trifluoromethylation with a reagent such as methyl 2,2-difluoro-2-(fluorosulfonyl)acetate in the presence of copper iodide and HMPA to afford intermediate 4. Oxidation of methylthio group of intermediate 4 could be accomplished such as with hydrogen peroxide and sodium tungstate to form sulfone 5, which could be then treated with an appropriate amine 6 like (3*S*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol in the presence of a base such as DIEA to afford intermediate compound 7.

SCHEME 16



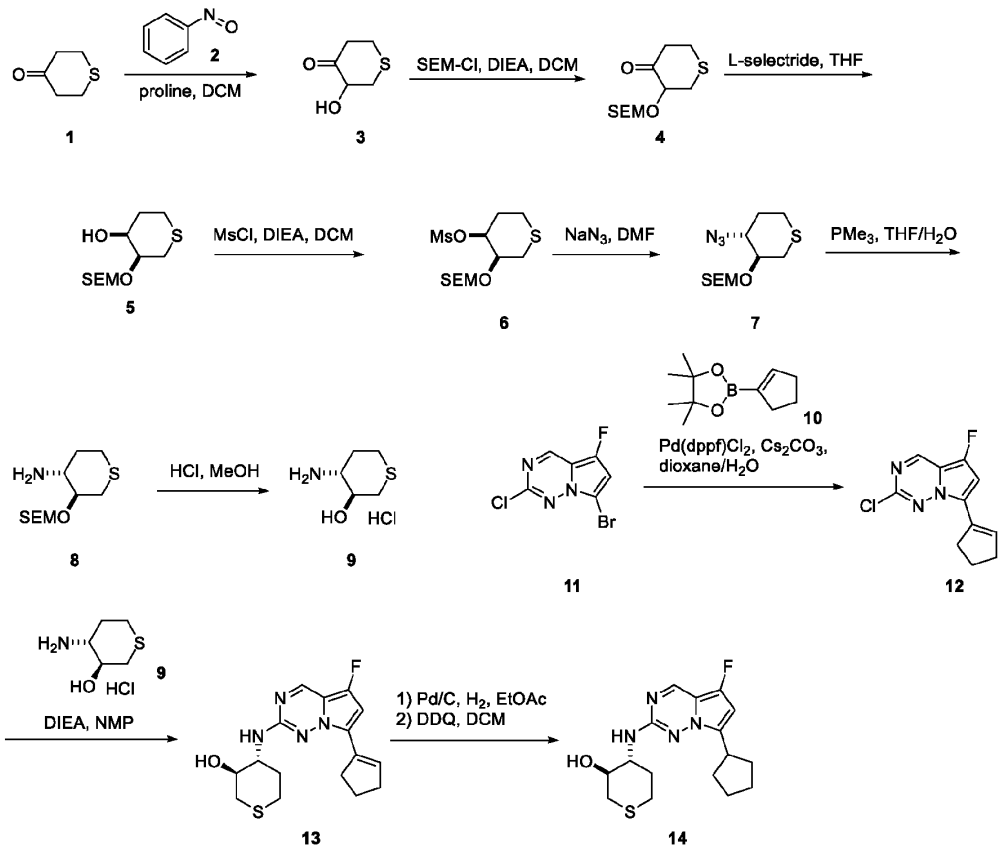
[0099] One common route is illustrated in Scheme 16. Protection of hydroxy intermediate 1 could be accomplished with acetic anhydride and TEA in DCM. Intermediate 2 could be treated with iodine in DMF to generate iodide 3, followed by palladium mediated cross-coupling with zinc cyanide. Subsequent removal of acetyl group in the presence of K_2CO_3 and MeOH would afford compounds 5 and 6.

SCHEME 17


Selectfluor, CH3CN
DIEA, DMP
1) NH2 HO Boc 9
DIEA, DMP
2) TFA, DCM
3) MeSO2Cl, NaHCO3, EtOAc, H2O
1) Ac2O, TEA, DCM
2)
Pd(dppf)Cl2.DCM, KOAc, dioxane
Pd catalyst
1) Pd/C, H2, EtOAc
2) DDQ, DCM
Pd catalyst
1) ArBr, Pd catalyst
2) K2CO3, MeOH
1) TFA, DCM
2) MeSO2Cl, NaHCO3, EtOAc, H2O
Pd catalyst
Pd(dppf)Cl2.DCM, KOAc, dioxane
ArBr
Pd catalyst

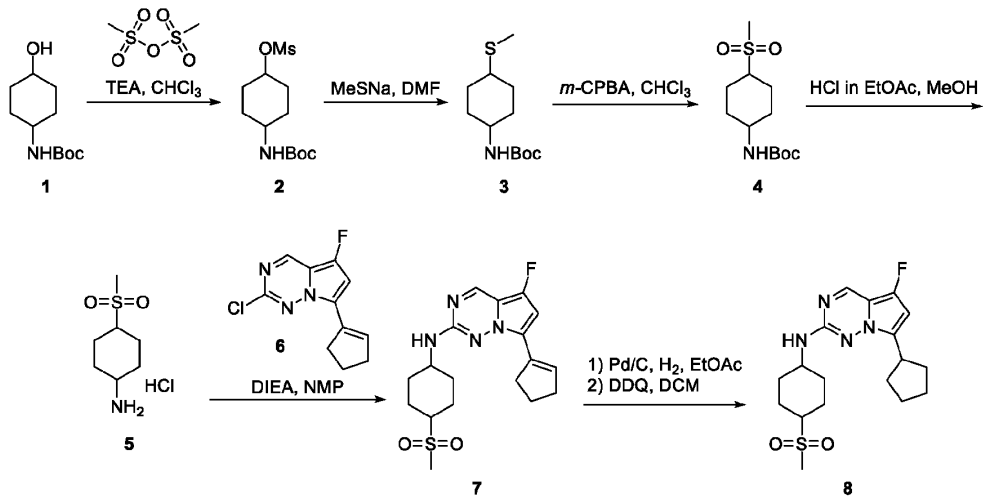
[00100] One common route is illustrated in Scheme 17. Bromide 1 can be fluorinated such as with selectfluor to form a mixture of 5-fluoro intermediate 2 and 6-fluoro intermediate 3. Intermediate 3 could be treated with an appropriate amine like *tert*-butyl (3*R*,4*R*)-4-amino-3-fluoropiperidine-1-carboxylate in the presence of a base such as DIEA to afford intermediate 5. Removal of the Boc group could be accomplished with TFA in DCM. Subsequent sulfonylation with a substituted sulfonyl chloride in the presence of a base such as sodium bicarbonate would afford bromide 6. Conversion of bromide 6 to corresponding boronic acid 15 followed by palladium mediated cross-coupling with a suitably substituted aryl bromide would generate compound 8. Bromide 6 could also be converted to compound 8 by direct palladium mediated cross-coupling with an appropriately substituted aryl boronic acid ester. Intermediate 3 could also be treated with an appropriate amine like *tert*-butyl (3*R*,4*R*)-4-amino-3-hydroxypiperidine-1-carboxylate in the presence of a base such as DIEA, then converted to bromide 13 in the sequence involved removal of the Boc group and methylsulfonylation in the presence of sodium bicarbonate. Boronic acid 14 could be generated by employing sequentially protection of hydroxy with acetyl and Miyaura borylation reaction. Subsequent direct palladium mediated cross-coupling with an appropriately substituted aryl bromide, followed by removal of acetyl group accomplished with potassium carbonate in methanol would generate compound 17. Alternatively, bromide 13 could also be converted to compound 17 by direct palladium mediated cross-coupling with an appropriately substituted aryl boronic acid ester. Olefin 11 could be generated through palladium mediated cross-coupling of bromide 13 with an appropriately substituted alkenyl boronic acid ester. Subsequent hydrogenation followed by oxidation in the presence of DDQ would generate alkyl compound 16.

SCHEME 18



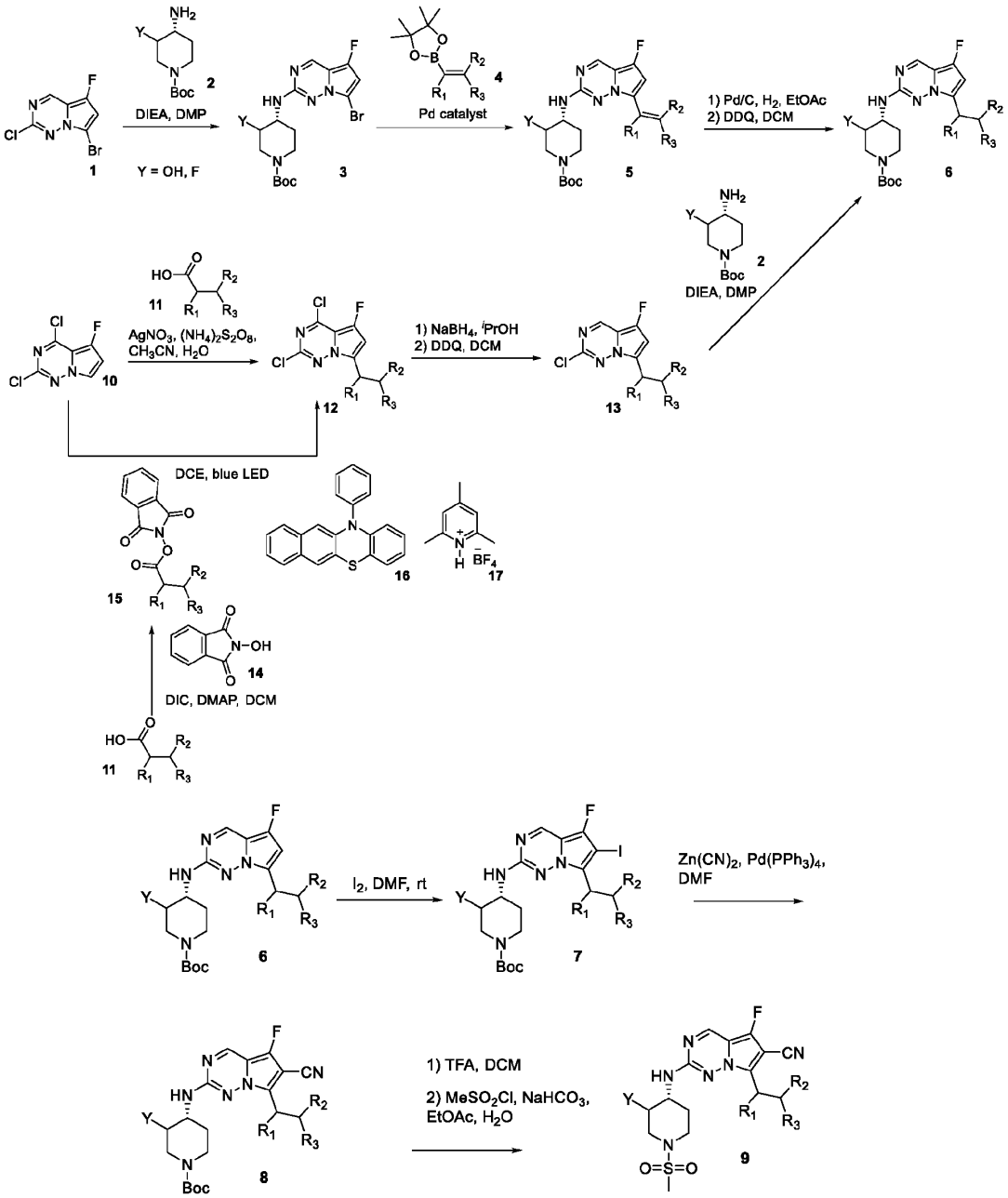
[00101] One common route is illustrated in Scheme 18. Asymmetric hydroxylation of ketone 1 could be accomplished with nitrosobenzene in the presence of corresponding proline to afford chiral α-hydroxyketone 3. Protection of hydroxy with SEM, followed by asymmetric reduction of carbonyl in the presence of an appropriately reductive reagent such as L-selectride would generate (*R*,*R*) or (*S*,*S*) mono protected diols 5. Subsequent methanesulfonylation in the presence of DIEA would afford mesylate 6, which could be converted to azide 7, followed by Staudinger reaction in the presence of trimethylphosphane to afford amine 8. Removal of SEM group could be accomplished with hydrogen chloride in methanol to afford corresponding (*R*,*S*) or (*S*,*R*) hydramine hydrochloride 9. Bromide 11 could be converted to intermediate 12 by direct palladium mediated cross-coupling with cyclopentenyl boronic acid ester 10. Intermediate 12 could be treated with corresponding hydramine hydrochloride 9 in the presence of a base such as DIEA to afford olefin 13. Subsequent hydrogenation followed by oxidation in the presence of DDQ would generate compound 14.

SCHEME 19



[00102] One common route is illustrated in Scheme 19. Methanesulfonylation of *cis* or *trans* alcohol 1 in the presence of TEA would afford mesylate 2, which could be converted to methylthio 3, followed by oxidation in the presence of metachloroperbenzoic acid to afford methylsulfonyl 4. Removal of Boc group could be accomplished with hydrogen chloride in ethyl acetate and methanol to afford corresponding *trans* or *cis* amine hydrochloride 5. Chloride 6 could be treated with corresponding amine hydrochloride 5 in the presence of a base such as DIEA to afford olefin 7. Subsequent hydrogenation followed by oxidation in the presence of DDQ would generate compound 8.

SCHEME 20

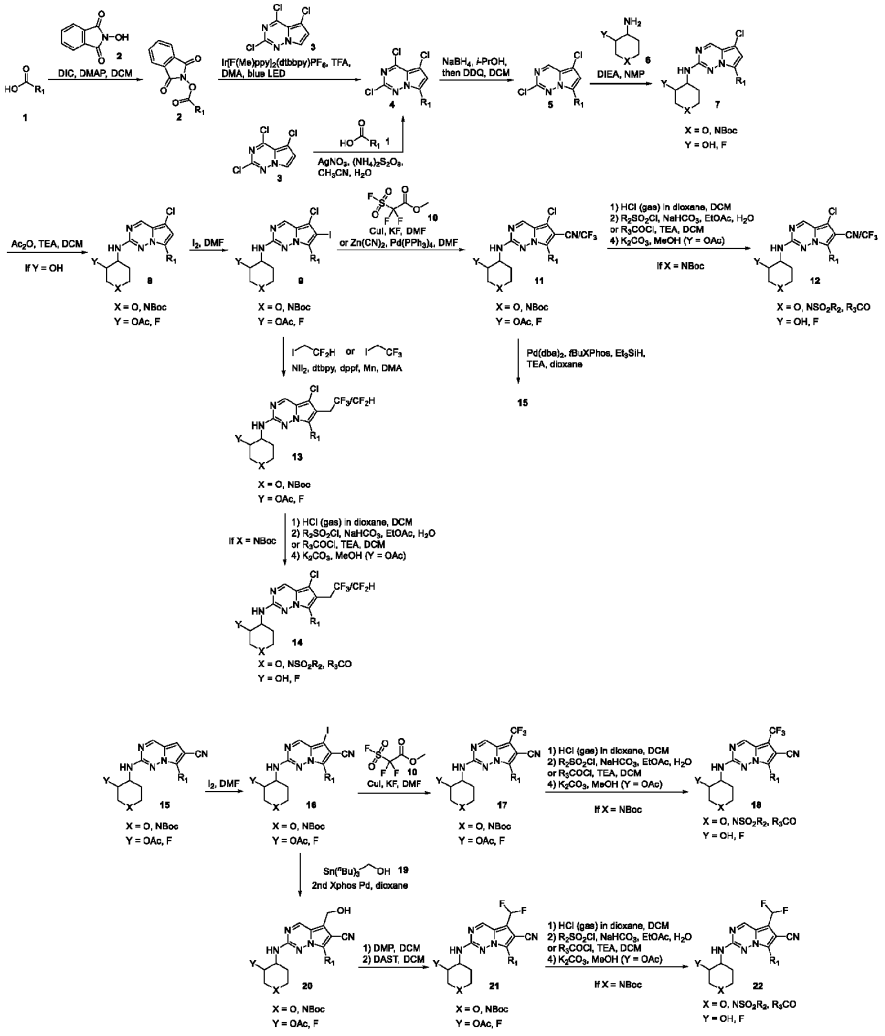


[00103] One common route is illustrated in Scheme 20. Bromide 1 could be treated with an appropriate amine like *tert*-butyl (3*R*,4*R*)-4-amino-3-fluoropiperidine-1-carboxylate in the presence of a base such as DIEA to afford intermediate 3. Then direct palladium mediated cross-coupling with an appropriately vinyl borate ester 4 to afford olefin compound 5. Subsequent hydrogenation followed by oxidation in the presence of DDQ would generate 6, which could be treated with iodine in DMF to form iodide 7, followed by palladium mediated cross-coupling with zinc

cyanide. Removal of the Boc group could be accomplished with TFA in DCM. Subsequent sulfonylation with a substituted sulfonyl chloride in the presence of a base such as sodium bicarbonate would afford compound 9.

[00104] Alternatively, intermediate 10 could also be converted to dichloride 12 by direct sliver mediated Minisci reaction with an appropriately substituted acid. It could be converted to mono chloride 13 in the sequence involved reduction by $NaBH_4$ and oxidation in the presence of DDQ. Intermediate 6 could be generated by employing substitution with an appropriate amine like *tert*-butyl (3*R*,4*R*)-4-amino-3-fluoropiperidine-1-carboxylate in the presence of a base such as DIEA. Intermediate 6 could also be generated through photoredox cross-coupling of intermediate 10 with corresponding active ester of substituted acid 11 in the presence of catalyst 16.

SCHEME 21



[00105] Another route is illustrated in Scheme 21. In the presence of DIC and DMAP, alkyl carboxylic acid 1 can be converted to active esters 2, then direct iridium mediated cross-coupling with chloride triazine core 3 to afford trichloride intermediate 4. Alternatively, Minisci reaction of alkyl carboxylic acid 1 and chloride triazine core 3 could also form intermediate 4. One chlorine was removed in the sequence involved reduction by $NaBH_4$ and oxidation in the presence of DDQ to afford dichloride intermediate 5. Intermediate 7 could be generated by employing substitution with an appropriate amine like *tert*-butyl (3*R*,4*R*)-4-amino-3-hydroxypiperidine-1-carboxylate in the presence of a base such as DIEA. Iodide 9 would be generated by employing sequentially protection of hydroxy with acetyl and iodination, which could be converted to cyano or trifluoromethyl intermediate 11 and trifluoroethyl or difluoroethyl intermediate 13 through metal mediated cross-coupling. Removal of the Boc group could be accomplished with HCl (gas) in DCM. Subsequent sulfonylation or acylation with a substituted sulfonyl chloride or acyl chloride, followed by removal of acetyl group could afford 6-cyano or 6-trifluoromethyl compound 12 and 6-trifluoroethyl or 6-difluoroethyl compound 14.

[00106] Iodide 16 could be generated from chloride 11 through subsequent palladium-catalyzed reduction accomplished with triethyl silicane, followed by iodination. Copper mediated cross-coupling in the presence of fluorinated reagent 10 would give intermediate 17. Removal of the Boc group could be accomplished with HCl (gas) in DCM. Subsequent sulfonylation or acylation with a substituted sulfonyl chloride or acyl chloride, followed by removal of acetyl group could afford 5-trifluoromethyl-6-cyano compound 18.

[00107] Hydroxymethyl intermediate 20 could be generated through palladium mediated cross-coupling with tin reagent 19. Subsequent oxidation in the presence of Dess-Martin reagent followed by fluorination with DAST would generate difluoromethyl intermediate 21. Removal of the Boc group could be accomplished with HCl (gas) in DCM. Subsequent sulfonylation or acylation with a substituted sulfonyl chloride or acyl chloride, followed by removal of acetyl group could afford 5-difluoromethyl-6-cyano compound 22.

[00108] Using appropriate starting materials, the CDK2/4/6 kinase inhibitory compounds described herein within Table 1, were synthesized using the methods described above in Schemes 1-21.

Pharmaceutical Compositions

[00109] In certain embodiments, the CDK2/4/6 kinase inhibitory compound described herein is administered as a pure chemical. In other embodiments, the CDK2/4/6 kinase inhibitory compound described herein is combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable (or acceptable) excipient, physiologically suitable (or acceptable) excipient, or physiologically suitable (or acceptable) carrier) selected on the basis of a chosen route of administration and standard pharmaceutical practice as described,

for example, in *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)).

[00110] Provided herein is a pharmaceutical composition comprising at least one CDK2/4/6 kinase inhibitory compound as described herein, or a stereoisomer, pharmaceutically acceptable salt, hydrate, or solvate thereof, together with one or more pharmaceutically acceptable carriers. The carrier(s) (or excipient(s)) is acceptable or suitable if the carrier is compatible with the other ingredients of the composition and not deleterious to the recipient (*i.e.,* the subject or the patient) of the composition.

[00111] One embodiment provides a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Table 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof.

[00112] One embodiment provides a method of preparing a pharmaceutical composition comprising mixing a compound of Table 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier.

[00113] In certain embodiments, the CDK2/4/6 kinase inhibitory compound as described by Table 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, is substantially pure, in that it contains less than about 5%, or less than about 2%, or less than about 1%, or less than about 0.5%, or less than about 0.1%, of other organic small molecules, such as unreacted intermediates or synthesis by-products that are created, for example, in one or more of the steps of a synthesis method.

[00114] One embodiment provides a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Table 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof.

[00115] One embodiment provides a method of preparing a pharmaceutical composition comprising mixing a compound of Table 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier.

[00116] In certain embodiments, the CDK2/4/6 kinase inhibitory compound as described by Table 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, is substantially pure, in that it contains less than about 5%, or less than about 2%, or less than about 1%, or less than about 0.5%, or less than about 0.1%, of other organic small molecules, such as unreacted intermediates or synthesis by-products that are created, for example, in one or more of the steps of a synthesis method.

[00117] Suitable oral dosage forms include, for example, tablets, pills, sachets, or capsules of hard or soft gelatin, methylcellulose or of another suitable material easily dissolved in the digestive tract. In some embodiments, suitable nontoxic solid carriers are used which include, for

example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like. (*See*, *e.g.*, *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)).

[00118] In some embodiments, the CDK2/4/6 kinase inhibitory compound as described by Table 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, is formulated for administration by injection. In some instances, the injection formulation is an aqueous formulation. In some instances, the injection formulation is a non-aqueous formulation. In some instances, the injection formulation is an oil-based formulation, such as sesame oil, or the like.

[00119] The dose of the composition comprising at least one CDK2/4/6 kinase inhibitory compound as described in Table 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, differs depending upon the subject or patient's (e.g., human) condition. In some embodiments, such factors include general health status, age, and other factors.

[00120] Pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (e.g., an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity. Optimal doses are generally determined using experimental models and/or clinical trials. The optimal dose depends upon the body mass, weight, or blood volume of the patient.

[00121] Oral doses typically range from about 1.0 mg to about 1000 mg, one to four times, or more, per day.

Methods of Treatment

[00122] One embodiment provides a compound of Table 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, for use in a method of treatment of the human or animal body.

[00123] One embodiment provides a compound of Table 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, for use in a method of treatment of cancer or neoplastic disease.

[00124] One embodiment provides a pharmaceutical composition comprising a compound of Table 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, and a pharmaceutically acceptable excipient for use in a method of treatment of cancer or neoplastic disease.

[00125] One embodiment provides a use of a compound of Table 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, in the manufacture of a medicament for the treatment of cancer or neoplastic disease.

[00126] In some embodiments is provided a method of treating cancer, in a patient in need thereof, comprising administering to the patient a compound of Table 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof. In some embodiments is provided a method of treating cancer, in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising a compound of Table 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, and a pharmaceutically acceptable excipient.

[00127] One embodiment provides a compound of Table 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, for use in a method of treatment of the human or animal body.

[00128] One embodiment provides a compound of Table 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, for use in a method of treatment of cancer or neoplastic disease.

[00129] One embodiment provides a pharmaceutical composition comprising a compound of Table 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, and a pharmaceutically acceptable excipient for use in a method of treatment of cancer or neoplastic disease.

[00130] One embodiment provides a use of a compound of Table 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, in the manufacture of a medicament for the treatment of cancer or neoplastic disease.

[00131] In some embodiments is provided a method of treating cancer, in a patient in need thereof, comprising administering to the patient a compound of Table 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof. In some embodiments is provided a method of treating cancer, in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising a compound of Table 1, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

[00132] In some embodiments, the cancer is breast cancer. In some embodiments, the cancer is skin cancer. In some embodiments, the cancer is melanoma. In some embodiments, the cancer is leukemia.

[00133] Provided herein is the method wherein the pharmaceutical composition is administered orally. Provided herein is the method wherein the pharmaceutical composition is administered by injection.

[00134] One embodiment provides a method of inhibiting a CDK2/4/6 kinase comprising contacting the CDK2/4/6 kinase with a compound of Table 1. Another embodiment provides the method of inhibiting a CDK2/4/6 kinase, wherein the CDK2/4/6 kinase is contacted in an *in vivo* setting.

Another embodiment provides the method of inhibiting a CDK2/4/6 kinase, wherein the CDK2/4/6 kinase is contacted in an *in vitro* setting.

[00135] Other embodiments and uses will be apparent to one skilled in the art in light of the present disclosures. The following examples are provided merely as illustrative of various embodiments and shall not be construed to limit the invention in any way.

EXAMPLES

I. Chemical Synthesis

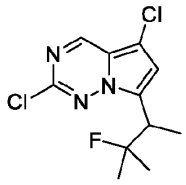
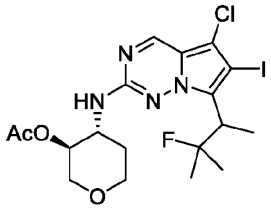
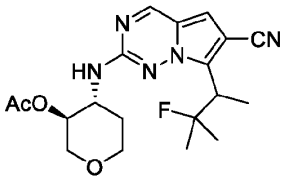
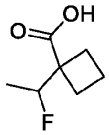
[00136] In some embodiments, the CDK2/4/6 kinase inhibitory compounds disclosed herein are synthesized according to the following examples. As used below, and throughout the description of the invention, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

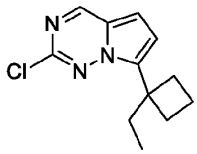
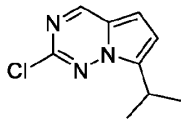
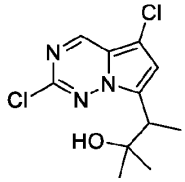
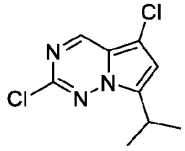
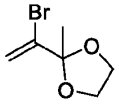
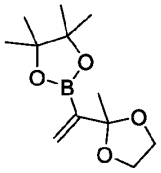
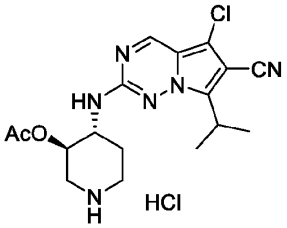
°C	degrees Celsius
δ_H	chemical shift in parts per million downfield from tetramethylsilane
DCM	dichloromethane (CH_2Cl_2)
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EA	ethyl acetate
ESI	electrospray ionization
Et	ethyl
g	gram(s)
h	hour(s)
HPLC	high performance liquid chromatography
Hz	hertz
J	coupling constant (in NMR spectrometry)
LCMS	liquid chromatography mass spectrometry
μ	micro
m	multiplet (spectral); meter(s); milli
M	molar
M^+	parent molecular ion
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s); molecular (as in mol wt)
mL	milliliter

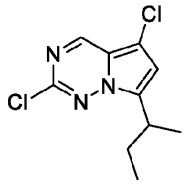
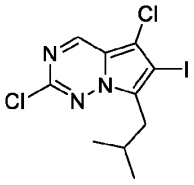
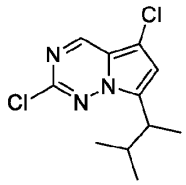
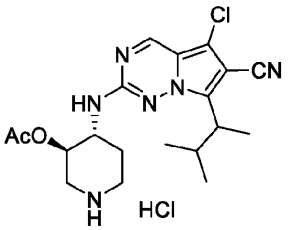
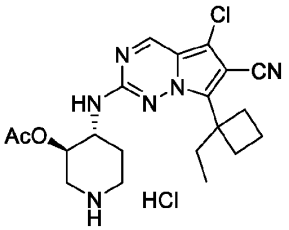
MS	mass spectrometry
nm	nanometer(s)
NMR	nuclear magnetic resonance
pH	potential of hydrogen; a measure of the acidity or basicity of an aqueous solution
PE	petroleum ether
RT	room temperature
s	singlet (spectral)
t	triplet (spectral)
T	temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran

[00137] Common intermediates are provided below in Table 4:

Table 4

Common Intermediate	Compound Structure	Intermediate Name
1		2,5-dichloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine
2		(3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate
3		(3*S*,4*R*)-4-{[6-cyano-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-*yl*]amino}oxan-3-yl acetate
4		1-(1-fluoroethyl)cyclobutane-1-carboxylic acid

Common Intermediate	Compound Structure	Intermediate Name
5		2-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine
6		2-chloropyrrolo[2,1-*f*][1,2,4]triazine
7		3-{2,5-dichloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl}-2-methylbutan-2-ol
8		2,5-dichloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine
9		2-(1-bromoethenyl)-2-methyl-1,3-dioxolane
10		4,4,5,5-tetramethyl-2-[1-(2-methyl-1,3-dioxolan-2-yl)ethenyl]-1,3,2-dioxaborolane
11		(3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidin-3-yl acetate hydrochloride

Common Intermediate	Compound Structure	Intermediate Name
12		2,5-dichloro-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazine
13		2,5-dichloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine
14		2,5-dichloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine
15		(3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride
16		(3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride

Common intermediate 1:

2,5-dichloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine

Step 1: methyl 3-hydroxy-2,2-dimethylbutanoate

[00138] A solution of methyl 2,2-dimethyl-3-oxobutanoate (4.00 g, 27.745 mmol) and $NaBH_4$ (1.05 g, 27.745 mmol) in MeOH (50 mL) was stirred for 2 h at 0 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica

gel column chromatography, eluted with PE/EtOAc (2/1) to afford methyl 3-hydroxy-2,2-dimethylbutanoate (2.10 g, 51%) as colorless oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 3.89-3.83 (m, 1H), 3.70 (s, 3H), 1.20-1.09 (m, 9H).

Step 2: 3-hydroxy-2,2-dimethylbutanoic acid

[00139] A solution of methyl 3-hydroxy-2,2-dimethylbutanoate (2.10 g, 14.365 mmol) and $LiOH{\cdot}H_2O$ (1.21 g, 28.730 mmol) in MeOH (15 mL) and H_2O (15 mL) were stirred for 16 h at room temperature. The reaction was diluted with water (200 mL). The mixture was acidified to pH 3 with HCl (aq., 1 M). The resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 3-hydroxy-2,2-dimethylbutanoic acid (1.70 g, 89%) as colorless oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 3.97-3.90 (m, 1H), 1.24-1.20 (m, 9H).

Step 3: 3-methyl-3-{2,4,5-trichloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl}butan-2-ol

[00140] To a stirred solution of 2,4,5-trichloropyrrolo[2,1-*f*][1,2,4]triazine (1.00 g, 4.495 mmol), 3-hydroxy-2,2-dimethylbutanoic acid (1.78 g, 13.485 mmol) and $AgNO_3$ (1.53 g, 8.990 mmol) in CH_3CN (60 mL) and H_2O (30 mL) was added $(NH_4)_2S_2O_8$ (5.13 g, 22.475 mmol) in H_2O (30 mL) dropwise at 50 °C under a nitrogen atmosphere. The resulting mixture was stirred for 2 h at 50 °C. The mixture was allowed to cool down to room temperature. The reaction was diluted with $NaHCO_3$ (15 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford 3-methyl-3-{2,4,5-trichloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl}butan-2-ol (0.47 g, 29%) as a yellow solid. MS ESI calculated for $C_{11}H_{12}Cl_3N_3O$ $[M + H]^+$, 308.00, found 307.85. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.83 (s, 1H), 4.56 (q, J = 6.4 Hz, 1H), 1.50 (s, 3H), 1.46 (s, 3H), 1.07 (d, J = 6.4 Hz, 3H).

Step 4: 3-{2,5-dichloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl}-3-methylbutan-2-ol

[00141] To a stirred solution of 3-methyl-3-{2,4,5-trichloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl}butan-2-ol (440 mg, 1.426 mmol) in *i*-PrOH (0.7 mL) and THF (17 mL) was added $NaBH_4$ (86 mg, 2.282 mmol). The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched with *sat.* NH_4Cl (20 mL). The resulting mixture was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. To this was added DDQ (485 mg, 2.139 mmol) in DCM (14 mL). The resulting mixture was stirred for additional 1 h at room temperature. The reaction was quenched with *sat.* $NaHCO_3$ (20 mL) at 0 °C. The resulting mixture was extracted with DCM (3 x 40 mL). The combined organic layers were

washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford 3-{2,5-dichloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl}-3-methylbutan-2-ol (270 mg, 69%) as a yellow solid. MS ESI calculated for $C_{11}H_{13}Cl_2N_3O$ $[M + H]^+$, 274.04, found 274.05. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.77 (s, 1H), 6.82 (s, 1H), 4.53 (q, *J* = 6.4 Hz, 1H), 1.52 (s, 3H), 1.48 (s, 3H), 1.07 (d, *J* = 6.4 Hz, 3H).

Step 5: 2,5-dichloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine

[00142] To a stirred solution of 3-{2,5-dichloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl}-3-methylbutan-2-ol (270 mg, 0.985 mmol) in DCM (40 mL) was added DAST (317 mg, 1.970 mmol) dropwise at-78 °C under nitrogen atmosphere. The reaction mixture was stirred for 30 min. The mixture was allowed to warm to at 0 °C. The reaction was quenched with EtOH (15 mL) at 0 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (10/1) to afford 2,5-dichloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (240 mg, 74%) as yellow oil. MS ESI calculated for $C_{11}H_{12}Cl_2FN_3$ $[M + H]^+$, 276.04, found 275.90 ^1H NMR (400 MHz, Chloroform-*d*) δ 8.77 (s, 1H), 6.89 (s, 1H), 3.88-3.79 (m, 1H), 1.48 (d, *J* = 21.2 Hz, 3H), 1.40 (d, *J* = 7.2 Hz, 3H), 1.26 (d, *J* = 21.2 Hz, 3H).

Common intermediate 2:

(3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

Step 1: (3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol

[00143] To a stirred solution of 2,5-dichloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (240 mg, 0.869 mmol) in NMP (4 mL) were added (3*S*,4*R*)-4-aminooxan-3-ol hydrochloride (200 mg, 1.304 mmol) and DIEA (562 mg, 4.345 mmol) at room temperature. The resulting mixture was stirred for 16 h at 80 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 30% to 70%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (174 mg, 56%) as yellow oil. MS ESI calculated for $C_{16}H_{22}ClFN_4O_2$ $[M + H]^+$, 357.14, found 357.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.57 (s, 1H), 6.54 (s, 1H), 4.87-4.84 (m, 1H), 4.09-3.96 (m, 2H), 3.75-3.62 (m, 3H), 3.52-3.45 (m, 1H), 3.26-3.20 (m, 1H), 2.11-2.06 (m, 1H), 1.77-1.62 (m, 1H), 1.44-1.26 (m, 9H).

Step 2: (3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00144] To a stirred solution of (3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (93 mg, 0.261 mmol) in DCM (3 mL) were added Ac_2O (53 mg, 0.522 mmol) and TEA (132 mg, 1.305 mmol) at room temperature. The resulting mixture was stirred for 16 h at 50 °C. The mixture was allowed to cool down to room temperature. The resulting was purified by Prep-TLC (PE/EtOAc = 1/1) to afford (3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (70 mg, 67%) as a yellow solid. MS ESI calculated for $C_{18}H_{24}ClFN_4O_3$ $[M + H]^+$, 399.15, found 399.40. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.58 (s, 1H), 6.54 (d, *J* = 6.4 Hz, 1H), 5.10-4.90 (m, 2H), 4.07-3.91 (m, 3H), 3.91-3.73 (m, 1H), 3.67-3.58 (m, 1H), 3.51-3.45 (m, 1H), 2.42-2.38 (m, 1H), 2.06 (s, 3H), 1.74-1.61 (m, 1H), 1.47-1.25 (m, 9H).

Step 3: (3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00145] A solution of (3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (70 mg, 0.176 mmol) and I_2 (178 mg, 0.704 mmol) in DMF (3 mL) was stirred for 16 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 35% to 70%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (72 mg, 78%) as yellow oil. MS ESI calculated for $C_{18}H_{23}ClFIN_4O_3$ $[M + H]^+$, 525.05 found 524.95. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.56 (s, 1H), 5.12-4.84 (m, 2H), 4.08-3.80 (m, 3H), 3.59-3.40 (m, 3H), 2.40-2.37 (m, 1H), 2.04 (s, 3H), 1.65-1.25 (m, 10H).

Common intermediate 3:

(3*S*,4*R*)-4-{[6-cyano-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

Step 1: (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00146] To a stirred solution of (3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (72 mg, 0.137 mmol) in DMF (7 mL) were added $Zn(CN)_2$ (19.33 mg, 0.164 mmol) and $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 130 °C under nitrogen atmosphere. The reaction was quenched with water (50 mL). The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (2 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced

pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 25% to 55%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (50 mg, 85%) as a yellow solid. MS ESI calculated for $C_{19}H_{23}ClFN_5O_3$ $[M + H]^+$, 424.15 found 424.25. ^1H NMR (400 MHz, Chloroform-d) δ 8.68 (s, 1H), 5.28-5.24 (m, 1H), 5.00-4.96 (m, 1H), 4.05-3.96 (m, 4H), 3.65-3.53 (m, 1H), 3.48-3.45 (m, 1H), 2.42-2.36 (m, 1H), 2.05 (s, 3H), 1.62-1.59 (m, 4H), 1.52-1.34 (m, 6H).

Step 2: (3*S*,4*R*)-4-{[6-cyano-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00147] A solution of (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (127 mg, 0.300 mmol), Et_3SiH (105 mg, 0.900 mmol), Et_3N (121 mg, 1.200 mmol), $Pd(dba)_2$ (17 mg, 0.030 mmol) and *t*-BuXPhos (25 mg, 0.060 mmol) in 1,4-dioxane (2 mL) was stirred for 2 h at 100 °C under nitrogen atmosphere. The reaction was quenched by the addition of water (50 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[6-cyano-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (110 mg, 94%) as a light yellow solid. MS ESI calculated for $C_{19}H_{24}FN_5O_3$ $[M + H]^+$, 390.19, found 390.00. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.65 (s, 1H), 7.05 (s, 1H), 5.31 (brs, 1H), 5.03-4.96 (m, 1H), 4.02-3.95 (m, 4H), 3.63-3.59 (m, 1H), 3.51-3.45 (m, 1H), 2.45-2.40 (m, 1H), 2.06 (s, 3H), 1.64 (d, J = 6.8 Hz, 3H), 1.50-1.34 (m, 6H).

Common intermediate 4:

1-(1-fluoroethyl)cyclobutane-1-carboxylic acid

Step 1: benzyl 1-{1-[(carboxycarbonyl)oxy]ethyl}cyclobutane-1-carboxylate

[00148] To a stirred mixture of $(COCl)_2$ (42.68 mL, 85.362 mmol) was added benzyl 1-(1-hydroxyethyl)cyclobutane-1-carboxylate (10 g, 42.681 mmol) in DCM (10 mL) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. To the above mixture was added H_2O (6.50 g, 360.654 mmol) dropwise over 3 min at 0 °C. The resulting mixture was stirred for additional 1 h at room temperature. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced

pressure to afford benzyl 1-{1-[(carboxycarbonyl)oxy]ethyl}cyclobutane-1-carboxylate (12.4 g, 94%) as brown oil. MS ESI calculated for $C_{16}H_{18}O_6$ [M – H]$^+$, 305.11, found 305.15. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41-7.31 (m, 5H), 5.43 (q, *J* = 6.4 Hz, 1H), 5.27-5.13 (m, 2H), 2.60-2.37 (m, 2H), 2.29-2.13 (m, 2H), 2.01-1.91 (m, 2H), 1.31 (d, *J* = 6.4 Hz, 3H).

Step 2: benzyl 1-(1-fluoroethyl)cyclobutane-1-carboxylate

[00149] To a stirred mixture of benzyl 1-{1-[(carboxycarbonyl)oxy]ethyl}cyclobutane-1-carboxylate (12 g, 39.175 mmol), Selectfluor (31.23 g, 88.144 mmol) in acetone (576 mL) and H_2O (144 mL) was added Na_2HPO_4 (11.12 g, 78.350 mmol), Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (2.2 g, 1.959 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was irradiated with Blue LED for 60 min at room temperature under nitrogen atmosphere. The resulting mixture was extracted with pentane (3 x 100 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% TFA), 45% to 75%; detector, UV 220 nm to afford benzyl 1-(1-fluoroethyl)cyclobutane-1-carboxylate (3.1 g, 33%) as yellow oil. MS ESI calculated for $C_{14}H_{17}FO_2$ [M + H]$^+$, 237.12, found 237.15. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41-7.35 (m, 5H), 5.19 (s, 2H), 4.99-4.83 (m, 1H), 2.51-2.21 (m, 4H), 2.05-1.81 (m, 2H), 1.24 (dd, *J* = 24.0, 6.0 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -184.35 (1F).

Step 3: 1-(1-fluoroethyl)cyclobutane-1-carboxylic acid

[00150] To a solution of benzyl 1-(1-fluoroethyl)cyclobutane-1-carboxylate (3 g, 12.696 mmol) in MeOH (60 mL) was added Pd/C (3.11 g, 2.920 mmol, 10%) under nitrogen atmosphere. The mixture was stirred for 1 h at room temperature under hydrogen atmosphere. The resulting mixture was filtered through a Celite pad and concentrated under reduced pressure to afford 1-(1-fluoroethyl)cyclobutane-1-carboxylic acid (1.5 g, 80%) as yellow oil. MS ESI calculated for $C_7H_{11}FO_2$ [M – H]$^+$, 145.07, found 145.00. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.01-4.85 (m, 1H), 2.54-2.20 (m, 4H), 2.05-1.90 (m, 2H), 1.35 (dd, *J* = 24.0, 6.0 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -184.32 (1F).

Common intermediate 5:

2-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine

Step 1: 2,4-dichloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine

[00151] To a stirred solution of 2,4-dichloropyrrolo[2,1-*f*][1,2,4]triazine (8 g, 42.551 mmol), 1-ethylcyclobutane-1-carboxylic acid (16.36 g, 127.653 mmol) and $AgNO_3$ (14.46 g, 85.102 mmol) in CH_3CN (80 mL) and H_2O (40 mL) was added $(NH_4)_2S_2O_8$ (48.55 g, 212.755 mmol) in H_2O (40 mL) dropwise at 50 °C . The resulting mixture was stirred for 2 h at 50 °C. The

resulting mixture was diluted with water (100 mL). The resulting mixture was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (10/1) to afford 2,4-dichloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (7.3 g, 63%) as yellow oil. MS ESI calculated for $C_{12}H_{13}Cl_2N_3$ $[M + H]^+$, 270.05, found 270.10; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.01 (d, *J* = 4.8 Hz, 1H), 6.77 (d, *J* = 4.8 Hz, 1H), 2.47-2.45 (m, 2H), 2.29-2.25 (m, 2H), 2.11-2.06 (m, 2H), 1.93-1.89 (m, 2H), 0.60 (t, *J* = 7.2 Hz, 3H).

Step 2: 2-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine

[00152] To a stirred mixture of 2,4-dichloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (1 g, 3.702 mmol) in *i*-PrOH (1 mL) and THF (10 mL) was added $NaBH_4$ (224.05 mg, 5.923 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (10 mL) at 0 °C. The aqueous layer was extracted with EtOAc (3 x 5 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. To this was added DCM (10 mL) and DDQ (1.26 g, 5.553 mmol). The reaction mixture was stirred for 1 h at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (10 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford 2-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (630 mg, 72%) as a light yellow oil; MS ESI calculated for $C_{12}H_{14}ClN_3$ $[M + H]^+$, 236.09, found 236.10; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 6.92 (d, *J* = 4.8 Hz, 1H), 6.80 (d, *J* = 4.8 Hz, 1H), 2.57-2.44 (m, 2H), 2.37-2.25 (m, 2H), 2.19-2.04 (m, 3H), 1.96-1.89 (m, 1H), 0.61 (t, *J* = 7.2 Hz, 3H).

Common intermediate 6:

2-chloropyrrolo[2,1-*f*][1,2,4]triazine

Step 1: 2,4-dichloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine

[00153] To a stirred solution of 2,4-dichloropyrrolo[2,1-*f*][1,2,4]triazine (24 g, 127.65 mmol) and isobutyric acid (33.74 g, 382.96 mmol) and $AgNO_3$ (43.37 g, 255.31 mmol) in CH_3CN (960 mL) was added $(NH_4)_2S_2O_8$ (145.65 g, 638.27 mmol) in H_2O (480 mL) dropwise at 50 °C.The resulting mixture was stirred for 3 h at 50 °C. The resulting mixture was extracted with EtOAc (2 x 1 L). The combined organic layers were washed with brine (500 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (8/1) to afford 2,4-

dichloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine (8 g, 27%) as a yellow solid. MS ESI calculated for $C_9H_9Cl_2N_3$ $[M + H]^+$, 230.02, found 230.00. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.03 (d, *J* = 4.8 Hz, 1H), 6.86-6.80 (m, 1H), 3.60-3.54 (m, 1H), 1.40-1.37 (m, 6H).

Step 2: 2-chloropyrrolo[2,1-*f*][1,2,4]triazine

[00154] A solution of 2,4-dichloropyrrolo[2,1-*f*][1,2,4]triazine (9.2 g, 48.93 mmol) and $NaBH_4$ (3.70 g, 97.87 mmol) in THF (92 mL) and *i*-PrOH (10 ml) was stirred for 2 h at room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (500 mL). The filtrate was concentrated under reduced pressure. To the residue was added DDQ (17.51 g, 77.13 mmol) in DCM (200 mL). The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq., 500 mL) at 0 °C.The resulting mixture was extracted with DCM (3 x 200 mL). The combined organic layers were washed with brine (500 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford 2-chloropyrrolo[2,1-*f*][1,2,4]triazine (7.4 g, 93%) as a yellow oil. MS ESI calculated for $C_9H_{10}ClN_3$ $[M + H]^+$, 196.06, found 195.95. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.72 (s, 1H), 6.93 (d, *J* = 4.8 Hz, 1H), 6.83 (d, *J* = 4.8 Hz, 1H), 3.60-3.58 (m, 1H), 1.41-1.37 (m, 6H).

Common intermediate 7:

3-{2,5-dichloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl}-2-methylbutan-2-ol

Step 1: ethyl 3-hydroxy-2,3-dimethylbutanoate

[00155] To a mixture of Zn (11.70 g, 178.978 mmol) in THF (200 mL) was added TMSCl (2.0 mL, 15.648 mmol) was added at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 20 min at 75 °C under nitrogen atmosphere. To this was added ethyl 2-bromopropanoate (20 g, 110.480 mmol) and acetone (5.77 g, 99.432 mmol) dropwise at 75 °C. The resulting mixture was stirred for additional 2 h at 75 °C. The mixture was allowed to cool down to 0 °C. The mixture was acidified to pH 3 with conc. HCl. The resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (3 x 200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford ethyl 3-hydroxy-2,3-dimethylbutanoate (10.3 g, 58%) as yellow oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 4.23-4.19 (m, 2H), 2.53-2.49 (m, 1H), 1.34-1.26 (m, 6H), 1.25-1.21 (m, 6H).

Step 2: 3-hydroxy-2,3-dimethylbutanoic acid

[00156] A mixture of ethyl 3-hydroxy-2,3-dimethylbutanoate (10 g, 62.417 mmol) and NaOH (4.99 g, 124.834 mmol) in THF (100 mL) and H_2O (100 mL) was stirred for 16 h at room temperature. The mixture was acidified to pH 2 with conc. HCl. The resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (3 x 100 mL), dried

over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 3-hydroxy-2,3-dimethylbutanoic acid (3.6 g, 43%) as yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.58 (q, *J* = 7.2 Hz, 1H), 1.34 (s, 3H), 1.28 (d, *J* = 6.8 Hz, 6H).

Step 3: 1,3-dioxoisoindol-2-yl 3-hydroxy-2,3-dimethylbutanoate

[00157] To a stirred solution of 3-hydroxy-2,3-dimethylbutanoic acid (1 g, 7.567 mmol, 1 equiv) and *N*-hydroxyphthalimide (1.36 g, 8.324 mmol), DMAP (92 mg, 0.757 mmol) in DCM (15 mL) was added DIC (1.05 g, 8.324 mmol) at 0 °C. The reaction mixture was stirred for 16 h at room temperature. The resulting mixture was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 1,3-dioxoisoindol-2-yl 3-hydroxy-2,3-dimethylbutanoate (1.6 g, 76%) as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93-7.89 (m, 2H), 7.85-7.80 (m, 2H), 2.95 (q, *J* = 7.2 Hz, 1H), 1.47-1.35 (m, 9H).

Step 4: 2-methyl-3-{2,4,5-trichloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl}butan-2-ol

[00158] To a mixture of 1,3-dioxoisoindol-2-yl 3-hydroxy-2,3-dimethylbutanoate (1 g, 3.607 mmol), 2,4,5-trichloropyrrolo[2,1-*f*][1,2,4]triazine (1.60 g, 7.214 mmol), TFA (1.23 g, 10.821 mmol) in DMA (25 mL) was added $Ir[dF(CF_3)PPy]_2(dtbpy)PF_6$ (81 mg, 0.072 mmol) under nitrogen atmosphere. The reaction mixture was irradiated with Blue LED for 16 h at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of water (20 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford 2-methyl-3-{2,4,5-trichloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl}butan-2-ol (100 mg, 8%) as a yellow solid. MS ESI calculated for $C_{11}H_{12}Cl_3N_3O$ $[M + H]^+$, 308.00; found 308.00.

Step 5: 3-{2,5-dichloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl}-2-methylbutan-2-ol

[00159] A mixture of 2-methyl-3-{2,4,5-trichloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl}butan-2-ol (150 mg, 0.486 mmol) and $NaBH_4$ (30 mg, 0.793 mmol) in *i*-PrOH (2 mL) was stirred for 2 h at room temperature. The resulting mixture was filtered, the filter cake was washed with EtOAc (3 x 20 mL). The filtrate was concentrated under reduced pressure. To this was added DDQ (132 mg, 0.581 mmol, 1.46 equiv) in DCM (3 mL). The reaction mixture was stirred for 1 h at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (20 mL). The resulting mixture was extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford 3-{2,5-dichloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl}-2-methylbutan-2-ol (80 mg, 73%) as yellow oil. MS ESI calculated for

$C_{11}H_{13}ClN_3O$ $[M + H]^+$, 274.04; found 274.05. ^1H NMR (Chloroform-*d*) δ 8.76 (s, 1H), 6.88 (s, 1H), 3.72-3.69 (m, 1H), 1.38 (d, *J* = 7.2 Hz, 3H), 1.28 (s, 3H), 1.22 (s, 3H).

Common intermediate 8:

2,5-dichloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine

Step 1: 2,4,5-trichloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine

[00160] To a stirred mixture of 2,4,5-trichloropyrrolo[2,1-*f*][1,2,4]triazine (1 g, 4.495 mmol) and isobutyric acid (1.19 g, 13.485 mmol) in CH_3CN (40 mL) and water (10 mL) was added $AgNO_3$ (1.53 g, 8.99 mmol) at room temperature. The resulting mixture was stirred for 10 min at room temperature. To this was added $(NH_4)_2S_2O_8$ (5.15 g, 22.475 mmol) in water (10 mL) over 10 min at room temperature. The resulting mixture was stirred for additional 2 h at 50 °C. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (120 mL) at room temperature. The resulting mixture was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 30% to 95%; detector, UV 254 nm to afford 2,4,5-trichloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine (560 mg, 42%) as a yellow oil. MS ESI calculated for $C_9H_8Cl_3N_3$ $[M + H]^+$, 263.98, found 263.95. ^1H NMR (400 MHz, Chloroform-*d*) δ 6.77 (s, 1H), 3.60-3.50 (m, 1H), 1.38-1.36 (m, 6H).

Step 2: 2,5-dichloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine

[00161] To a stirred mixture of 2,4,5-trichloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine (560 mg, 2.117 mmol) in THF (5.6 mL) and *i*-PrOH (0.28 mL) was added $NaBH_4$ (128 mg, 3.388 mmol) in portions at room temperature. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (3 x 10 mL). The filtrate was concentrated under reduced pressure. The residue was dissolved in DCM (6 mL). To this was added DDQ (721 mg, 3.175 mmol). The resulting mixture was stirred for additional 1 h at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (20 mL). The resulting mixture was extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (0~40%) to afford 2,5-dichloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine (430 mg, 77%) as yellow oil. MS ESI calculated for $C_9H_9Cl_2N_3$ $[M + H]^+$, 230.02, found 230.05. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.76 (s, 1H), 6.75 (s, 1H), 3.62-3.52 (m, 1H), 1.38-1.37 (m, 6H).

Common intermediate 9:

2-(1-bromoethenyl)-2-methyl-1,3-dioxolane

Step 1: 2-(1-chloroethyl)-2-methyl-1,3-dioxolane

[00162] To a stirred solution of 3-chloro-2-butanone (15.45 g, 145.002 mmol) and ethylene glycol (8.63 g, 139.041 mmol) in cyclohexane (150 mL) was added *p*-TsOH (0.21 g, 1.249 mmol) at room temperature. The resulting mixture was stirred for 16 h at 95 °C. The resulting mixture was concentrated under reduced pressure to afford 2-(1-chloroethyl)-2-methyl-1,3-dioxolane (18.0 g, 82%) as brown oil. $C_6H_{11}ClO_2$, ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.07-3.96 (m, 5H), 1.54 (d, *J* = 6.9 Hz, 3H), 1.45 (s, 3H).

Step 2: 2-ethenyl-2-methyl-1,3-dioxolane

[00163] To a stirred solution of 2-(1-chloroethyl)-2-methyl-1,3-dioxolane (18.0 g, 119.522 mmol) in DMSO (100 mL) was added KOH (44.00 g, 784.244 mmol) at room temperature. The reaction mixture was stirred for 3 h at 120 °C. The resulting mixture was purified by distillation and the fraction was collected at 110~115 °C at atmospheric pressure to afford 2-ethenyl-2-methyl-1,3-dioxolane (13.8 g, crude) as colorless liquid. $C_6H_{10}O_2$, ^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.81 (dd, *J* = 17.2, 10.5 Hz, 1H), 5.39 (dd, *J* = 17.2, 1.8 Hz, 1H), 5.15 (dd, *J* = 10.5, 1.8 Hz, 1H), 4.03-3.82 (m, 4H), 1.48 (s, 3H).

Step 3: 2-(1-bromoethenyl)-2-methyl-1,3-dioxolane

[00164] To a stirred solution of 2-ethenyl-2-methyl-1,3-dioxolane (39 g, 256.255 mmol, 75% purity) in DCM (100 mL) was added Br_2 (9.19 mL, 179.378 mmol) in DCM (100 mL) dropwise at 0°C. The reaction mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure and dissolved in THF (400 mL). To this was added DBU (58.52 g, 384.382 mmol). The resulting mixture was stirred for additional 1 h at room temperature. The resulting mixture was diluted with water (500 mL). The resulting mixture was extracted with DCM (3 x 400mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (10/1) to afford 2-(1-bromoethenyl)-2-methyl-1,3-dioxolane (18.7 g, 38%) as colorless oil. $C_6H_9BrO_2$, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.06 (d, *J* = 1.6 Hz, 1H), 5.61 (d, *J* = 1.6 Hz, 1H), 4.05-3.88 (m, 4H), 1.63 (s, 3H).

Common intermediate 10:

4,4,5,5-tetramethyl-2-[1-(2-methyl-1,3-dioxolan-2-yl)ethenyl]-1,3,2-dioxaborolane

Step 1: 4,4,5,5-tetramethyl-2-[1-(2-methyl-1,3-dioxolan-2-yl)ethenyl]-1,3,2-dioxaborolane

[00165] To a mixture of 2-ethynyl-2-methyl-1,3-dioxolane (20 g, 178.368 mmol) and bis(pinacolato)diboron (49.8 g, 196.205 mmol) in toluene (340 mL) was added CuCl (1.77 g, 17.837 mmol), *t*-BuONa (2.57 g, 26.755 mmol, 0.15 equiv), tri-*tert*-butylphosphane (43.30 g,

10%, 21.404 mmol) and MeOH (11.43 g, 356.736 mmol, 2 equiv) at 0 °C. The resulting mixture was stirred for 16 h at room temperature under a nitrogen atmosphere. The reaction was diluted with MeOH (200 mL). The resulting mixture was filtered, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (10/1) to afford 4,4,5,5-tetramethyl-2-[1-(2-methyl-1,3-dioxolan-2-yl)ethenyl]-1,3,2-dioxaborolane (16 g, 37%) as light yellow liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.97 (d, *J* = 3.6 Hz, 1H), 5.84 (d, *J* = 3.6 Hz, 1H), 3.98-3.94 (m, 2H), 3.85-3.79 (m, 2H), 1.56 (s, 3H), 1.29 (s, 12H).

Common intermediate 11: (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidin-3-yl acetate hydrochloride

Step 1: *tert*-butyl (3*R*,4*R*)-4-({5-chloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-hydroxypiperidine-1-carboxylate

[00166] A mixture of 2,5-dichloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine (430 mg, 1.869 mmol), *tert*-butyl (3*R*,4*R*)-4-amino-3-hydroxypiperidine-1-carboxylate (1.62 g, 7.490 mmol) and DIEA (1.6 mL, 9.358 mmol) in NMP (4 mL) was stirred for 16 h at 120 °C. The mixture was allowed to cool down to room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 10% to 80%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-4-({5-chloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-hydroxypiperidine-1-carboxylate (760 mg, 89%) as a yellow solid. MS ESI calculated for $C_{19}H_{28}ClN_5O_3$ $[M + H]^+$, 410.19, found 410.35. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.56 (s, 1H), 6.49 (s, 1H), 5.06 (m, 1H), 4.34-4.28 (m, 1H), 4.21-4.16 (m, 1H), 3.75-3.71 (m, 1H), 3.62-3.58 (m, 1H), 3.42-3.39 (m, 1H), 2.89-2.85 (m, 1H), 2.79-2.73 (m, 1H), 2.13-2.09 (m, 1H), 1.60-1.53 (m, 1H), 1.49 (s, 9H), 1.35-1.33 (m, 6H).

Step 2: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00167] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-4-({5-chloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-hydroxypiperidine-1-carboxylate (500 mg, 1.220 mmol) and TEA (0.85 mL, 6.115 mmol) in DCM (5 mL) was added Ac_2O (0.17 mL, 1.830 mmol) at room temperature. The resulting mixture was stirred for 16 h at 50 °C. The mixture was allowed to cool down to room temperature. The resulting mixture was purified by silica gel column chromatography, eluted with PE/EtOAc (0~60%) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (630 mg, 97%) as a yellow solid. MS ESI calculated for $C_{21}H_{30}ClN_5O_4$ $[M + H]^+$, 452.20, found 452.15. ^{1}H NMR

(400 MHz, Chloroform-*d*) δ 8.56 (s, 1H), 6.42 (s, 1H), 4.98-4.88 (m, 2H), 3.99-3.90 (m, 2H), 3.85-3.80 (m, 1H), 3.44-3.40 (m, 1H), 3.26-3.23 (m, 2H), 2.37-2.33 (m, 1H), 2.06 (s, 3H), 1.51-1.48 (m, 10H), 1.35-1.32 (m, 6H).

Step 3: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-iodo-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00168] A mixture of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (300 mg, 0.664 mmol) and I_2 (674 mg, 2.656 mmol) in DMF (3 mL) was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (10 mL) at room temperature. The resulting mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-iodo-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (400 mg, 93%) as a yellow solid. MS ESI calculated for $C_{21}H_{29}ClIN_5O_4$ $[M + H]^+$, 578.10, found 578.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.55 (s, 1H), 5.10-4.92 (m, 2H), 4.16-4.12 (m, 1H), 3.91-3.83 (m, 2H), 3.59-3.55 (m, 1H), 3.30-3.22 (m, 2H), 2.34-2.25 (m, 1H), 2.07 (s, 3H), 1.49-1.45 (m, 16H).

Step 4: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00169] A mixture of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-iodo-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (400 mg, 0.692 mmol), $Zn(CN)_2$ (98 mg, 0.830 mmol) and $Pd(PPh_3)_4$ (80 mg, 0.069 mmol) in DMA (4 mL) was stirred for 2 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of water/ice (20 mL). The resulting mixture was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (270 mg, 77%) as a yellow solid. MS ESI calculated for $C_{22}H_{29}ClN_6O_4$ $[M + H]^+$, 477.19, found 477.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.66 (s, 1H), 5.19 (s, 1H), 4.93-4.92(m, 1H) 4.08-4.04 (m, 1H), 3.95-3.87 (m, 3H), 3.68-3.63 (m, 1H), 3.17-3.12 (m, 1H), 2.36-2.32 (m, 1H), 2.08-2.06 (m, 3H), 1.79-1.75 (m, 1H), 1.50-1.47 (m, 15H).

Step 5: (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidin-3-yl acetate hydrochloride

[00170] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (70 mg, 0.147 mmol) in DCM (1 mL) was added HCl (gas) in 1,4-dioxane (1 mL) at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidin-3-yl acetate hydrochloride (60 mg, 89%) (crude) as yellow oil. MS ESI calculated for $C_{17}H_{22}Cl_2N_6O_2$ $[M - Cl]^+$, 377.14, found 377.20.

Common intermediate 12:

2,5-dichloro-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazine

Step 1: 2,4,5-trichloro-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazine

[00171] To a stirred mixture of 2,4,5-trichloropyrrolo[2,1-*f*][1,2,4]triazine (700 mg, 3.147 mmol) and 2-methylbutanoic acid (964 mg, 9.441 mmol) and CH_3CN (8 mL) was added $AgNO_3$ (1.07 g, 6.294 mmol) at room temperature. To this was added $(NH_4)_2S_2O_8$ (3.59 g, 15.735 mmol) in water (4 mL) at 50 °C. The reaction mixture was stirred for 16 h at 50 °C. The resulting mixture was diluted with water (50 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 2,4,5-trichloro-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazine (450 mg, 51%) as a yellow solid; MS ESI calculated for $C_{10}H_{10}Cl_3N_3$ $[M + H]^+$, 277.99, found 278.05. ^1H NMR (400 MHz, Chloroform-*d*) δ 6.75 (s, 1H), 3.44-3.40 (m, 1H), 1.87-1.73 (m, 2H), 1.33 (d, J = 7.2 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H).

Step 2: 2,5-dichloro-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazine

[00172] To a stirred mixture of 2,4,5-trichloro-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazine (450 mg, 1.615 mmol) in *i*-PrOH (0.25 mL) and THF (5 mL) was added $NaBH_4$ (92 mg, 2.422 mmol) in portions at 0 °C. The reaction mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (10 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. To this was added DCM (5 mL) and DDQ (692 mg, 3.046 mmol) at 0 °C. The reaction mixture was stirred for 1 h at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (5 mL) at 0 °C. The aqueous layer was extracted with EtOAc (3 x 3 mL). After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (10/1) to afford 2,5-dichloro-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazine (370 mg, 75%) as yellow oil. MS ESI calculated for $C_{10}H_{11}Cl_2N_3$ $[M + H]^+$, 244.03, found 244.05. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.75 (s,

1H), 6.74 (s, 1H), 3.49-3.40 (m, 1H), 1.88-1.69 (m, 2H), 1.34 (d, J = 7.2 Hz, 4H), 0.92 (t, J = 7.2 Hz, 3H).

Common intermediate 13:

2,5-dichloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine

Step 1: 1,3-dioxoisoindol-2-yl 3-methylbutanoate

[00173] To a stirred solution of isovaleric acid (1.1 g, 10.770 mmol), isovaleric acid (1.1 g, 10.770 mmol) and DMAP (0.13 g, 1.077 mmol) in DCM (15 mL) was added DIC (1.50 g, 11.847 mmol) at room temperature. The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was filtered, the filter cake was washed with EtOAc (10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford 1,3-dioxoisoindol-2-yl 3-methylbutanoate (1.8 g, 67.59%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.92-7.87 (m, 2H), 7.83-7.78 (m, 2H), 2.56 (d, J = 7.2 Hz, 2H), 2.33-2.22 (m, 1H), 1.12 (d, J = 6.8 Hz, 6H).

Step 2: 2,4-dichloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine

[00174] A mixture of 2,4-dichloropyrrolo[2,1-*f*][1,2,4]triazine (3 g, 15.957 mmol), 1,3-dioxoisoindol-2-yl 3-methylbutanoate (7.89 g, 31.914 mmol) and TFA (5.46 g, 47.871 mmol) in DMA (48 mL) was added $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.90 g, 0.798 mmol) under nitrogen atmosphere. The reaction mixture was irradiated with Blue LED for 48 h at room temperature under nitrogen atmosphere. The resulting mixture was diluted with water (300 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in Water (0.1% formic acid), 20% to 50%; detector, UV 254 nm to afford 2,4-dichloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine (1.5 g, 27%) as brown oil. MS ESI calculated for $C_{10}H_{11}Cl_2N_3$ $[M + H]^+$, 244.03, found 244.10. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.05 (d, J = 4.8 Hz, 1H), 6.82 (d, J = 4.8 Hz, 1H), 2.91 (d, J = 7.2 Hz, 2H), 2.20-2.17 (m, 1H), 0.99 (d, J = 6.8 Hz, 6H).

Step 3: 2-chloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine

[00175] To a stirred mixture of 2,4-dichloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine (1.64 g, 4.703 mmol) in THF (20 mL) and *i*-PrOH (1 mL) was added $NaBH_4$ (284.64 mg, 7.525 mmol) in portions at 0 °C. The resulting mixture was stirred for 4 h at room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (3 x 50 mL). The filtrate was concentrated under reduced pressure. The residue was dissolved in DCM (20 mL). To this was added DDQ (1.77 g, 7.794 mmol).

[00176] The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (3 x 100 mL). The combined filtrare was extracted with water (100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford 2-chloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine (700 mg, 64%) as light yellow oil. MS ESI calculated for $C_{10}H_{12}ClN_3$ $[M + H]^+$, 210.07, found 210.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.73 (s, 1H), 6.99 (d, J = 4.8 Hz, 1H), 6.85 (d, J = 4.8 Hz, 1H), 2.93 (d, J = 7.2 Hz, 2H), 2.25-2.19 (m, 1H), 1.00 (d, J = 6.8 Hz, 6H).

Step 4: 2,5-dichloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine

[00177] To a stirred mixture of 2-chloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine (110 mg, 0.525 mmol) in DMF (1.5 mL) was added NCS (63.05 mg, 0.473 mmol) at room temperature. The resulting mixture was stirred for 16 h at room temperature. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, MeOH in water (0.1% $NH_3.H_2O$), 50% to 95%; detector, UV 254 nm to afford 2,5-dichloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine (100 mg, 72%) as yellow oil. MS ESI calculated for $C_{10}H_{11}Cl_2N_3$ $[M + H]^+$, 244.03, found 244.05.

Step 5: 2,5-dichloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine

[00178] To a stirred mixture of 2,5-dichloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine (50 mg, 0.205 mmol) in DMF (1 mL) was added I_2 (208 mg, 0.820 mmol) at room temperature. The resulting mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (30 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (10/1) to afford 2,5-dichloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine (20 mg, 25%) as brown yellow oil. MS ESI calculated for $C_{10}H_{10}Cl_2IN_3$ $[M + H]^+$, 369.93, found 370.00. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.75 (s, 1H), 2.88 (d, J = 7.2 Hz, 2H), 2.21-2.11 (m, 1H), 1.00-0.97 (m, 6H).

Common intermediate 14:

2,5-dichloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine

Step 1: 2,4,5-trichloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine

[00179] To a stirred mixture of 2,4,5-trichloropyrrolo[2,1-*f*][1,2,4]triazine (350 mg, 1.573 mmol) and 2,3-dimethylbutanoic acid (548 mg, 4.71 mmol) in CH_3CN (10 mL) were added $(NH_4)_2S_2O_8$ (1.80 g, 7.86 mmol) and water (7 mL) at room temperature. The resulting mixture was stirred for

2 h at 50 °C. The mixture was allowed to cool down to room temperature. The reaction was diluted with sat. NH_4Cl (aq.) (20 mL. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% TFA), 10% to 50%; detector, UV 254 nm to afford 2,4,5-trichloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (310 mg, 67%) as yellow oil. MS ESI calculated for $C_{11}H_{12}Cl_3N_3$ $[M + H]^+$, 292.01 found 292.00. ^{1}H-NMR (400 MHz, Chloroform-*d*) δ 6.74 (s, 1H), 3.40-3.35 (m, 1H), 2.06-2.00 (m, 1H), 1.29 (d, *J* = 7.2 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H).

Step 2: 2,5-dichloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine

[00180] To a stirred mixture of 2,4,5-trichloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (310 mg, 1.06 mmol) and *i*-PrOH (0.2 mL) in THF (4 mL) was added $NaBH_4$ (64 mg, 1.69 mmol) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (3 x 20 mL). The filtrate was concentrated under reduced pressure. To this was added DDQ (360 mg, 1.59 mmol) and DCM (4 mL) at 0 °C. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (20 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford 2,5-dichloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (220 mg, 80%) as yellow oil. MS ESI calculated for $C_{11}H_{13}Cl_2N_3$ $[M + H]^+$, 258.05 found 258.05. ^{1}H-NMR (400 MHz, Chloroform-*d*) δ 8.75 (s, 1H), 6.74 (d, *J* = 1.6 Hz, 1H), 3.41-3.36 (m, 1H), 2.08-2.02 (m, 1H), 1.30 (d, *J* = 7.2 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H).

Common intermediate 15:

(3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride

Step 1: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00181] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (150 mg, 0.3 mmol) in DMF (3 mL) was added I_2 (317 mg, 1.24 mmol). The resulting mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (20 mL) at room

temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (175 mg, 92%) as a yellow solid. MS ESI calculated for $C_{23}H_{33}ClIN_5O_4$ $[M + H]^+$, 606.13, found 606.20.

Step 2: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00182] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (175 mg, 0.28 mmol) and $Zn(CN)_2$ (15 mg, 0.23 mmol) in DMA (3 mL) was added $Pd(PPh_3)_4$ (66 mg, 0.05 mmol). The resulting mixture was stirred for 2 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (20 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (98 mg, 67%) as a yellow solid. MS ESI calculated for $C_{27}H_{33}ClN_6O_4$ $[M + H]^+$, 505.23, found 505.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.52 (s, 1H), 5.48 (brs, 1H), 4.95-4.91 (m, 1H), 3.90-3.86 (m, 2H), 3.77-3.73 (m, 1H), 3.38-3.34 (m, 2H), 3.10-3.00 (m, 1H), 2.54-2.43 (m, 1H), 2.35-2.30 (m, 1H), 2.08-2.07 (m, 3H), 1.62-1.56 (m, 1H), 1.49 (s, 9H), 1.45-1.41 (m, 3H), 1.11-1.07 (m, 3H), 0.72-068 (m, 3H).

Step 3: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride

[00183] To a stirred mixture of *tert*-butyl (3R,4R)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (98 mg, 0.194 mmol) in DCM (4 mL) was added HCl (gas) in 1,4-dioxane (4 mL) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (80 mg, 93%) as a yellow solid. MS ESI calculated for $C_{19}H_{26}Cl_2N_6O_2$ $[M - Cl]^+$, 405.17, found 405.20.

Common intermediate 16:

(3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride

Step 1: 2,5-dichloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine

[00184] A mixture of 2-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (3.3 g, 14.000 mmol) and NCS (1.96 g, 14.700 mmol) in DMF (50 mL) was stirred for 16 h at room temperature. The reaction was quenched by the addition of water (100 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 2,5-dichloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (3.0 g, 79%) as a yellow solid. MS ESI calculated for $C_{12}H_{13}Cl_2N_3$ $[M + H]^+$, 270.05; found 270.05. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.75 (s, 1H), 6.72 (s, 1H), 2.51-2.40 (m, 2H), 2.34-2.24 (m, 2H), 2.14-2.06 (m, 3H), 1.97-1.87 (m, 1H), 0.63 (t, J = 7.2 Hz, 3H).

Step 2: 2,5-dichloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazine

[00185] A mixture of 2,5-dichloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (3.0 g, 11.105 mmol) and I_2 (11.27 g, 44.420 mmol) in DMF (60 mL) was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (100 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 2,5-dichloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazine (3.0 g, 68%) as a yellow solid. MS ESI calculated for $C_{12}H_{12}Cl_2IN_3$ $[M + H]^+$, 395.95; found 395.95. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 2.79-2.62 (m, 2H), 2.56-2.40 (m, 2H), 2.20-2.05 (m, 3H), 1.91-1.82 (m, 1H), 0.88-0.74 (m, 3H).

Step 3: *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate

[00186] A mixture of 2,5-dichloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazine (2.5 g, 6.312 mmol), *tert*-butyl (3*R*,4*R*)-4-amino-3-hydroxypiperidine-1-carboxylate (1.64 g, 7.574 mmol) and DIEA (3.26 g, 25.248 mmol) in NMP (50 mL) was stirred for 16 h at 80 °C. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of water (100 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was

purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (3.3 g, 90%) as a yellow solid. MS ESI calculated for $C_{22}H_{31}ClIN_5O_3$ $[M + H]^+$, 576.12; found 576.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.51 (s, 1H), 4.94 (brs, 1H), 4.32-4.25 (m, 1H), 4.15-4.11 (m, 2H), 3.66-3.47 (m, 3H), 2.89-2.84 (m, 1H), 2.80-2.66 (m, 3H), 2.42-2.38 (m, 2H), 2.25-1.99 (m, 6H), 1.87-1.83 (m, 1H), 1.48 (s, 9H), 0.83-0.79 (m, 3H).

Step 4: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00187] A mixture of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (3.3 g, 5.730 mmol), Ac_2O (0.88 g, 8.595 mmol) and TEA (2.32 g, 22.920 mmol) in DCM (50 mL) was stirred for 16 h at 50 °C. The resulting mixture was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (3.3 g, 93%) as a yellow solid. MS ESI calculated for $C_{24}H_{33}ClIN_5O_4$ $[M + H]^+$, 618.13; found 618.15.

Step 5: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00188] A mixture of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (3.3 g, 5.341 mmol), $Zn(CN)_2$ (345 mg, 2.938 mmol) and $Pd(PPh_3)_4$ (617 mg, 0.534 mmol) in DMF (40 mL) was stirred for 2 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of water (100 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (2.3 g, 83%) as a yellow solid. MS ESI calculated for $C_{25}H_{33}ClN_6O_4$ $[M + H]^+$, 517.23; found 517.30. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.65 (s, 1H), 5.25 (brs, 1H), 4.92-4.88 (m, 1H), 4.14-4.10 (m, 1H), 3.94-3.87 (m, 1H), 3.79-3.76 (m, 1H), 3.13-3.09 (m, 2H), 2.73-2.69 (m, 2H), 2.37-2.28 (m, 3H), 2.23-2.15 (m, 1H), 2.13-2.04 (m, 5H), 2.01-1.92 (m, 1H), 1.53-1.49 (m, 10H), 0.81 (t, J = 7.2 Hz, 3H).

Step 6: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride

[00189] A mixture of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (1 g, 1.934 mmol) and HCl (gas)in 1,4-dioxane (10 mL) in DCM (10 mL) was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (800 mg, 91%) as a yellow solid. MS ESI calculated for $C_{20}H_{26}Cl_2N_6O_2$ $[M - Cl]^+$, 417.17; found 417.25.

Example 1:

(3*S*,4*R*)-4-((5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-(trifluoromethyl)pyrrolo[2,1-f][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK ID, Hexane/^{i}PrOH = 93/7, 1st peak)

Example 2:

(3*S*,4*R*)-4-((5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-(trifluoromethyl)pyrrolo[2,1-f][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK ID, Hexane/^{i}PrOH = 93/7, 2nd peak)

Step 1: (3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00190] To a stirred solution of (3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (200 mg, 0.38 mmol) and KF (66 mg, 1.14 mmol), CuI (72 mg, 0.38 mmol) in DMF (3 mL) was added methyl 2,2-difluoro-2-sulfoacetate (366 mg, 1.91mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 50 °C under nitrogen atmosphere. The resulting mixture was allowed to cool down to room temperature and purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% $NH_3.H_2O$), 10% to 50%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (177 mg, 79%) as a yellow solid. MS ESI calculated for $C_{19}H_{23}ClF_4N_4O_3$ $[M + H]^+$, 467.14, found 467.30.

Step 2: (3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol

[00191] A solution of (3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (177 mg, 0.38 mmol) and K_2CO_3 (105 mg, 0.76mmol) in MeOH (3 mL, 1.14 mmol) was stirred for 20 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the

following conditions: C18 column; mobile phase, CH_3CN in water (0.1% $NH_3.H_2O$), 10% to 50%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (90 mg, 56%) as yellow oil. MS ESI calculated for $C_{17}H_{21}ClF_4N_4O_2$ $[M + H]^+$, 425.13 found 425.30.

Example 1:

(3*S*,4*R*)-4-((5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK ID, Hexane/^{i}PrOH = 93/7, 1st peak)

Example 2: (3*S*,4*R*)-4-((5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK ID, Hexane/^{i}PrOH = 93/7, 2nd peak)

[00192] (3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (40 mg, 0.09 mmol) was purified by Chiral-HPLC with the following conditions (Column: CHIRALPAK ID, 2*25 cm, 5 μm; Mobile Phase A: hexane, Mobile Phase B: ^{i}PrOH; Flow rate: 20 mL/min; Gradient: A:B = 93:7; Wave Length: 254/220 nm;

[00193] RT_1: 14.81 min to afford (3*S*,4*R*)-4-((5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK ID, Hexane/^{i}PrOH = 93/7, 1st peak) (8.1 mg, 20%) as a off-white solid. MS ESI calculated for $C_{17}H_{21}ClF_4N_4O_2$ $[M + H]^+$, 425.13, found 425.15. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 (s, 1H), 7.32 (brs, 1H), 4.98 (brs, 1H), 3.86-3.81 (m, 2H), 3.66-3.49 (m, 3H), 3.31-3.24 (m, 1H), 3.09-3.04 (m, 1H), 2.05-1.98 (m, 1H), 1.62 (d, J = 7.2 Hz, 3H), 1.49-1.37 (m, 4H), 1.36-1.28 (m, 3H). ^{19}F NMR (377 MHz, DMSO-d_6) δ -52.37 (3F), -130.12 (1F).

[00194] RT_2: 20.14 min to afford (3*S*,4*R*)-4-((5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK ID, Hexane/^{i}PrOH = 93/7, 2nd peak) (8.5 mg, 21%) as a off-white solid. MS ESI calculated for $C_{17}H_{21}ClF_4N_4O_2$ $[M + H]^+$, 425.13, found 425.15. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (s, 1H), 7.28 (brs, 1H), 4.98 (brs, 1H), 3.86-3.81 (m, 2H), 3.65-3.50 (m, 3H), 3.31-3.24 (m, 1H), 3.09-3.04 (m, 1H), 2.05-1.98 (m, 1H), 1.59-1.56 (m, 3H), 1.53-1.40 (m, 4H), 1.35-1.29 (m, 3H). ^{19}F NMR (377 MHz, DMSO-d_6) -52.37 (3F), -128.68 (1F).

Example 3:

(3*S*,4*R*)-4-({5-chloro-7-[5-(2,2,2-trifluoroethyl)pyridin-2-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol

[00195] To a stirred solution of 2-bromo-5-(2,2,2-trifluoroethyl)pyridine (104 mg, 0.432 mmol) and $Pd(OAc)_2$ (5 mg, 0.020 mmol) in hexabutyldistannane (275 mg, 0.475 mmol) was added PCy_3 (12 mg, 0.043 mmol) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 24 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. To this was added (3*S*,4*R*)-4-({7-bromo-5-chloropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol (100 mg, 0.288 mmol), CuI (22 mg, 0.115 mmol) and $Pd(PPh_3)_4$ (17 mg, 0.014 mmol). The resulting mixture was stirred for an additional 16 h at 120 °C under nitrogen atmosphere. The resulting mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The resulting mixture was purified by silica gel column chromatography, eluted with PE/EtOAc (1/2). The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep Shield RP18 OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: water (0.1% formic acid), Mobile Phase B: CH_3CN; Flow rate: 60 mL/min mL/min; Gradient: 33% B to 63 % B; Wave Length: 254nm/220 nm to afford (3*S*,4*R*)-4-({5-chloro-7-[5-(2,2,2-trifluoroethyl)pyridin-2-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol (10 mg, 8%) as a light yellow solid. MS ESI calculated for $C_{18}H_{17}ClF_3N_5O_2$ $[M + H]^+$, 428.10, found 428.10. ^1H NMR (400 MHz, DMSO-d_6) δ 8.93 (s, 1H), 8.81 (d, J = 8.0 Hz, 1H), 8.65 (s, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.36 (s, 1H), 7.28 (d, J = 7.2 Hz, 1H), 5.02 (d, J = 5.2 Hz, 1H), 4.03-3.75 (m, 5H), 3.60-3.58 (m, 1H), 3.51-3.47 (m, 1H), 3.17-3.12 (m, 1H), 2.16-2.12 (m, 1H), 1.63-1.41 (m, 1H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -64.35 (3F).

Example 4:

5-fluoro-7-[1-(1-fluoroethyl)cyclobutyl]-2-{[(3S,4R)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile

Step 1: 2,4-dichloro-5-fluoro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazine

[00196] To a stirred mixture of 2,4-dichloro-5-fluoropyrrolo[2,1-*f*][1,2,4]triazine (1.6 g, 7.767 mmol), 1-(1-fluoroethyl)cyclobutane-1-carboxylic acid (2.27 g, 15.534 mmol) and Ag_2CO_3 (4.28 g, 15.534 mmol) in CH_3CN (40 mL) was added $(NH_4)_2S_2O_8$ (8.86 g, 38.835 mmol) in H_2O (32 mL) dropwise at 50 °C under nitrogen atmosphere. The resulting mixture was stirred for 3.5 h at 50 °C. The resulting mixture was diluted with water (100 mL) and extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was

purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 60% to 80%; detector, UV 220 nm to afford 2,4-dichloro-5-fluoro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazine (85 mg, 3%) as a yellow green solid. MS ESI calculated for $C_{12}H_{11}Cl_2F_2N_3$ $[M + H]^+$, , 306.03, found 305.90. ^1H NMR (400 MHz, Chloroform-*d*) δ 6.55 (s, 1H), 5.26-5.09 (m, 1H), 2.67-2.61 (m, 2H), 2.55-2.39 (m, 2H), 2.15-2.01 (m, 1H), 1.97-1.86 (m, 1H), 1.15 (dd, *J* = 24.0, 6.4 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -151.08 (1F), 181.60 (1F).

Step 2: 2-chloro-5-fluoro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazine

[00197] To a stirred mixture of 2,4-dichloro-5-fluoro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazine (70 mg, 0.229 mmol) in THF (2 mL) and *i*-PrOH (0.1 mL) was added $NaBH_4$ (13.84 mg, 0.366 mmol) at 0 °C. The resulting mixture was stirred for 1 h at 0 °C. The resulting mixture was filtered, and the filter cake was washed with THF (3 x 1 mL). The filtrate was concentrated under reduced pressure. To this were added DDQ (77.86 mg, 0.344 mmol) and DCM (2 mL) at room temperature. The resulting mixture was stirred for an additional 1 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (10 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 3 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 2-chloro-5-fluoro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazine (55 mg, 88%) as a yellow green solid. MS ESI calculated for $C_{12}H_{12}ClF_2N_3$ $[M + H]^+$, 272.07, found 272.00. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.79 (s, 1H), 6.53 (s, 1H), 5.29-5.12 (m, 1H), 2.71-2.60 (m, 2H), 2.59-2.38 (m, 2H), 2.16-1.86 (m, 2H), 1.15 (dd, *J* = 24.0, 6.4 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -157.15 (1F), 181.75 (1F).

Step 3: (3*S*,4*R*)-4-({5-fluoro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol

[00198] To a stirred mixture of 2-chloro-5-fluoro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazine (55 mg, 0.202 mmol) and (3*S*,4*R*)-4-aminooxan-3-ol hydrochloride (93 mg, 0.606 mmol) in NMP (2.5 mL) was added DIEA (157 mg, 1.212 mmol). The resulting mixture was stirred for 16 h at 80 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 40% to 60%; detector, UV 254 nm to afford (3*S*,4*R*)-4-({5-fluoro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol (50 mg, 70%) as a yellow green solid. MS ESI calculated for $C_{17}H_{22}F_2N_4O_2$ $[M + H]^+$, , 353.17, found 353.00. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.58 (s, 1H), 6.23 (d, *J* = 7.2 Hz, 1H), 5.44-5.03 (m, 1H),

4.11-4.07 (m, 1H), 4.01-3.96 (m, 1H), 3.73-3.70 (m, 1H), 3.50-3.46 (m, 1H), 3.28-3.25 (m, 2H), 2.70-2.44 (m, 4H), 2.20-2.07 (m, 2H), 1.89-1.85 (m, 1H), 1.69-1.58 (m, 1H), 1.22-1.09 (m, 3H).

Step 4: (3*S*,4*R*)-4-({5-fluoro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00199] To a stirred mixture of (3*S*,4*R*)-4-({5-fluoro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol (50 mg, 0.142 mmol) and TEA (86.15 mg, 0.852 mmol) in DCM (2 mL) was added Ac_2O (28.97 mg, 0.284 mmol) at room temperature. The resulting mixture was stirred for 16 h at 50 °C. The reaction was quenched by the addition of water/ice (50 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 50% to 65%; detector, UV 254 nm to afford (3*S*,4*R*)-4-({5-fluoro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (48 mg, 85%) as a yellow green solid. MS ESI calculated for $C_{19}H_{24}F_2N_4O_3$ $[M + H]^+$, 395.18, found 395.00.

Step 5: (3*S*,4*R*)-4-({5-fluoro-7-[1-(1-fluoroethyl)cyclobutyl]-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00200] A mixture of (3*S*,4*R*)-4-({5-fluoro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (50 mg, 0.127 mmol) and I_2 (161 mg, 0.635 mmol) in DMF (2 mL) was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (20 mL) The resulting mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 60% to 75%; detector, UV 254 nm to afford (3*S*,4*R*)-4-({5-fluoro-7-[1-(1-fluoroethyl)cyclobutyl]-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (55 mg, 83%) as a yellow green solid. MS ESI calculated for $C_{19}H_{23}F_2IN_4O_3$ $[M + H]^+$, , 521.08, found 520.85.

Step 6: (3*S*,4*R*)-4-({6-cyano-5-fluoro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00201] To a stirred mixture of (3*S*,4*R*)-4-({5-fluoro-7-[1-(1-fluoroethyl)cyclobutyl]-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (50 mg, 0.096 mmol) and $Zn(CN)_2$ (15.71 mg, 0.240 mmol) in DMF (2 mL) was added $Pd(PPh_3)_4$ (11 mg, 0.010 mmol) under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 130 °C under nitrogen atmosphere. The

reaction was quenched by the addition of water (30 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 50% to 65%; detector, UV 254 nm to afford (3*S*,4*R*)-4-({6-cyano-5-fluoro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (17 mg, 42%) as a yellow green solid. MS ESI calculated for $C_{20}H_{23}F_2N_5O_3$ $[M + H]^+$, , 420.18, found 420.00. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 5.29 (brs, 1H), 5.21-5.03 (m, 1H), 4.96-4.92 (m, 1H), 4.08-3.94 (m, 2H), 3.83-3.79 (m, 1H), 3.54-3.51 (m, 1H), 3.43-3.39 (m, 1H), 2.91-2.64 (m, 4H), 2.53-2.31 (m, 2H), 2.24-2.19 (m, 1H), 2.08 (s, 3H), 1.73-1.68 (m, 1H), 1.33-1.25 (m, 3H).

Example 4:

5-fluoro-7-[1-(1-fluoroethyl)cyclobutyl]-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00202] A mixture of (3*S*,4*R*)-4-({6-cyano-5-fluoro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (12 mg, 0.029 mmol) and K_2CO_3 (11.86 mg, 0.087 mmol) in MeOH (1 mL) was stirred for 30 min at 0 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 45% to 60%; detector, UV 254 nm to afford 5-fluoro-7-[1-(1-fluoroethyl)cyclobutyl]-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (8.4 mg, 77%) as an off-white solid. MS ESI calculated for $C_{18}H_{21}F_2N_5O_2$ $[M + H]^+$, , 378.17, found 378.20. ^1H NMR (400 MHz, DMSO-d_6) δ 9.02 (s, 1H), 7.33 (brs, 1H), 5.26-5.10 (m, 1H), 4.93 (brs, 1H), 3.85-3.78 (m, 2H), 3.53-3.49 (m, 2H), 3.47-3.25 (m, 1H), 3.05-3.02 (m, 1H), 2.81-2.62 (m, 3H), 2.42-2.37 (m, 1H), 2.16-1.98 (m, 2H), 1.90-1.87 (m, 1H), 1.48-1.27 (m, 1H), 1.19 (dd, J = 24.0, 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -156.18 (1F), -178.00 (1F).

Example 5:

5-chloro-7-[1-(1-fluoroethyl)cyclobutyl]-2-{[(3S,4R)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile

Step 1: 2,4,5-trichloro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazine

[00203] To a stirred mixture of 2,4,5-trichloropyrrolo[2,1-*f*][1,2,4]triazine (1.2 g, 5.394 mmol), Ag_2CO_3 (2.97 g, 10.788 mmol), and 1-(1-fluoroethyl)cyclobutane-1-carboxylic acid (1.58 g, 10.788 mmol) in CH_3CN (60 mL) was added $(NH_4)_2S_2O_8$ (6.15 g, 26.970 mmol) in H_2O (48 mL) dropwise over 2 min at 50 °C. The resulting mixture was stirred for 2.5 h at 50 °C. The resulting

mixture was diluted with water (200 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (2 x 200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 50% to 80%; detector, UV 254 nm to afford 2,4,5-trichloro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazine (60 mg, 3%) as a yellow solid. MS ESI calculated for $C_{12}H_{11}Cl_3FN_3$ $[M + H]^+$, , 321.00, found 321.85. ^1H NMR (400 MHz, Chloroform-*d*) δ 6.82 (s, 1H), 5.27-5.10 (m, 1H), 2.72-2.60 (m, 2H), 2.50-2.41 (m, 2H), 2.15-2.04 (m, 1H). 1.97-1.84 (m, 1H), 1.15 (dd, *J* = 24.0, 6.4 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ 181.88 (1F).

Step 2: 2,5-dichloro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazine

[00204] To a stirred mixture of 2,4,5-trichloro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazine (80 mg, 0.248 mmol) in THF (2 mL) and *i*-PrOH (0.1 mL) was added $NaBH_4$ (15.01 mg, 0.397 mmol) at 0 °C. The resulting mixture was stirred for 1 h at 0 °C. The resulting mixture was filtered, the filter cake was washed with THF (3 x 1 mL). The combined filtrate was concentrated under reduced pressure. To the residue were added DDQ (84.44 mg, 0.372 mmol) and DCM (2 mL) at room temperature. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (10 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 3 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 2,5-dichloro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazine (60 mg, 83%) as a yellow green solid. MS ESI calculated for $C_{12}H_{12}Cl_2FN_3$ $[M + H]^+$, 288.04, found 287.90. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.79 (s, 1H), 6.81 (s, 1H), 5.28-5.12 (m, 1H), 2.71-2.61 (m, 2H), 2.56-2.41 (m, 2H), 2.09-2.03 (m, 1H), 1.97-1.91 (m, 1H), 1.14 (dd, *J* = 24.0, 6.4 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ 181.89 (1F).

Step 3: (3*S*,4*R*)-4-({5-chloro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol

[00205] A mixture of 2,5-dichloro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazine (60 mg, 0.208 mmol), (3*S*,4*R*)-4-aminooxan-3-ol hydrochloride (38 mg, 0.250 mmol) and DIEA (81 mg, 0.624 mmol) in NMP (2 mL) was stirred for 16 h at 80 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 50% to 70%; detector, UV 254 nm to afford (3*S*,4*R*)-4-({5-chloro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol (55 mg,

71%) as a yellow green solid. MS ESI calculated for $C_{17}H_{22}ClFN_4O_2$ $[M + H]^+$, , 369.14, found 369.00. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.58 (s, 1H), 6.54-6.52 (m, 1H), 5.29-5.09 (m, 1H), 4.11-4.07 (m, 1H), 4.04-3.94 (m, 1H), 3.72-3.67 (m, 2H), 3.52-3.47 (m, 1H), 3.30-3.23 (m, 1H), 2.70-2.36 (m, 4H), 2.19-2.03 (m, 2H), 1.97-1.92 (m, 1H), 1.74-1.66 (m, 1H), 1.21-1.09 (m, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ 181.54 (1F).

Step 4: (3*S*,4*R*)-4-({5-chloro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00206] To a stirred mixture of (3*S*,4*R*)-4-({5-chloro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol (55 mg, 0.149 mmol) and TEA (90.54 mg, 0.894 mmol) in DCM (2 mL) was added Ac_2O (30.45 mg, 0.298 mmol). The resulting mixture was stirred for 16 h at 50 °C. The reaction was quenched by the addition of water/ice (50 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 50% to 70%; detector, UV 254 nm to afford (3*S*,4*R*)-4-({5-chloro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (40 mg, 65%) as a yellow green solid. MS ESI calculated for $C_{19}H_{24}ClFN_4O_3$ $[M + H]^+$, 411.15, found 411.05.

Step 5: (3*S*,4*R*)-4-({5-chloro-7-[1-(1-fluoroethyl)cyclobutyl]-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00207] A mixture of (3*S*,4*R*)-4-({5-chloro-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (40 mg, 0.097 mmol) and I_2 (123.55 mg, 0.485 mmol) in DMF (2 mL) was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (10 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 55% to 75%; detector, UV 254 nm to afford (3*S*,4*R*)-4-({5-chloro-7-[1-(1-fluoroethyl)cyclobutyl]-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (45 mg, 86%) (crude) as a yellow green solid. MS ESI calculated for $C_{19}H_{23}ClFIN_4O_3$ $[M + H]^+$, , 537.05, found 536.85.

Step 6: (3*S*,4*R*)-4-({5-chloro-6-cyano-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00208] To a stirred mixture of (3*S*,4*R*)-4-({5-chloro-7-[1-(1-fluoroethyl)cyclobutyl]-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (40 mg, 0.075 mmol) and $Zn(CN)_2$ (5.25 mg, 0.045 mmol) in DMF (1.5 mL) was added $Pd(PPh_3)_4$ (8 mg, 0.007 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1.5 h at 130 °C under nitrogen atmosphere. The reaction was quenched by the addition of water (20 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 50% to 65%; detector, UV 254 nm to afford (3*S*,4*R*)-4-({5-chloro-6-cyano-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (13 mg, 40%) as a yellow green solid. MS ESI calculated for $C_{20}H_{23}ClFN_5O_3$ $[M + H]^+$, , 436.15, found 436.00. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 5.45 (brs, 1H), 5.22-5.04 (m, 1H), 4.99-4.94 (m, 1H), 4.06-3.96 (m, 2H), 3.84-3.80 (m, 1H), 3.56-3.50 (m, 1H), 3.44-3.39 (m, 1H), 2.88-2.70 (m, 3H), 2.57-2.51 (m, 1H), 2.38-2.31 (m, 1H), 2.24-2.19 (m, 1H), 2.08-2.05 (m, 3H), 2.03-1.97 (m, 1H), 1.48-1.40 (m, 1H), 1.30 (dd, *J* = 23.6, 6.0 Hz, 3H).

Example 5:

5-chloro-7-[1-(1-fluoroethyl)cyclobutyl]-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00209] A mixture of (3*S*,4*R*)-4-({5-chloro-6-cyano-7-[1-(1-fluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (15 mg, 0.034 mmol) and K_2CO_3 (14.27 mg, 0.102 mmol) in MeOH (1 mL) was stirred for 30 min at 0 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford 5-chloro-7-[1-(1-fluoroethyl)cyclobutyl]-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (10.6 mg, 77%) as an off-white solid. MS ESI calculated for $C_{18}H_{21}ClFN_5O_2$ $[M + H]^+$, , 394.14, found 394.15. ^1H NMR (400 MHz, DMSO-*d*$_6$) δ 8.96 (s, 1H), 7.40 (brs, 1H), 5.31-5.06 (m, 1H), 4.94 (brs, 1H), 3.84-3.80 (m, 2H), 3.53-3.49 (m, 2H), 3.34-3.30 (m, 1H), 3.07-3.02 (m, 1H), 2.81-2.64 (m, 3 H), 2.42-2.33 (m, 1H), 2.20-1.96 (m, 2H), 1.91-1.85 (m, 1H), 1.48-1.38 (m, 1H), 1.19 (dd, *J* = 24.0, 6.0 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ -177.98 (1F).

Example 6:

5-chloro-7-[1-(1,1-difluoroethyl)cyclobutyl]-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: benzyl cyclobutanecarboxylate

[00210] To a stirred mixture of cyclobutanecarboxylic acid (100 g, 998.831 mmol, 1 equiv) and $KHCO_3$ (200 g, 1997.662 mmol) in DMF (1 L) was added BnBr (118.8 mL, 998.831 mmol) at room temperature. The resulting mixture was stirred for 16 h at room temperature. The reaction was quenched with water (10 L). The resulting mixture was extracted with EtOAc (3 x 2 L). The combined organic layers were washed with brine (3 x 2 L), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (50/1) to afford benzyl cyclobutanecarboxylate (121 g, 57%) as colorless oil. $C_{12}H_{14}O_2$, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41-7.32 (m, 5H), 5.14 (s, 2H), 3.23-3.17 (m, 1H), 2.38-2.18 (m, 4H), 2.03-1.90 (m, 2H).

Step 2: benzyl 1-(1-hydroxyethyl)cyclobutane-1-carboxylate

[00211] To a stirred mixture of bis(propan-2-yl)amine (38.6 mL, 273.330 mmol) in THF (120 mL) was added *n*-BuLi (100.9 mL, 2.5 M, 252.300 mmol) dropwise at -78 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0 °C under nitrogen atmosphere. To this was added benzyl cyclobutanecarboxylate (40.0 g, 210.259 mmol) dropwise over 30 min at -78 °C. The resulting mixture was stirred for 1 h at -78 °C. To this was added acetaldehyde (84.1 mL, 420.518 mmol) dropwise over 30 min at -78 °C. The resulting mixture was stirred for additional 16 h at room temperature. The reaction was quenched by the addition of *sat.* NH_4Cl (aq.) (800 mL) at 0 °C. The resulting mixture was extracted with EtOAc/PE (1/1) (2 x 1000 mL). The combined organic layers were washed with brine (1000 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1). The resulting crude product was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% TFA), 50% to 95%; detector, UV 254 nm to afford benzyl 1-(1-hydroxyethyl)cyclobutane-1-carboxylate (10.3 g, 19%) as yellow oil. MS ESI calculated for $C_{14}H_{18}O_3$ $[M + H]^+$, 235.13, found 235.25. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40-7.36 (m, 5H), 5.24-5.20 (m, 2H), 4.02 (q, J = 6.4 Hz, 1H), 2.70 (brs, 1H), 2.53-2.49 (m, 1H), 2.34-2.28 (m, 2H), 2.00-1.93 (m, 3H), 1.16 (d, J = 6.4 Hz, 3H).

Step 3: benzyl 1-acetylcyclobutane-1-carboxylate

[00212] To a stirred solution of oxalic dichloride (10.9 mL, 128.043 mmol) in DCM (100 mL) was added DMSO (15 mL) dropwise at -78 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at -78 °C. To this was added benzyl 3-hydroxy-2,2-dimethylpropanoate (10 g, 42.681 mmol) dropwise over 30 min at -78 °C. The resulting mixture was stirred for additional 1 h at -78 °C. To this was added Et_3N (59 mL, 426.810 mmol) dropwise over 30 min at -78 °C. The mixture was allowed to warm up to room temperature. The resulting mixture was stirred for

additional 16 h at room temperature. The reaction was diluted with water (100 mL). The resulting mixture was extracted with DCM (3 x 100 mL). The combined organic layers were washed with brinw (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (7/1) to afford benzyl 1-acetylcyclobutane-1-carboxylate (7.0 g, 71%) as yellow oil. MS ESI calculated for $C_{14}H_{16}O_3$ $[M + H]^+$, 233.11 found 232.95. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.44-7.31 (m, 5H), 5.21 (s, 2H), 2.53-2.48 (m, 4H), 2.07 (s, 3H), 2.00-1.96 (m, 1H), 1.90-1.83 (m, 1H).

Step 4: enzyl 1-(1,1-difluoroethyl)cyclobutane-1-carboxylate

[00213] To benzyl 1-acetylcyclobutane-1-carboxylate (3.8 g, 16.360 mmol) was added DAST (20 mL) at 0 °C. The resulting mixture was stirred for 2 days at room temperature. The reaction was quenched with EtOH (50 mL) at 0 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (8/1) to afford benzyl 1-(1,1-difluoroethyl)cyclobutane-1-carboxylate (2.5 g, 60%) as colorless oil. MS ESI calculated for $C_{14}H_{16}F_2O_2$ $[M + H]^+$, 255.11 found 255.05. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.42-7.34 (m, 5H), 5.23 (s, 2H), 2.53-2.42 (m, 4H), 1.99-1.91 (m, 2H), 1.59 (t, J = 20.0 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -99.00 (2F).

Step 5: 1-(1,1-difluoroethyl)cyclobutane-1-carboxylic acid

[00214] To a solution of benzyl 1-(1,1-difluoroethyl)cyclobutane-1-carboxylate (3.0 g, 11.798 mmol) in 30 mL MeOH was added Pd/C (10%, 2.00 g) under nitrogen atmosphere. The mixture was hydrogenated for 1 h at room temperature under hydrogen atmosphere. The solid was filtered out and washed with DCM (3 x 50 mL). The filtrate was concentrated under reduced pressure to afford 1-(1,1-difluoroethyl)cyclobutane-1-carboxylic acid (1.4 g, 72%) as colorless oil. MS ESI calculated for $C_7H_{10}F_2O_2$ $[M + H]^+$, 165.06 found 165.10. ^1H NMR (400 MHz, DMSO-d_6) δ 13.08 (s, 1H), 2.47-2.15 (m, 4H), 1.92-1.71 (m, 2H), 1.62 (t, J = 19.2 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -97.34 (2F).

Step 6: 1,3-dioxoisoindol-2-yl 1-(1,1-difluoroethyl)cyclobutane-1-carboxylate

[00215] To a stirred solution of 1-(1,1-difluoroethyl)cyclobutane-1-carboxylic acid (2.20 g, 13.402 mmol) and *N*-hydroxyphthalimide (2.40 g, 14.742 mmol), DMAP (0.16 g, 1.340 mmol) in DCM (30 mL) was added *N*,*N*'-diisopropylcarbodiimide (1.86 g, 14.742 mmol) at 0 °C. The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was purified by silica gel column chromatography, eluted with PE/EtOAc (6/1) to afford 1,3-dioxoisoindol-2-yl 1-(1,1-difluoroethyl)cyclobutane-1-carboxylate (4.00 g, 96%) as a white solid. $C_{15}H_{13}F_2NO_4$, ^1H NMR (400 MHz, Chloroform-*d*) δ 7.94-7.85 (m, 2H), 7.85-7.74 (m, 2H), 2.80-2.56 (m, 4H), 2.23-1.97 (m, 2H), 1.81 (t, J = 18.8 Hz, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -99.56 (2F).

Step 7: 2,4,5-trichloro-7-[1-(1,1-difluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazine

[00216] To a stirred solution of 1,3-dioxoisoindol-2-yl 1-(1,1-difluoroethyl)cyclobutane-1-carboxylate (2 g, 6.467 mmol) and 2,4,5-trichloropyrrolo[2,1-*f*][1,2,4]triazine (2.88 g, 12.934 mmol) in DMA (60 mL) were added $Ir[dF(CF_3)PPy]_2(dtbpy)PF_6$ (0.15 g, 0.129 mmol) and TFA (2.21 g, 19.401 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was irradiated with Blue LED for 16 h at room temperature under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 70% to 90%; detector, UV 254 nm to afford 2,4,5-trichloro-7-[1-(1,1-difluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazine (187 mg, 8%) as a yellow solid. MS ESI calculated for $C_{12}H_{10}Cl_3F_2N_3$ $[M + H]^+$, 339.99 found 340.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 6.84 (s, 1H), 2.86-2.74 (m, 2H), 2.70-2.64 (m, 2H), 2.19-2.13 (m, 1H), 1.94-1.88 (m, 1H), 1.51 (t, J = 18.8 Hz, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -100.27 (2F).

Step 8: 2,5-dichloro-7-[1-(1,1-difluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazine

[00217] To a stirred solution of 2,4,5-trichloro-7-[1-(1,1-difluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazine (187 mg, 0.549 mmol) in THF (5 mL) and *i*-PrOH (0.25 mL) was added $NaBH_4$ (33 mg, 0.872 mmol) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (3 x 10 mL). The filtrate was concentrated under reduced pressure. To the residue was added DCM (5 mL) and DDQ (150 mg, 0.661 mmol) at room temperature. The resulting mixture was stirred for additional 1 h at room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (3 x 20 mL). The combined filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (9/1) to afford 2,5-dichloro-7-[1-(1,1-difluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazine (160 mg, 95%) as a light yellow solid. MS ESI calculated for $C_{12}H_{11}Cl_2F_2N_3$ $[M + H]^+$, 306.03 found 305.90. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.82 (s, 1H), 6.83 (s, 1H), 2.87-2.78 (m, 2H), 2.76-2.65 (m, 2H), 2.23-2.11 (m, 1H), 1.98-1.89 (m, 1H), 1.51 (t, J = 18.8 Hz, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -100.41 (2F).

Step 9:(3*S*,4*R*)-4-({5-chloro-7-[1-(1,1-difluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol

[00218] To a stirred solution of 2,5-dichloro-7-[1-(1,1-difluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazine (160 mg, 0.523 mmol) and (3*S*,4*R*)-4-aminooxan-3-ol hydrochloride (120 mg, 0.781 mmol) in NMP (3 mL) was added DIEA (270 mg, 2.089 mmol). The resulting mixture was stirred for 16 h at 80 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water

(0.1% formic acid), 40% to 55%; detector, UV 254 nm to afford (3*S*,4*R*)-4-({5-chloro-7-[1-(1,1-difluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol (90 mg, 44%) as a yellow solid. MS ESI calculated for $C_{17}H_{21}ClF_2N_4O_2$ $[M + H]^+$, 387.13 found 386.95. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.59 (s, 1H), 6.48 (s, 1H), 5.09 (brs, 1H), 4.09-4.05 (m, 1H), 3.99-.394 (m, 1H), 3.67-3.63 (m, 2H), 3.51-3.46 (m, 1H), 3.42 -3.36 (m, 1H), 3.28 -3.18 (m, 1H), 2.78-2.69 (m, 3H), 2.65-2.58 (m, 1H), 2.20-2.10 (m, 1H), 2.08-2.01 (m, 1H), 1.95-1.85 (m, 1H), 1.69-1.58 (m, 1H), 1.46 (t, *J* = 18.8 Hz, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -100.19 (2F).

Step 10: (3*S*,4*R*)-4-({5-chloro-7-[1-(1,1-difluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00219] To a stirred solution of (3*S*,4*R*)-4-({5-chloro-7-[1-(1,1-difluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol (90 mg, 0.233 mmol) and Ac_2O (38.00 mg, 0.373 mmol) in DCM (3 mL) was added TEA (141 mg, 1.393 mmol) at room temperature. The resulting mixture was stirred for 16 h at 50 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford (3*S*,4*R*)-4-({5-chloro-7-[1-(1,1-difluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (96 mg, 96%) as yellow oil. MS ESI calculated for $C_{19}H_{23}ClF_2N_4O_3$ $[M + H]^+$, 429.14 found 429.05.

Step 11: (3*S*,4*R*)-4-({5-chloro-7-[1-(1,1-difluoroethyl)cyclobutyl]-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00220] To a stirred solution of (3*S*,4*R*)-4-({5-chloro-7-[1-(1,1-difluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (96 mg, 0.224 mmol) in DMF (2 mL) was added I_2 (227.26 mg, 0.896 mmol) at room temperature. The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 40% to 60%; detector, UV 254 nm to afford (3*S*,4*R*)-4-({5-chloro-7-[1-(1,1-difluoroethyl)cyclobutyl]-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (70 mg, 56%) as a yellow solid. MS ESI calculated for $C_{19}H_{22}ClF_2IN_4O_3$ $[M + H]^+$, 555.04 found 555.00.

Step 12: (3*S*,4*R*)-4-({5-chloro-6-cyano-7-[1-(1,1-difluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00221] To a stirred solution of (3*S*,4*R*)-4-({5-chloro-7-[1-(1,1-difluoroethyl)cyclobutyl]-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (70 mg, 0.126 mmol) and $Zn(CN)_2$ (12 mg, 0.184 mmol) in DMF (2 mL) was added $Pd(PPh_3)_4$ (15 mg, 0.013 mmol) at room temperature. The resulting mixture was stirred for 2 h at 130 °C under nitrogen

atmosphere. The mixture was allowed to cool down to room temperature. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 40% to 55%; detector, UV 254 nm to afford (3*S*,4*R*)-4-({5-chloro-6-cyano-7-[1-(1,1-difluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (40 mg, 69%) as a yellow solid. MS ESI calculated for $C_{20}H_{22}ClF_2N_5O_3$ $[M + H]^+$, 454.14 found 454.05.

Example 6:

5-chloro-7-[1-(1,1-difluoroethyl)cyclobutyl]-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00222] To a stirred solution of (3*S*,4*R*)-4-({5-chloro-6-cyano-7-[1-(1,1-difluoroethyl)cyclobutyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (40 mg, 0.088 mmol) in MeOH (2 mL) was added K_2CO_3 (36.54 mg, 0.264 mmol) at room temperature. The resulting mixture was stirred for 30 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 35% to 50%; detector, UV 254 nm. The crude product was purified by Prep-HPLC with the following conditions (Column: XselectCSH Prep Fluoro-Phenyl OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: water (0.1% formic acid), Mobile Phase B: CH_3CN; Flow rate: 60 mL/min; Gradient: 36% B to 43% B; Wave Length: 254nm/220nm nm to afford 5-chloro-7-[1-(1,1-difluoroethyl)cyclobutyl]-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (10.4 mg, 28%) as a white solid. MS ESI calculated for $C_{18}H_{20}ClF_2N_5O_2$ $[M + H]^+$, 412.13 found 411.95. ^1H NMR (400 MHz, DMSO-d_6) δ 8.99 (s, 1H), 7.45 (d, J = 6.8 Hz, 1H), 4.94 (d, J = 4.8 Hz, 1H), 3.85-3.77 (m, 2H), 3.55-3.50 (m, 2H), 3.35-3.30 (m, 1H), 3.09-3.04 (m, 1H), 2.90-2.84 (m, 2H), 2.70-2.65 (m, 2H), 2.15-2.00 (m, 2H), 1.98-1.92 (m, 1H), 1.58 (t, J = 19.2 Hz, 3H), 1.47-1.41 (m, 1H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -73.45 (2F).

Example 7:

5-chloro-7-{3-fluorobicyclo[1.1.1]pentan-1-yl}-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: 1,3-dioxoisoindol-2-yl 3-fluorobicyclo[1.1.1]pentane-1-carboxylate

[00223] A solution of 3-fluorobicyclo[1.1.1]pentane-1-carboxylic acid (1 g, 7.685 mmol), *N*-hydroxyphthalimide (1 g, 8.454 mmol) and DMAP (0.09 g, 0.768 mmol) in DCM (10 mL) was stirred for 5 min at 0 °C. To this was added DIC (1.07 g, 8.454 mmol) at 0 °C. The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (5 x 40 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to

afford 1,3-dioxoisoindol-2-yl 3-fluorobicyclo[1.1.1]pentane-1-carboxylate (1.7 g, 80%) as a white solid. MS ESI calculated for $C_{14}H_{10}FNO_4$ $[M + H]^+$, 276.06, found 276.05. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.91 (d, *J* = 5.6 Hz, 2H), 7.82 (d, *J* = 5.6 Hz, 2H), 2.63 (s, 6H).

Step 2: 2,4,5-trichloro-7-{3-fluorobicyclo[1.1.1]pentan-1-yl}pyrrolo[2,1-*f*][1,2,4]triazine

[00224] To a stirred solution of 1,3-dioxoisoindol-2-yl 3-fluorobicyclo[1.1.1]pentane-1-carboxylate (1.9 g, 6.903 mmol), 2,4,5-trichloropyrrolo[2,1-*f*][1,2,4]triazine (3.07 g, 13.806 mmol) and TFA (2.36 g, 20.709 mmol) in DMA (58 mL) was added $Ir[dF(CF_3)PPy]_2(dtbpy)PF_6$ (0.16 g, 0.138 mmol) under nitrogen atmosphere. The reaction mixture was irradiated with Blue LED for 16 h at 60 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 70% to 85%; detector, UV 254 nm to afford 2,4,5-trichloro-7-{3-fluorobicyclo[1.1.1]pentan-1-yl}pyrrolo[2,1-*f*][1,2,4]triazine (160 mg, 7%) as a light yellow solid. MS ESI calculated for $C_{11}H_7Cl_3FN_3$ $[M + H]^+$, 305.97, found 305.90. ^1H NMR (400 MHz, Chloroform-*d*) δ 6.74 (s, 1H), 2.61 (d, *J* = 2.4 Hz, 6H).

Step 3: 2,5-dichloro-7-{3-fluorobicyclo[1.1.1]pentan-1-yl}pyrrolo[2,1-*f*][1,2,4]triazine

[00225] A solution of 2,4,5-trichloro-7-{3-fluorobicyclo[1.1.1]pentan-1-yl}pyrrolo[2,1-*f*][1,2,4]triazine (60 mg, 0.196 mmol) and $NaBH_4$ (12 mg, 0.314 mmol) in THF (2 mL) and *i*-PrOH (0.1 mL) was stirred for 1 h at room temperature under nitrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with DCM (5 x 30 mL). The filtrate was concentrated under reduced pressure. The residue was dissolved in DCM (2 mL). To this was added DDQ (67 mg, 0.294 mmol). The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (3 x 30 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 50% to 70%; detector, UV 254 nm to afford 2,5-dichloro-7-{3-fluorobicyclo[1.1.1]pentan-1-yl}pyrrolo[2,1-*f*][1,2,4]triazine (41 mg, 76%) as a light yellow solid. MS ESI calculated for $C_{11}H_8Cl_2FN_3$ $[M + H]^+$, 272.01, found 271.85. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.80 (s, 1H), 6.72 (s, 1H), 2.62 (d, *J* = 2.4 Hz, 6H).

Step 4: (3*S*,4*R*)-4-[(5-chloro-7-{3-fluorobicyclo[1.1.1]pentan-1-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol

[00226] A solution of 2,5-dichloro-7-{3-fluorobicyclo[1.1.1]pentan-1-yl}pyrrolo[2,1-*f*][1,2,4]triazine (42 mg, 0.154 mmol), (3*S*,4*R*)-4-aminooxan-3-ol hydrochloride (57 mg, 0.370 mmol) and DIEA (100 mg, 0.770 mmol) in NMP (1 mL) was stirred for 16 h at 80 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 40% to 65%;

detector, UV 254 nm to afford (3*S*,4*R*)-4-[(5-chloro-7-{3-fluorobicyclo[1.1.1]pentan-1-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol (30 mg, 55%) as a light yellow solid. MS ESI calculated for $C_{16}H_{18}ClFN_4O_2$ $[M + H]^+$, 353.11, found 352.95. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.59 (s, 1H), 6.41 (s, 1H), 4.94 (d, *J* = 6.4 Hz, 1H), 4.13-4.09 (m, 1H), 4.06-3.97 (m, 1H), 3.79-3.73 (m, 1H), 3.71-3.68 (m, 1H), 3.55-3.51 (m, 1H), 3.30-2.26 (m, 1H), 2.56 (d, *J* = 2.4 Hz, 6H), 2.17-2.11 (m, 1H), 1.74-1.65 (m, 1H).

Step 5: (3*S*,4*R*)-4-[(5-chloro-7-{3-fluorobicyclo[1.1.1]pentan-1-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate

[00227] A solution of (3*S*,4*R*)-4-[(5-chloro-7-{3-fluorobicyclo[1.1.1]pentan-1-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol (102 mg, 0.289 mmol), Ac_2O (44 mg, 0.433 mmol) and TEA (117 mg, 1.156 mmol) in DCM (2 mL) was stirred for 16 h at 50 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-[(5-chloro-7-{3-fluorobicyclo[1.1.1]pentan-1-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate (103 mg, 90%) as a light yellow solid. MS ESI calculated for $C_{18}H_{20}ClFN_4O_3$ $[M + H]^+$, 395.12, found 395.00.

Step 6: (3*S*,4*R*)-4-[(5-chloro-7-{3-fluorobicyclo[1.1.1]pentan-1-yl}-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate

[00228] A solution of (3*S*,4*R*)-4-[(5-chloro-7-{3-fluorobicyclo[1.1.1]pentan-1-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate (103 mg, 0.261 mmol) and I_2 (265 mg, 1.044 mmol) in DMF (2 mL) was stirred for 16 h at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (40 mL). The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-[(5-chloro-7-{3-fluorobicyclo[1.1.1]pentan-1-yl}-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate (110 mg, 80%) as a light yellow solid. MS ESI calculated for $C_{18}H_{19}ClFIN_4O_3$ $[M + H]^+$, 521.02, found 520.85. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.57 (s, 1H), 5.09 (d, *J* = 7.2 Hz, 1H), 4.97-4.92 (m, 1H), 4.08-3.98 (m, 1H), 3.98-3.86 (m, 2H), 3.64-3.56 (m, 1H), 3.53-3.46 (m, 1H), 2.75 (d, *J* = 3.2 Hz, 6H), 2.44-2.38 (m, 1H), 2.10 (s, 3H), 1.72-1.67 (m, 1H).

Step 7: (3*S*,4*R*)-4-[(5-chloro-6-cyano-7-{3-fluorobicyclo[1.1.1]pentan-1-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate

[00229] A solution of (3*S*,4*R*)-4-[(5-chloro-7-{3-fluorobicyclo[1.1.1]pentan-1-yl}-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate (100 mg, 0.192 mmol), $Zn(CN)_2$ (20 mg, 0.173

mmol) and $Pd(PPh_3)_4$ (22 mg, 0.019 mmol) in DMA (1.5 mL) was stirred for 2 h at 130 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of water (30 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-[(5-chloro-6-cyano-7-{3-fluorobicyclo[1.1.1]pentan-1-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate (44 mg, 54 %) as a light yellow solid. MS ESI calculated for $C_{19}H_{19}ClFN_5O_3$, $[M + H]^+$, 420.12, found 419.90.

Example 7:

5-chloro-7-{3-fluorobicyclo[1.1.1]pentan-1-yl}-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00230] A solution of (3*S*,4*R*)-4-[(5-chloro-6-cyano-7-{3-fluorobicyclo[1.1.1]pentan-1-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate (40 mg, 0.095 mmol) and K_2CO_3 (40 mg, 0.285 mmol) in MeOH (1 mL) was stirred for 30 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford 5-chloro-7-{3-fluorobicyclo[1.1.1]pentan-1-yl}-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (17.3 mg, 45%) as a white solid. MS ESI calculated for $C_{17}H_{17}ClFN_5O_2$ $[M + H]^+$, 378.11; found 377.95. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 5.08 (d, *J* = 6.8 Hz, 1H), 4.14-4.08 (m, 1H), 4.03-3.99 (m, 1H), 3.83-3.79 (m, 1H), 3.75-3.67 (m, 1H), 3.58-3.53 (m, 1H), 3.34-3.26 (m, 1H), 2.73 (d, *J* = 2.0 Hz, 6H), 2.30-2.22 (m, 1H), 1.74-1.64 (m, 1H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -145.53 (1F).

Example 8:

7-[3-(1,1-difluoroethyl)oxetan-3-yl]-5-fluoro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: 1,3-dioxoisoindol-2-yl 3-(1,1-difluoroethyl)oxetane-3-carboxylate

[00231] To a mixture of 3-(1,1-difluoroethyl)oxetane-3-carboxylic acid (780 mg, 4.695 mmol) in DCM (8 mL) were added *N*-hydroxyphthalimide (843 mg, 5.165 mmol) and DMAP (58 mg, 0.470 mmol), followed by the addition of DIC (652 mg, 5.165 mmol) at 0 °C. The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (2 x 5 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 1,3-dioxoisoindol-2-yl 3-(1,1-difluoroethyl)oxetane-3-carboxylate (1.3 g, 80%) as an off-white solid. $C_{14}H_{11}F_2NO_5$, ^1H NMR (400 MHz, Chloroform-*d*) δ 7.97-7.92 (m, 2H), 7.88-7.84 (m,

2H), 5.15-5.13 (m, 2H), 5.03-4.97 (m, 2H), 1.89 (t, J = 18.4 Hz, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -99.96 (2F).

Step 2: 2,4-dichloro-7-[3-(1,1-difluoroethyl)oxetan-3-yl]-5-fluoropyrrolo[2,1-*f*][1,2,4]triazine

[00232] A mixture of 2,4-dichloro-5-fluoropyrrolo[2,1-*f*][1,2,4]triazine (821 mg, 3.984 mmol), 1,3-dioxoisoindol-2-yl 3-(1,1-difluoroethyl)oxetane-3-carboxylate (620 mg, 1.992 mmol), Ir[dF(CF$_3$)PPy]$_2$(dtbpy)PF$_6$ (45 mg, 0.040 mmol) and TFA (0.4 mL, 5.924 mmol) in DMA (18.6 mL). The reaction mixture was irradiated with Blue LED for 16 h at room temperature under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH$_3$CN in water (0.1% formic acid), 10% to 70%; detector, UV 254 nm to afford 2,4-dichloro-7-[3-(1,1-difluoroethyl)oxetan-3-yl]-5-fluoropyrrolo[2,1-*f*][1,2,4]triazine (45 mg, 6%) as yellow oil. MS ESI calculated for $C_{11}H_8Cl_2F_3N_3O$ $[M + H]^+$, 326.00, found 326.20. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.55 (s, 1H), 5.11 (s, 4H), 1.67-1.62 (m, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -100.57 (2F), -149.92 (1F).

Step 3: 2-chloro-7-[3-(1,1-difluoroethyl)oxetan-3-yl]-5-fluoropyrrolo[2,1-*f*][1,2,4]triazine

[00233] To a stirred mixture of 2,4-dichloro-7-[3-(1,1-difluoroethyl)oxetan-3-yl]-5-fluoropyrrolo[2,1-*f*][1,2,4]triazine (40 mg, 0.123 mmol) in *i*-PrOH (50 uL) and THF (1 mL) was added NaBH$_4$ (9.3 mg, 0.246 mmol) at room temperature. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (3 x 10 mL). The filtrate was concentrated under reduced pressure. The resulting mixture was concentrated under reduced pressure. To the resudue was added DDQ (42 mg, 0.184 mmol) in DCM (1 mL). The resulting mixture was stirred for additional 1 h at room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (3 x 15 mL). The filtrate was concentrated under reduced pressure. The resulting mixture was diluted with sat. NaHCO$_3$ (30 mL). The resulting mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over anhydrous Na$_2$SO$_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 2-chloro-7-[3-(1,1-difluoroethyl)oxetan-3-yl]-5-fluoropyrrolo[2,1-*f*][1,2,4]triazine (22 mg, 55%) as a yellow solid. MS ESI calculated for $C_{11}H_9ClF_3N_3O$ $[M + H]^+$, 292.04, found 292.00. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.90 (s, 1H), 6.53 (s, 1H), 5.12 (s, 4H), 1.64 (t, J = 18.8 Hz, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -100.81 (2F), -156.22 (1F).

Step 4: (3*S*,4*R*)-4-({7-[3-(1,1-difluoroethyl)oxetan-3-yl]-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol

[00234] A mixture of 2-chloro-7-[3-(1,1-difluoroethyl)oxetan-3-yl]-5-fluoropyrrolo[2,1-*f*][1,2,4]triazine (20 mg, 0.069 mmol), (3*S*,4*R*)-4-aminooxan-3-ol hydrochloride (53 mg, 0.345 mmol) and DIEA (72 uL, 0.411 mmol) in NMP (1 mL) was stirred for 16 h at 80 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 10% to 70%; detector, UV 254 nm to afford (3*S*,4*R*)-4-({7-[3-(1,1-difluoroethyl)oxetan-3-yl]-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol (10 mg, 35%) (crude) as yellow oil. MS ESI calculated for $C_{16}H_{19}F_3N_4O_3$ $[M + H]^+$, 373.14, found 373.15.

Step 5: (3*S*,4*R*)-4-({7-[3-(1,1-difluoroethyl)oxetan-3-yl]-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00235] A mixture of (3*S*,4*R*)-4-({7-[3-(1,1-difluoroethyl)oxetan-3-yl]-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol (10 mg, 0.027 mmol), Ac_2O (4 uL, 0.041 mmol) and TEA (19 uL, 0.135 mmol) in DCM (0.5 mL) was stirred for 16 h at 50 °C. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (3 mL) at 0 °C. The resulting mixture was extracted with DCM (2 x 3 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-({7-[3-(1,1-difluoroethyl)oxetan-3-yl]-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (10 mg, 80%) as a yellow solid. MS ESI calculated for $C_{18}H_{21}F_3N_4O_4$ $[M + H]^+$, 415.15, found 415.25.

Step 6: (3*S*,4*R*)-4-({7-[3-(1,1-difluoroethyl)oxetan-3-yl]-5-fluoro-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00236] A mixture of (3*S*,4*R*)-4-({7-[3-(1,1-difluoroethyl)oxetan-3-yl]-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (10 mg, 0.024 mmol) and I_2 (49 mg, 0.192 mmol) in DMF (0.5 mL) was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (10 mL) at room temperature. The resulting mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-({7-[3-(1,1-difluoroethyl)oxetan-3-yl]-5-fluoro-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (13 mg, 74%) as a yellow solid. MS ESI calculated for $C_{18}H_{20}F_3IN_4O_4$ $[M + H]^+$, 541.05, found 541.00.

[00237] Step 7: (3*S*,4*R*)-4-({6-cyano-7-[3-(1,1-difluoroethyl)oxetan-3-yl]-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00238] A mixture of (3*S*,4*R*)-4-({7-[3-(1,1-difluoroethyl)oxetan-3-yl]-5-fluoro-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (13 mg, 0.024 mmol), $Zn(CN)_2$ (3.4 mg, 0.029 mmol) and $Pd(PPh_3)_4$ (2.8 mg, 0.002 mmol) in DMA (0.5 mL) was stirred for 1 h at 130 °C under nitrogen atmosphere. The reaction was quenched by the addition of water (10 mL) at room temperature. The resulting mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (2/1) to afford (3*S*,4*R*)-4-({6-cyano-7-[3-(1,1-difluoroethyl)oxetan-3-yl]-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (8 mg, 68%) as an off-white solid. MS ESI calculated for $C_{19}H_{20}F_3N_5O_4$ $[M + H]^+$, 440.15, found 440.25.

[00239] Example 8: 7-[3-(1,1-difluoroethyl)oxetan-3-yl]-5-fluoro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00240] A solution of (3*S*,4*R*)-4-({6-cyano-7-[3-(1,1-difluoroethyl)oxetan-3-yl]-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (3.5 mg, 0.008 mmol) and K_2CO_3 (3.30 mg, 0.024 mmol) in MeOH (0.5 mL) was stirred for 30 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 30% to 50%; detector, UV 254 nm to afford 7-[3-(1,1-difluoroethyl)oxetan-3-yl]-5-fluoro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (1.2 mg, 37%) as a light yellow solid. MS ESI calculated for $C_{17}H_{18}F_3N_5O_3$ $[M + H]^+$, 398.14; found 398.05. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.79 (s, 1H), 5.32-5.27 (m, 2H), 5.08-5.02 (m, 3H), 4.06-3.96 (m, 2H), 3.69-3.63 (m, 2H), 3.53-3.47 (m, 1H), 3.29-3.23 (m, 1H), 2.19-2.13 (m, 1H), 1.82 (t, J = 18.8 Hz, 3H), 1.68-1.63 (m, 1H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -99.66 (2F), -151.86 (1F).

Example 9:

5-fluoro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*S*,4*R*)-4-{[5-fluoro-7-(2-methylprop-1-en-1-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol

[00241] A mixture of (3*S*,4*R*)-4-({7-bromo-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol (200 mg, 0.604 mmol), 4,4,5,5-tetramethyl-2-(2-methylprop-1-en-1-yl)-1,3,2-dioxaborolane (165 mg, 0.906 mmol), $Pd(dppf)Cl_2.CH_2Cl_2$ (49.20 mg, 0.060 mmol) and Cs_2CO_3 (393 mg, 1.208 mmol) in 1,4-dioxane (5 mL) and H_2O (1 mL) was stirred for 2 h at 100 °C under a nitrogen atmosphere. The resulting mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was

concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[5-fluoro-7-(2-methylprop-1-en-1-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (180 mg, 97%) as a light yellow solid. MS ESI calculated for $C_{15}H_{19}FN_4O_2$ $[M + H]^+$, 307.15, found 307.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.59 (s, 1H), 6.51 (s, 1H), 6.37 (s, 1H), 4.98 (brs, 1H), 4.17-4.04 (m, 2H), 3.81-3.76 (m, 1H), 3.67-3.61 (m, 1H), 3.53-3.48 (m, 1H), 3.28-3.22 (m, 1H), 2.08-2.01 (m, 4H), 1.98 (s, 3H), 1.72-1.64 (m, 1H).

Step 2: (3*S*,4*R*)-4-{[5-fluoro-7-(2-methylprop-1-en-1-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00242] To a stirred solution of (3*S*,4*R*)-4-{[5-fluoro-7-(2-methylprop-1-en-1-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (280 mg, 0.914 mmol) in DCM (5 mL) were added Ac_2O (140 mg, 1.371 mmol) and TEA (370 mg, 3.656 mmol) at room temperature. The resulting mixture was stirred for 16 h at 50 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[5-fluoro-7-(2-methylprop-1-en-1-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (290 mg, 91%) as a yellow solid. MS ESI calculated for $C_{17}H_{21}FN_4O_3$ $[M + H]^+$, 349.16, found 349.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.54 (s, 1H), 6.69 (s, 1H), 6.41 (s, 1H), 5.21 (brs, 1H), 5.03-4.99 (m, 1H), 4.09-4.04 (m, 2H), 3.98-3.93 (m, 1H), 3.67-3.62 (m, 1H), 3.53-3.47 (m, 1H), 2.46-2.41 (m, 1H), 2.14-2.04 (m, 6H), 2.01 (s, 3H), 1.72-1.64 (m, 1H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -159.69 (1F).

Step 3: (3*S*,4*R*)-4-{[7-(1,2-dihydroxy-2-methylpropyl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00243] A solution of (3*S*,4*R*)-4-{[5-fluoro-7-(2-methylprop-1-en-1-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (430 mg, 1.234 mmol), NMO (289 mg, 2.468 mmol) and $K_2OsO_4.2H_2O$ (45 mg, 0.123 mmol,) in acetone (7.5 mL) and H_2O (2.5 mL) was stirred for 2 h at room temperature. The reaction was quenched by the addition of $Na_2S_2O_3$ (10 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous $Na_2SO/$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[7-(1,2-dihydroxy-2-methylpropyl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (470 mg, 99%) as a yellow solid. MS ESI calculated for $C_{17}H_{23}FN_4O_5$ $[M + H]^+$, 383.17, found 383.95. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.61 (d, *J* = 3.2 Hz, 1H), 6.34 (d, *J* = 9.6 Hz, 1H), 5.09-4.87 (m, 2H), 4.04-3.86 (m, 4H), 3.73-3.67 (m, 1H), 3.57-3.51 (m, 1H), 2.40-2.35 (m, 1H), 2.11 (d, *J*

= 5.6 Hz, 3H), 1.78-1.60 (m, 1H), 1.37 (d, *J* = 8.0 Hz, 3H), 1.20 (s, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -159.15 (1F).

Step 4: (3*S*,4*R*)-4-{[5-fluoro-7-(2-hydroxy-2-methylpropanoyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00244] A solution of (3*S*,4*R*)-4-{[7-(1,2-dihydroxy-2-methylpropyl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (460 mg, 1.203 mmol) and IBX (673 mg, 2.406 mmol) in CH_3CN (10 mL) was stirred for 2 h at 80 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[5-fluoro-7-(2-hydroxy-2-methylpropanoyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (325 mg, 71%) as a yellow solid. MS ESI calculated for $C_{17}H_{21}FN_4O_5$ $[M + H]^+$, 381.15, found 381.20. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.82 (s, 1H), 6.98 (s, 1H), 5.51 (d, *J* = 8.0 Hz, 1H), 4.96-4.90 (m, 1H), 4.11-3.89 (m, 3H), 3.59-3.54 (m, 1H), 3.49-3.34 (m, 1H), 2.40-2.31 (m, 1H), 2.05 (s, 3H), 1.79-1.66 (m, 1H), 1.57 (d, *J* = 7.2 Hz, 6H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -159.03 (1F).

Step 5: (3*S*,4*R*)-4-{[5-fluoro-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00245] To a stirred solution of (3*S*,4*R*)-4-{[5-fluoro-7-(2-hydroxy-2-methylpropanoyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (310 mg, 0.815 mmol) in DCM (10 mL) was added DAST (525 mg, 3.260 mmol) in DCM (10 mL) dropwise at -30 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at -30 °C under nitrogen atmosphere. The reaction was quenched by the addition of $NaHCO_3$ (20 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford (3*S*,4*R*)-4-{[5-fluoro-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (40 mg, 12%) as yellow oil. MS ESI calculated for $C_{17}H_{20}F_4N_4O_3$ $[M + H]^+$, 405.15, found 405.20. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.73 (s, 1H), 6.48 (s, 1H), 5.18 (d, *J* = 7.2 Hz, 1H), 4.97-4.89 (m, 1H), 4.06-4.01 (m, 1H), 3.99-3.88 (m, 2H), 3.56-3.51 (m, 1H), 3.45-3.40 (m, 1H), 2.51-2.41 (m, 1H), 2.06 (s, 3H), 1.70-1.61 (m, 1H), 1.58 (d, *J* = 6.4 Hz, 3H), 1.53 (d, *J* = 6.4 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -106.86--103.36 (2F), -152.81 (1F), -161.36 (1F).

Step 6: (3*S*,4*R*)-4-{[5-fluoro-6-iodo-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00246] A solution of (3*S*,4*R*)-4-{[5-fluoro-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (40 mg, 0.099 mmol) and I_2 (200 mg, 0.792 mmol)

in DMF (2 mL) was stirred for 48 h at 80 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: column, C18; mobile phase, CH_3CN in water (0.1% formic acid), 20% to 70%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-fluoro-6-iodo-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (12 mg, 22%) as a yellow solid. MS ESI calculated for $C_{17}H_{19}F_4IN_4O_3$ $[M + H]^+$, 531.04, found 530.85.

Step 7: (3*S*,4*R*)-4-{[6-cyano-5-fluoro-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00247] To a stirred solution of (3*S*,4*R*)-4-{[5-fluoro-6-iodo-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (10 mg, 0.019 mmol) and $Zn(CN)_2$ (3 mg, 0.028 mmol) in DMF (0.5 mL) was added $Pd(PPh_3)_4$ (2 mg, 0.002 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 130 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: column, C18; mobile phase, CH_3CN in water (0.1% formic acid), 20% to 65%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[6-cyano-5-fluoro-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (4 mg, 49%) as a yellow solid. MS ESI calculated for $C_{18}H_{19}F_4N_5O_3$ $[M + H]^+$, 430.14, found 430.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.82 (s, 1H), 5.51 (d, $J = 6.8$ Hz, 1H), 4.96-4.92 (m, 1H), 4.11-3.93 (m, 2H), 3.92-3.80 (m, 1H), 3.53-3.48 (m, 1H), 3.44-3.38 (m, 1H), 2.48-2.39 (m, 1H), 2.07 (s, 3H), 1.70-1.54 (m, 7H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -105.86--107.71 (2F), -152.55 (1F), -153.01 (1F).

Example 9: 5-fluoro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00248] A mixture of (3*S*,4*R*)-4-{[6-cyano-5-fluoro-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (4 mg, 0.009 mmol) and K_2CO_3 (4 mg, 0.027 mmol) in MeOH (0.5 mL) was stirred for 30 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: column, C18; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford 5-fluoro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (2.6 mg, 71%) as a white solid. MS ESI calculated for $C_{16}H_{17}F_4N_5O_2$ $[M + H]^+$, 388.13, found 387.90. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.83 (s, 1H), 5.17 (brs, 1H), 4.10-3.94 (m, 2H), 3.81-3.63 (m, 2H), 3.53-3.46 (m, 1H), 3.28-3.20 (m, 1H), 3.14-3.08 (m, 1H), 2.20-2.11 (m, 1H), 1.72-1.49 (m, 7H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -105.77--107.73 (2F), -152.45 (1F), -152.63 (1F).

Example 10:

5-(difluoromethyl)-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH = 70/30, 1st peak)

Example 11:

5-(difluoromethyl)-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH = 70/30, 2nd peak)

Step 1: (3*S*,4*R*)-4-{[6-cyano-7-(3-fluoro-3-methylbutan-2-yl)-5-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00249] To a stirred solution of (3*S*,4*R*)-4-{[6-cyano-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (160 mg, 0.411 mmol) in DMF (2.5 mL) was added I_2 (417 mg, 1.644 mmol). The reaction mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (5 mL) at room temperature. The aqueous layer was extracted with EtOAc (3 x 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*S*,4*R*)-4-{[6-cyano-7-(3-fluoro-3-methylbutan-2-yl)-5-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (190 mg, 89%) as an off-white solid. MS ESI calculated for $C_{19}H_{23}FIN_5O_3$ $[M + H]^+$, 516.08, found 516.25; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.50 (s, 1H), 5.47 (brs, 1H), 5.04-4.93 (m, 1H), 4.06-3.95 (m, 4H), 3.62-3.59 (m, 1H), 3.50-3.45 (m, 1H), 2.43-2.38 (m, 1H), 2.07 (s, 3H), 1.73-1.61 (m, 4H), 1.50-1.34 (m, 6H).

Step 2: (3*S*,4*R*)-4-{[6-cyano-7-(3-fluoro-3-methylbutan-2-yl)-5-(hydroxymethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00250] To a solution of (3*S*,4*R*)-4-{[6-cyano-7-(3-fluoro-3-methylbutan-2-yl)-5-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (74 mg, 0.144 mmol) in dioxane (10 mL) were added 2nd Generation XPhos Precatalyst (11 mg, 0.014 mmol) and (tributylstannyl)methanol (92 mg, 0.288 mmol). The reaction mixture was stirred for 3 h at 80 °C under nitrogen atmosphere. The reaction was quenched with sat. KF (aq.) (5 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: column, C18; mobile phase, CH_3CN in water (0.1% formic acid), 25% to

60%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[6-cyano-7-(3-fluoro-3-methylbutan-2-yl)-5-(hydroxymethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (25 mg, 41%) as a yellow solid. MS ESI calculated for $C_{20}H_{26}FN_5O_4$ $[M + H]^+$, 420.20, found 420.35. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.93 (s, 1H), 5.20-5.14 (m, 1H), 5.02 (s, 2H), 4.97-4.93 (m, 1H), 4.00-3.91 (m, 4H), 3.63-3.56 (m, 1H), 3.49-3.44 (m, 1H), 2.43-2.39 (m, 1H), 2.07 (d, J = 8.4 Hz, 3H), 1.78-1.66 (m, 1H), 1.62-1.60 (m, 3H), 1.49-1.41 (m, 3H), 1.39-1.33 (m, 3H).

Step 3: (3*S*,4*R*)-4-{[6-cyano-7-(3-fluoro-3-methylbutan-2-yl)-5-formylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00251] A solution of (3*S*,4*R*)-4-{[6-cyano-7-(3-fluoro-3-methylbutan-2-yl)-5-(hydroxymethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (25 mg, 0.060 mmol) and DMP (50 mg, 0.120 mmol) in DCM (1 mL) was stirred for 2 h at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq.) (2 mL) at 0 °C. The resulting mixture was extracted with DCM (3 x 5 mL). The combined organic layers were washed with brine (2 x 2 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc/EtOH (6/5/1) to afford (3*S*,4*R*)-4-{[6-cyano-7-(3-fluoro-3-methylbutan-2-yl)-5-formylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (17 mg, 68%) as a light yellow solid. MS ESI calculated for $C_{20}H_{24}FN_5O_4$ $[M + H]^+$, 418.18, found 418.30.

Step 4: (3*S*,4*R*)-4-{[6-cyano-5-(difluoromethyl)-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00252] To a stirred mixture of (3*S*,4*R*)-4-{[6-cyano-7-(3-fluoro-3-methylbutan-2-yl)-5-formylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (17 mg, 0.041 mmol) in DCM (1.5 mL) was added DAST (52 mg, 0.328 mmol) dropwise at 0 °C. The reaction mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (2 mL) at room temperature. The aqueous layer was extracted with EtOAc (3 x 3 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[6-cyano-5-(difluoromethyl)-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (11 mg, 61%) as a light yellow solid. MS ESI calculated for $C_{20}H_{24}F_3N_5O_3$ $[M + H]^+$, 440.18, found 440.05.

Step 5: 5-(difluoromethyl)-7-(3-fluoro-3-methylbutan-2-yl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00253] A solution of (3*S*,4*R*)-4-{[6-cyano-5-(difluoromethyl)-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (10 mg, 0.023 mmol) and K_2CO_3 (9.44 mg, 0.069 mmol, 3 equiv) in MeOH (1 mL) was stirred for 1 h at room temperature. The

resulting mixture was purified by reversed-phase chromatography with the following conditions: column, C18; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 25% to 50%; detector, UV 254 nm to afford 5-(difluoromethyl)-7-(3-fluoro-3-methylbutan-2-yl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (6 mg, 66%) as a light yellow oil. MS ESI calculated for $C_{18}H_{22}F_3N_5O_2$ [M + H]$^+$, 398.17, found 398.20.

Example 10:

5-(difluoromethyl)-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH = 70/30, 1st peak)

Example 11:

5-(difluoromethyl)-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH = 70/30, 2nd peak)

[00254] 5-(difluoromethyl)-7-(3-fluoro-3-methylbutan-2-yl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (6 mg) was purified by Chiral-HPLC with the following conditions: Column: CHIRAL ART Amylose-SA, 2 x 25 cm, 5 μm; Mobile Phase A: hexane, Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: A:B = 70:30; Wave Length: 254/220 nm;

[00255] RT_1: 9.29 min to afford 5-(difluoromethyl)-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH = 70/30, 1st peak) (2.2 mg, 36%) as a light yellow solid MS ESI calculated for $C_{18}H_{22}F_3N_5O_2$ [M + H]$^+$, 398.17, found 398.20. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.97 (s, 1H), 7.02 (t, *J* = 54.8 Hz,1H), 5.36 (brs, 1H), 5.18 (brs, 1H), 4.11-4.06 (m, 1H), 4.04-3.91 (m, 1H), 3.86-3.83 (m, 1H), 3.71-3.66 (m, 1H), 3.56-3.50 (m, 1H), 3.30-3.25 (m, 1H), 3.19-3.15 (m, 1H), 2.26-2.14 (m, 1H), 1.76-1.62 (m, 4H), 1.51-1.38 (m, 3H), 1.35-1.28 (m, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -105.54--107.92 (2F), -138.97 (1F).

[00256] RT_2: 15.38 min to afford 5-(difluoromethyl)-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH = 70/30, 2nd peak) (1.3 mg, 21%) as an off-white solid MS ESI calculated for $C_{18}H_{22}F_3N_5O_2$ [M + H]$^+$, 398.17, found 398.20. ^{1}H NMR

(400 MHz, Chloroform-*d*) δ 8.96 (s, 1H), 7.02 (t, *J* = 54.8 Hz,1H), 5.36 (brs, 1H), 5.13 (brs, 1H), 4.12-4.08 (m, 1H), 4.01-3.96 (m, 1H), 3.92-3.81 (m, 1H), 3.73-3.70 (m, 1H), 3.56-3.50 (m, 1H), 3.32-3.27 (m, 1H), 3.03-2.99 (m, 1H), 2.26-2.18 (m, 1H), 1.73-1.62 (m, 4H), 1.50-1.27 (m, 6H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -106.76 (2F), -140.40 (1F).

Example 12:

5-(difluoromethyl)-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*S*,4*R*)-4-{[7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol

[00257] A mixture of 2-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (1.3 g, 5.515 mmol), (3*S*,4*R*)-4-aminooxan-3-ol (2.59 g, 22.109 mmol) and DIEA (4.28 g, 33.090 mmol) in NMP (30 mL) was stirred for 16 h at 80 °C. The reaction was quenched by the addition of water (100 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography with PE/EtOAc (1/2) to afford (3*S*,4*R*)-4-{[7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (1.5 g, 86%) as a yellow solid. MS ESI calculated for $C_{17}H_{24}N_4O_2$ $[M + H]^+$, 317.19, found 317.10

Step 2: (3*S*,4*R*)-4-{[7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00258] To a solution of (3*S*,4*R*)-4-{[7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (130 mg, 0.411 mmol) and Ac_2O (50 mg, 0.493 mmol) in DCM (4 mL) was added TEA (249 mg, 2.466 mmol) at room temperature. The resulting mixture was stirred for 5 h at 50 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (140 mg, 95%) as light yellow oil. MS ESI calculated for $C_{19}H_{26}N_4O_3$ $[M + H]^+$, 359.20, found 359.15. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.50 (s, 1H), 6.65 (d, *J* = 4.4 Hz, 1H), 6.45 (d, *J* = 4.4 Hz, 1H), 4.94-4.77 (m, 2H), 4.05-3.99 (m, 1H), 3.98-3.85 (m, 2H), 3.63-3.53 (m, 1H), 3.47-3.40 (m, 1H), 2.54-2.48 (m, 2H), 2.19-2.12 (m, 2H), 2.12-1.99 (m, 7H), 1.95-1.87 (m, 1H), 1.65 (m, 1H), 0.62 (t, *J* = 7.2 Hz, 3H).

Step 3: (3*S*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl

[00259] To a stirred solution of (3*S*,4*R*)-4-{[7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (1 g, 2.790 mmol) in DMF (10 mL) was added NCS (0.75 g, 5.580 mmol) at room temperature. The resulting mixture was stirred for 16 h at room temperature. The

reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (100 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (800 mg, 69%) as a yellow solid. MS ESI calculated for $C_{19}H_{25}ClN_4O_3$ $[M + H]^+$, 393.16, found 393.30. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.54 (s, 1H), 6.42 (s, 1H), 5.26 (brs, 1H), 4.99-4.92 (m, 1H), 4.07-4.00 (m, 1H), 3.99-3.92 (m, 1H), 3.91-3.83 (m, 1H), 3.60-3.52 (m, 1H), 3.48-3.41 (m, 1H), 2.52-2.38 (m, 3H), 2.23-2.13 (m, 2H), 2.13-1.99 (m, 6H), 1.97-1.86 (m, 1H), 1.76-1.94 (m, 1H), 0.70-0.63 (m, 3H).

Step 4: (3*S*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00260] To a stirred solution of (3*S*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (800 mg, 2.036 mmol) in DMF (8 mL) was added I_2 (2.07 g, 8.144 mmol) at room temperature. The resulting mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (500 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford (3*S*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (900 mg, 82%) as a yellow solid. MS ESI calculated for $C_{19}H_{24}ClIN_4O_3$ $[M + H]^+$, 519.06, found 519.30. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.52 (s, 1H), 5.09 (s, 1H), 4.97-4.90 (m, 1H), 4.06-4.00 (m, 1H), 3.99-3.92 (m, 1H), 3.90-3.81 (m, 1H), 3.59-3.50 (m, 1H), 3.47-3.40 (m, 1H), 2.81-2.63 (m, 2H), 2.44-2.32 (m, 3H), 2.19-2.08 (m, 2H), 2.07-2.02 (m, 4H), 1.91-1.81 (m, 1H), 1.72-1.61 (m, 1H), 0.84-0.78 (m, 3H).

Step 5: (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00261] To a stirred solution of (3*S*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (750 mg, 1.446 mmol) and $Zn(CN)_2$ (102 mg, 0.868 mmol) in DMF (8 mL) was added $Pd(PPh_3)_4$ (334 mg, 0.289 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for additional 2 h at 140 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (300 mL). The resulting mixture was extracted with EtOAc (3 x

100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (480 mg, 80%) as a yellow solid. MS ESI calculated for $C_{20}H_{24}ClN_5O_3$ $[M + H]^+$, 418.16, found 418.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.65 (s, 1H), 5.28 (s, 1H), 4.99-4.91 (m, 1H), 4.07-4.01 (m, 2H), 3.87-3.77 (m, 1H), 3.56-3.48 (m, 1H), 3.44-3.71 (m, 1H), 2.79-2.62 (m, 2H), 2.44-2.27 (m, 3H), 2.25-2.06 (m, 6H), 2.02-1.91 (m, 1H), 1.94-1.61 (m, 1H), 0.85-0.77 (m, 3H).

Step 6: (3*S*,4*R*)-4-{[6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00262] To a stirred solution of (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (600 mg, 1.436 mmol) and $Pd(dba)_2$ (82.56 mg, 0.144 mmol) and t-BuXPhos (121.94 mg, 0.287 mmol, 0.2 equiv) in dioxane (6 mL) were added Et_3SiH (0.70 mL, 4.308 mmol) and TEA (0.60 mL, 4.308 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 100 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford (3*S*,4*R*)-4-{[6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (440 mg, 79%) as a yellow solid. MS ESI calculated for $C_{20}H_{25}N_5O_3$ $[M + H]^+$, 384.20, found 384.30.

Step 7: (3*S*,4*R*)-4-{[6-cyano-7-(1-ethylcyclobutyl)-5-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00263] To a stirred mixture of (3*S*,4*R*)-4-{[6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (440 mg, 1.147 mmol) in DMF (5 mL) was added I_2 (1.16 g, 4.588 mmol) at room temperature. The resulting mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (50 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford (3*S*,4*R*)-4-{[6-cyano-7-(1-ethylcyclobutyl)-5-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (400 mg, 66%) as a yellow solid. MS ESI calculated for $C_{20}H_{24}IN_5O_3$ $[M + H]^+$, 510.09, found 510.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.44 (s, 1H), 5.29-5.20 (m, 1H) 5.00-4.91 (m, 1H), 4.09-3.94 (m, 2H), 3.86-3.77 (m, 1H), 3.57-3.48 (m, 1H), 3.45-3.67 (m, 1H), 2.79-2.63 (m, 2H), 2.42-2.28 (m, 3H), 2.24-2.10 (m, 2H), 2.09-2.04 (m, 4H), 2.00-1.88 (m, 1H), 0.97-0.86 (m, 1H), 0.84-0.77 (m, 3H).

Step 8: (3*S*,4*R*)-4-{[6-cyano-7-(1-ethylcyclobutyl)-5-(hydroxymethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00264] To a solution of (3*S*,4*R*)-4-{[6-cyano-7-(1-ethylcyclobutyl)-5-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (200 mg, 0.393 mmol, 1 equiv)in dioxane (5 mL) were added 2nd Generation XPhos Precatalyst (30.90 mg, 0.039 mmol) and (tributylstannyl)methanol (252.16 mg, 0.786 mmol). The reaction mixture was stirred for 4 h at 80 °C under nitrogen atmosphere. The reaction was quenched with sat. KF (aq.) (20 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[6-cyano-7-(1-ethylcyclobutyl)-5-(hydroxymethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (35 mg, 19%) as a yellow solid. MS ESI calculated for $C_{21}H_{27}N_5O_4$ $[M + H]^+$, 414.21, found 414.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.99 (s, 1H), 5.81 (s, 1H), 5.04 (s, 2H), 5.00-4.93 (m, 1H), 4.09-4.02 (m, 1H), 4.00-3.94 (m, 1H), 3.88-3.81 (m, 1H), 3.61-3.51 (m, 1H), 3.47-3.38 (m, 1H), 2.77-2.64 (m, 1H), 2.41-2.30 (m, 3H), 2.25-2.11 (m, 2H), 2.10-2.06 (m, 4H), 1.99-1.91 (m, 1H), 1.79-1.70 (m, 1H), 1.01-0.91 (m, 1H), 0.85-0.79 (m, 3H).

Step 9: (3*S*,4*R*)-4-{[6-cyano-7-(1-ethylcyclobutyl)-5-formylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00265] A solution of (3*S*,4*R*)-4-{[6-cyano-7-(1-ethylcyclobutyl)-5-(hydroxymethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (30 mg, 0.073 mmol) and DMP (61.55 mg, 0.146 mmol) in DCM (1 mL) was stirred for 2 h at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq.) (2 mL). The resulting mixture was extracted with DCM (3 x 5 mL). The combined organic layers were washed with brine (2 x 2 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[6-cyano-7-(1-ethylcyclobutyl)-5-formylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (24 mg, 77%) as a yellow solid. MS ESI calculated for $C_{21}H_{25}N_5O_4$ $[M + H]^+$, 412.19, found 412.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 10.09 (s, 1H), 9.34 (s, 1H), 5.45-5.39 (m, 1H), 5.01-4.93 (m, 1H), 4.08-3.96 (m, 2H), 3.90-3.81 (m, 1H), 3.56-3.48 (m, 1H), 3.44-3.38 (m, 1H), 2.82-2.67 (m, 2H), 2.42-3.34 (m, 3H), 2.20-2.09 (m, 2H), 2.208-2.06 (m, 3H), 2.03-1.96 (m, 1H), 1.76-1.63 (m, 1H), 1.31-1.25 (m, 1H), 0.85-0.80 (m, 3H).

Step 10: (3*S*,4*R*)-4-{[6-cyano-5-(difluoromethyl)-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00266] To a stirred mixture of (3*S*,4*R*)-4-{[6-cyano-7-(1-ethylcyclobutyl)-5-formylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (24 mg, 0.058 mmol) in DCM (1 mL) was added DAST (61.15 uL, 0.464 mmol) dropwise at 0 °C . The reaction mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (3 mL) at room temperature. The aqueous layer was extracted with EtOAc (3 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (3/1) to afford (3*S*,4*R*)-4-{[6-cyano-5-(difluoromethyl)-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (20 mg, 77%) as an off-white solid. MS ESI calculated for $C_{21}H_{25}F_2N_5O_3$ $[M + H]^+$, 434.19, found 434.35.

Example 12:

5-(difluoromethyl)-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00267] A solution of (3*S*,4*R*)-4-{[6-cyano-5-(difluoromethyl)-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (20 mg, 0.046 mmol) and K_2CO_3 (12.75 mg, 0.092 mmol) in MeOH (1 mL) was stirred for 1 h at 0 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: column, C18; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 25% to 50%; detector, UV 254 nm to afford 5-(difluoromethyl)-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (8.6 mg, 47%) as an off-white solid. MS ESI calculated for $C_{19}H_{23}F_2N_5O_2$ $[M + H]^+$, 392.18, found 392.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.92 (s, 1H), 7.00 (t, *J* = 54.8 Hz, 1H), 5.21 (brs, 1H), 4.12-4.06 (m, 1H), 4.03-3.96 (m, 1H), 3.78-3.67(m, 2H), 3.57-3.48 (m, 1H), 3.34-3.25 (m, 1H), 2.78-2.65 (m, 2H), 2.46-2.32 (m, 2H), 2.28-2.18 (m, 2H), 2.17-1.95 (m, 3H), 1.76-1.62 (m, 1H), 0.85-0.78 (m, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -106.62--106.77 (2F).

Example 13:

(3*S*,4*R*)-4-((5-chloro-7-(5-(1,2-difluoro-2-methylpropyl)pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 1,2-difluoro-2-methylpropyl was not determined) (CHIRALPAK IG, Hexane/EtOH = 50/50, 1st peak)

Example 14:

(3*S*,4*R*)-4-((5-chloro-7-(5-(1,2-difluoro-2-methylpropyl)pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 1,2-difluoro-2-methylpropyl was not determined) (CHIRALPAK IG, Hexane/EtOH = 50/50, 2nd peak)

Step 1: 2-bromo-5-(2-methylprop-1-en-1-yl)pyridine

[00268] To a stirred mixture of isopropyltriphenylphosphanium iodide (72 g, 166.649 mmol) in DMF (200 mL) was added *t*-BuOK (179 mL, 178.490 mmol). The resulting mixture was stirred for 30 min at room temperature. To this was added 6-bromopyridine-3-carbaldehyde (20 g, 107.522 mmol) in DMF (200 mL). The resulting mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (3000 mL). The resulting mixture was extracted with EtOAc (2 x 2000 mL). The combined organic layers were washed with brine (2000 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 2-bromo-5-(2-methylprop-1-en-1-yl)pyridine (9.9 g, 41%) as a yellow oil. MS ESI calculated for $C_9H_{10}BrN$ $[M + H]^+$, 212.00, 214.00, found 212.00, 214.00. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.27 (s, 1H), 7.48-7.43 (m, 2H), 6.16-6.15 (m, 1H), 1.96-1.94 (m, 3H), 1.87-1.85 (m, 3H).

Step 2: 2-bromo-5-(1,2-difluoro-2-methylpropyl)pyridine

[00269] To a stirred mixture of 2-bromo-5-(2-methylprop-1-en-1-yl)pyridine (1 g, 4.715 mmol), 1-iodo-4-methylbenzene (206 mg, 0.943 mmol) and HF-Pyridine (13 mL, 532.182 mmol, 70%) was added *m*-CPBA (1.24 g, 6.130 mmol, 85%) in portions at room temperature. The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was diluted with DCM (100 mL) and was cooled to -78 °C. The resulting mixture was quenched by the addition of sat. NaOH (aq.) (4 M) (150 mL) at -78 °C. The mixture was allowed to warm to room temperature. The aqueous layers was extracted with DCM (2 x 100 mL). The combined organic layers were washed with aqueous copper sulfate solution (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 2-bromo-5-(1,2-difluoro-2-methylpropyl)pyridine (650 mg, 52%) as an off-white solid. MS ESI calculated for $C_9H_{10}BrF_2N$ $[M + H]^+$, 250.00, 252.00, found 249.95, 251.95. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.37 (s, 1H), 7.64-7.62 (m, 1H), 7.56-7.47 (m, 1H), 5.39-5.24 (m, 1H), 1.45-1.42 (m, 3H), 1.40-1.34 (m, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -152.84 (1F), -190.38 (1F).

Step 3: (3*S*,4*R*)-4-({5-chloro-7-[5-(1,2-difluoro-2-methylpropyl)pyridin-2-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol

[00270] A mixture of (3*S*,4*R*)-4-({7-bromo-5-chloropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol (382 mg, 1.100 mmol), 2-bromo-5-(1,2-difluoro-2-methylpropyl)pyridine (250 mg, 1.000 mmol), pyridine-2-carboximidamide hydrochloride (16 mg, 0.100 mmol), nickel(II) iodide (31 mg, 0.100 mmol), NaI (37 mg, 0.250 mmol), Mn (110 mg, 2.000 mmol) and TFA (11.40 mg,

0.100 mmol) in DMA (5 mL) was stirred for 24 h at 60 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered, the filter cake was washed with ethyl acetate (3 x 30 mL). The filtrate was washed with 3 x 20 mL of NH_4Cl/NH_4OH (9/1) and brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc/EtOH (4/3/1). The crude product was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 10% to 70%; detector, UV 254 nm to afford (3*S*,4*R*)-4-({5-chloro-7-[5-(1,2-difluoro-2-methylpropyl)pyridin-2-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol (40 mg, 9%) as a yellow solid. MS ESI calculated for $C_{20}H_{22}ClF_2N_5O_2$ [M + H]$^+$, 438.14 found 438.00. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.72 (s, 1H), 8.67 (s, 1H), 8.57-8.51 (m, 1H),7.90-7.83 (m, 1H), 7.39 (s, 1H), 5.48-5.32 (m, 1H), 5.09-4.92 (m, 1H), 4.17-4.09 (m, 1H), 4.05-3.98 (m, 1H), 3.93-3.85 (m, 1H), 3.77-3.69 (m, 1H), 3.58-3.49 (m, 1H), 3.34-3.26 (m, 1H), 2.39-2.07 (m, 1H), 2.24-2.16 (m, 1H), 1.80-1.68 (m, 1H), 1.51-1.40 (m, 6H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -152.34 (1F), -190.18 (1F).

Example 13:

(3*S*,4*R*)-4-((5-chloro-7-(5-(1,2-difluoro-2-methylpropyl)pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 1,2-difluoro-2-methylpropyl was not determined) (CHIRALPAK IG, Hexane/EtOH = 50/50, 1st peak)

Example 14:

(3*S*,4*R*)-4-((5-chloro-7-(5-(1,2-difluoro-2-methylpropyl)pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 1,2-difluoro-2-methylpropyl was not determined) (CHIRALPAK IG, Hexane/EtOH = 50/50, 2nd peak)

[00271] (3*S*,4*R*)-4-({5-chloro-7-[5-(1,2-difluoro-2-methylpropyl)pyridin-2-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol (40 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hexane, Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: A:B = 50:50; Wave Length: 254/220 nm;

[00272] RT_1: 8.57 min to afford (3*S*,4*R*)-4-((5-chloro-7-(5-(1,2-difluoro-2-methylpropyl)pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 1,2-difluoro-2-methylpropyl was not determined) (CHIRALPAK IG, Hexane/EtOH = 50/50, 1st peak) (23.9 mg, 57%). MS ESI calculated for $C_{20}H_{22}ClF_2N_5O_2$ [M + H]$^+$, 438.14 found 438.00. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (s, 1H),

8.86 (d, J = 8.4 Hz, 1H), 8.67 (s, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.39-7.37 (m, 1H), 7.28 (d, J = 7.6 Hz, 1H), 5.80-5.60 (m, 1H), 5.02-4.98 (m, 1H), 3.89-3.81 (m, 2H), 3.79-3.70 (m, 1H), 3.63-3.53 (m, 1H), 3.49-3.41 (m, 1H), 3.19-3.10 (m, 1H), 2.17-2.10 (m, 1H), 1.59-1.40 (m, 4H), 1.35-1.25 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -151.59 (1F), -188.28 (1F).

[00273] RT_2: 12.04 min to afford ((3*S*,4*R*)-4-((5-chloro-7-(5-(1,2-difluoro-2-methylpropyl)pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 1,2-difluoro-2-methylpropyl was not determined) (CHIRALPAK IG, Hexane/EtOH = 50/50, 2nd peak) (16.5 mg, 41%) as a yellow solid. MS ESI calculated for $C_{20}H_{22}ClF_2N_5O_2$ [M + H]$^+$, 438.14 found 438.05. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (s, 1H), 8.86 (d, J = 8.4 Hz, 1H), 8.67 (s, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.39-7.37 (m, 1H), 7.28 (d, J = 7.6 Hz, 1H), 5.80-5.60 (m, 1H), 5.02-4.98 (m, 1H), 3.89-3.81 (m, 2H), 3.79-3.70 (m, 1H), 3.63-3.53 (m, 1H), 3.49-3.41 (m, 1H), 3.19-3.10 (m, 1H), 2.17-2.10 (m, 1H), 1.59-1.40 (m, 4H), 1.35-1.25 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -151.65 (1F), -188.39 (1F).

Example 15:

5-fluoro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: 2,4-dichloro-5-fluoro-7-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]pyrrolo[2,1-*f*][1,2,4]triazine

[00274] A solution of 2,4-dichloro-5-fluoropyrrolo[2,1-*f*][1,2,4]triazine (500 mg, 2.427 mmol) and Ag_2CO_3 (669 mg, 2.427 mmol) in CH_3CN (5 mL) and H_2O (2.5 mL) was treated with TFA (276.75 mg, 2.427 mmol) for 5 min at 50 °C under nitrogen atmosphere, followed by the addition of 3-(trifluoromethyl)bicyclo[1.1.1]pentane-1-carboxylic acid (874 mg, 4.854 mmol), $(NH_4)_2S_2O_8$ (1772 mg, 7.766 mmol) in CH_3CN (2.5 mL) and H_2O (5 mL). The resulting mixture was stirred for 48 h at 50 °C under nitrogen atmosphere. The reaction was diluted with water (100 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 50% to 70%; detector, UV 254 nm to afford 2,4-dichloro-5-fluoro-7-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]pyrrolo[2,1-*f*][1,2,4]triazine (60 mg, 7 %) as a light yellow solid. MS ESI calculated for $C_{12}H_7Cl_2F_4N_3$ [M + H]$^+$, 340.00, found 339.85. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.46 (s, 1H), 2.52 (s, 6H).

Step 2: 2-chloro-5-fluoro-7-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]pyrrolo[2,1-*f*][1,2,4]triazine

[00275] A solution of 2,4-dichloro-5-fluoro-7-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]pyrrolo[2,1-*f*][1,2,4]triazine (160 mg, 0.470 mmol) and $NaBH_4$ (28 mg, 0.752 mmol) in THF (2 mL) and *i*-PrOH (0.1 mL) was stirred for 1 h at room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (5 x 50 mL). The filtrate was concentrated under reduced pressure. The residue was dissolved in DCM (2 mL). To this was added DDQ (160 mg, 0.705 mmol). The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (3 x 50 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 50% to 70%; detector, UV 254 nm to afford 2-chloro-5-fluoro-7-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]pyrrolo[2,1-*f*][1,2,4]triazine (104 mg, 72%) as a light yellow solid. MS ESI calculated for $C_{12}H_8ClF_4N_3$ $[M + H]^+$, 306.03, found 305.90. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.81 (s, 1H), 6.44 (s, 1H), 2.53 (s, 6H).

Step 3: (3*S*,4*R*)-4-({5-fluoro-7-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol

[00276] A solution of 2-chloro-5-fluoro-7-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]pyrrolo[2,1-*f*][1,2,4]triazine (102 mg, 0.334 mmol), (3*S*,4*R*)-4-aminooxan-3-ol hydrochloride (128 mg, 0.835 mmol) and DIEA (216 mg, 1.670 mmol) in NMP (2 mL) was stirred for 16 h at 60 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 40% to 65%; detector, UV 254 nm to afford (3*S*,4*R*)-4-({5-fluoro-7-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol (110 mg, 85%) as a light yellow solid. MS ESI calculated for $C_{17}H_{18}F_4N_4O_2$ $[M + H]^+$, 387.14, found 387.00. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.57 (s, 1H), 6.08 (s, 1H), 5.23 (d, J = 6.4 Hz, 1H), 4.92 (br, 1H), 4.11-4.17 (m, 1H), 4.04-3.98 (m, 1H), 3.72-3.67 (m, 2H), 3.53-3.49 (m, 1H), 3.31-3.25 (m, 1H), 2.48-2.42 (m, 6H), 2.18-2.14 (m, 1H), 1.71-1.63 (m, 1H).

Step 4: (3*S*,4*R*)-4-({5-fluoro-7-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00277] A solution of (3*S*,4*R*)-4-({5-fluoro-7-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol (32 mg, 0.083 mmol), Ac_2O (12.68 mg, 0.124 mmol, 1.5 equiv) and TEA (34 mg, 0.332 mmol) in DCM (1 mL) was stirred for 16 h at 50 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The resulting mixture was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-({5-fluoro-7-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]pyrrolo[2,1-

f][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (34 mg, 95%) as a light yellow solid. MS ESI calculated for $C_{19}H_{20}F_4N_4O_3$ $[M + H]^+$, 429.15, found 429.15.

Step 5: (3*S*,4*R*)-4-({5-fluoro-6-iodo-7-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00278] A solution of (3*S*,4*R*)-4-({5-fluoro-7-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (36 mg, 0.084 mmol) and I_2 (85 mg, 0.336 mmol) in DMF (0.5 mL) was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (20 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-({5-fluoro-6-iodo-7-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (34 mg, 72%) as a light yellow solid. MS ESI calculated for $C_{19}H_{19}F_4IN_4O_3$ $[M + H]^+$, 555.04, found 554.90.

Step 6: (3*S*,4*R*)-4-({6-cyano-5-fluoro-7-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00279] A solution of (3*S*,4*R*)-4-({5-fluoro-6-iodo-7-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (30 mg, 0.054 mmol), $Zn(CN)_2$ (8 mg, 0.065 mmol) and $Pd(PPh_3)_4$ (6 mg, 0.005 mmol) in DMA (1 mL) was stirred for 2 h at 130 °C under nitrogen atmosphere. The reaction was quenched by the addition of water (15 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-({6-cyano-5-fluoro-7-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (14 mg, 57%) as a light yellow solid. MS ESI calculated for $C_{20}H_{19}F_4N_5O_3$ $[M + H]^+$, 454.14, found 453.95. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 5.36 (d, *J* = 7.2 Hz, 1H), 4.99-4.94 (m, 1H), 4.06-3.83 (m, 3H), 3.62-3.47 (m, 2H), 2.64-2.57 (m, 6H), 2.45-2.39 (m, 2H), 2.13-2.06 (m, 3H), 1.71-1.67 (m, 1H).

Example 15:

5-fluoro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00280] A solution of (3*S*,4*R*)-4-({6-cyano-5-fluoro-7-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (14 mg, 0.031 mmol) and K_2CO_3 (13 mg, 0.093 mmol) in MeOH (0.5 mL) was stirred for 30 min at room temperature. The

resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford 5-fluoro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (4.8 mg, 34%) as a light yellow solid. MS ESI calculated for $C_{18}H_{17}F_4N_5O_2$ $[M + H]^+$, 412.13; found 412.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.73 (s, 1H), 5.11 (brs, 1H), 4.13-3.95 (m, 2H), 3.81-3.68 (m, 2H), 3.56-3.50 (m, 1H), 3.33-3.27 (m, 1H), 2.67 (s, 6H), 2.26-2.15 (m, 1H), 1.71-1.66 (m, 1H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -73.19 (3F), -152.79 (1F).

Example 16:

(3*S*,4*R*)-4-({5-chloro-7-[5-(2,2-difluoroethyl)pyridin-2-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol

Step 1: 2-(6-chloropyridin-3-yl)ethanol

[00281] To a stirred mixture of (6-chloropyridin-3-yl)acetic acid (50 g, 291.40 mmol) in THF (125 mL) was added BH_3-THF (400 mL, 400.00 mmol) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of MeOH (500 mL) at 0 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (10/1) to afford 2-(6-chloropyridin-3-yl)ethanol (41.5 g, 90%) as yellow oil. MS ESI calculated for C_7H_8ClNO $[M + H]^+$, 157.03 found 158.15 ^1H NMR (400 MHz, Chloroform-*d*) δ 8.22 (dd, *J* = 9.6, 2.8 Hz, 1H), 7.57 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.25 (dd, *J* = 8.0, 5.2 Hz, 1H), 3.88 (t, *J* = 6.4 Hz, 2H), 2.85 (t, *J* = 6.4 Hz, 2H).

Step 2: 2-(6-chloropyridin-3-yl)acetaldehyde

[00282] To a stirred solution of 2-(6-chloropyridin-3-yl)ethanol (2.00 g, 12.690 mmol) in DCM (40 mL) was added Dess-Martin (6.46 g, 15.228 mmol). The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (2 x 80 mL). The filtrate was concentrated under reduced pressure to afford 2-(6-chloropyridin-3-yl)acetaldehyde (1.9 g, crude) as colorless oil which was used in the next step directly without further purification. MS ESI calculated for C_7H_6ClNO $[M + H]^+$, 156.01, found 156.10.

Step 3: 2-chloro-5-(2,2-difluoroethyl)pyridine

[00283] To a stirred solution of 2-(6-chloropyridin-3-yl)acetaldehyde (2.00 g, 12.855 mmol) in DCM (100 mL) was added DAST (3.40 mL, 25.710 mmol) dropwise at -30 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0 °C under nitrogen atmosphere. The resulting mixture was purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford 2-chloro-5-(2,2-difluoroethyl)pyridine (130 mg, 4%) as colorless oil. MS ESI calculated for $C_7H_6ClF_2N$ $[M + H]^+$, 178.02, found 177.95. ^1H NMR (400 MHz, Chloroform-*d*)

δ 8.32 (d, *J* = 2.4 Hz, 1H), 7.62 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 5.97 (t, *J* = 56.0 Hz, 1H), 3.22-3.12 (m, 2H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -115.69 (2F).

Step 4: (3*S*,4*R*)-4-({7-[5-(2,2-difluoroethyl)pyridin-2-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00284] To a stirred solution of (3*S*,4*R*)-4-({7-bromopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (200 mg, 0.56 mmol) and bis(pinacolato)diboron (286 mg, 1.12 mmol) in dioxane (12 mL) was added $Pd(PPh_3)_2Cl_2$ (40 mg, 0.05 mmol) and KOAc (166 mg, 1.68 mmol) under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 100 °C under nitrogen atmosphere. To this was added 2-chloro-5-(2,2-difluoroethyl)pyridine (200 mg, 1.12 mmol) and $Pd(dppf)Cl_2$.DCM (46 mg, 0.05 mmol) and Cs_2CO_3 (367 mg, 1.12 mmol) and water (3 mL) at room temperature. The resulting mixture was stirred for additional 2 h at 100 °C under nitrogen atmosphere. The resulting mixture was diluted with EtOAc (150 mL). The organic layers were washed with water (3 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-({7-[5-(2,2-difluoroethyl)pyridin-2-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (100 mg, 42%) as yellow oil. MS ESI calculated for $C_{20}H_{21}F_2N_5O_3$[M + H]$^+$, 418.16 found 418.20.

Step 5: (3*S*,4*R*)-4-({5-chloro-7-[5-(2,2-difluoroethyl)pyridin-2-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00285] A solution of (3*S*,4*R*)-4-({7-[5-(2,2-difluoroethyl)pyridin-2-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (110 mg, 0.264 mmol) and 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (36 mg, 0.185 mmol) in CH_3CN (2 mL) was stirred for 20 min at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (30 mL). The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in Water (0.1% formic acid), 40% to 60%; detector, UV 254 nm to afford (3*S*,4*R*)-4-({5-chloro-7-[5-(2,2-difluoroethyl)pyridin-2-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (55 mg, 46%) as a light yellow solid. MS ESI calculated for $C_{20}H_{20}ClF_2N_5O_3$ [M + H]$^+$, 452.12, found 452.20.

Example 16:

(3*S*,4*R*)-4-({5-chloro-7-[5-(2,2-difluoroethyl)pyridin-2-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol

[00286] To a stirred mixture of (3*S*,4*R*)-4-({5-chloro-7-[5-(2,2-difluoroethyl)pyridin-2-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (40 mg, 0.089 mmol) in MeOH (1 mL) was added

K_2CO_3 (24 mg, 0.177 mmol) at 0 °C. The resulting mixture was stirred for 30 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 30% to 75%; detector, UV 254 nm to afford (3*S*,4*R*)-4-({5-chloro-7-[5-(2,2-difluoroethyl)pyridin-2-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol (10.3 mg, 28%) as a yellow solid. MS ESI calculated for $C_{18}H_{18}ClF_2N_5O_2$ $[M + H]^+$, 410.11, found 410.20. ^1H NMR (400 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.78 (d, *J* = 4.4 Hz, 1H), 8.59 (d, *J* = 1.6 Hz, 1H), 7.91 (d, *J* = 6.4 Hz, 1H), 7.34 (s, 1H), 7.25 (d, *J* = 7.2 Hz, 1H), 6.49-6.21 (m, 1H), 5.00-4.99 (m, 1H), 3.88-3.84 (m, 2H), 3.76-3.71 (m, 1H), 3.60-3.58 (m, 1H), 3.57-3.43 (m, 1H), 3.32-3.24 (m, 2H), 3.16-3.10 (m, 1H), 2.21-2.13 (m, 1H), 1.60-1.40 (m, 1H). ^{19}F NMR (377 MHz, DMSO-d_6) δ -115.44 (2F).

Example 17:

2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1,1,1-trifluoropropan-2-yl was not determined) (CHIRALPAK IG, Hexane/EtOH = 70/30, 1st peak)

Example 18:

2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1,1,1-trifluoropropan-2-yl was not determined) (CHIRALPAK IG, Hexane/EtOH = 70/30, 2nd peak)

Step 1: (3*S*,4*R*)-4-({7-bromopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol

[00287] A solution of 7-bromo-2-chloropyrrolo[2,1-*f*][1,2,4]triazine (1.00 g, 4.302 mmol), (3*S*,4*R*)-4-aminooxan-3-ol (0.60 g, 5.162 mmol) and DIEA (2.22 g, 17.208 mmol) in NMP (10 mL) was stirred for 16 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in Water (10 mM NH_4HCO_3), 30% to 60%; detector, UV 254 nm to afford (3*S*,4*R*)-4-({7-bromopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol (1.10 g, 81%) as a brown solid. MS ESI calculated for $C_{11}H_{13}BrN_4O_2$ $[M + H]^+$, 313.02, 315.02, found 313.00, 315.00. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.53 (s, 1H), 6.80 (d, *J* = 4.8 Hz, 1H), 6.71 (d, *J* = 4.8 Hz, 1H), 5.04 (d, *J* = 5.6 Hz, 1H), 4.13-4.09 (m, 1H), 4.04-4.00 (m, 1H), 3.86-3.79 (m, 1H), 3.70-3.66 (m, 1H), 3.54-3.48 (m, 1H), 3.29-3.24 (m, 1H), 2.16-2.04 (m, 1H), 1.77-1.71 (m, 1H).

Step 2: (3*S*,4*R*)-4-({7-bromopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00288] A solution of (3*S*,4*R*)-4-({7-bromopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol (1.10 g, 3.513 mmol), Ac_2O (0.54 g, 5.269 mmol, 1.5 equiv) and TEA (1.42 g, 14.052 mmol) in DCM

(15 mL) was stirred for 16 h at 50 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*S*,4*R*)-4-({7-bromopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (1.20 g, 96%) as light yellow oil. MS ESI calculated for $C_{13}H_{15}BrN_4O_3$ $[M + H]^+$, 355.03, 357,03, found 355.00, 357.00. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.52 (s, 1H), 6.79 (d, *J* = 4.8 Hz, 1H), 6.71 (d, *J* = 4.8 Hz, 1H), 5.32 (brs, 1H), 4.99-4.96 (m, 1H), 4.15-4.04 (m, 2H), 4.00-3.96 (m, 1H), 3.64-3.60 (m, 1H), 3.48-3.43 (m, 1H), 2.53-2.48 (m, 1H), 2.06 (s, 3H), 1.72-1.68 (m, 1H).

Step 3: (3*S*,4*R*)-4-{[7-(3,3,3-trifluoroprop-1-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00289] A solution of (3*S*,4*R*)-4-({7-bromopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (1.20 g, 3.378 mmol), 4,4,6-trimethyl-2-(3,3,3-trifluoroprop-1-en-2-yl)-1,3,2-dioxaborinane (0.90 g, 4.054 mmol), Cs_2CO_3 (2.20 g, 6.756 mmol) and $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (0.28 g, 0.338 mmol) in 1,4-dioxane (12 mL) and H_2O (2 mL) were stirred for 2 h at 100 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of water (100 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[7-(3,3,3-trifluoroprop-1-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (1.23 g, 98%) as a light yellow solid. MS ESI calculated for $C_{16}H_{17}F_3N_4O_3$ $[M + H]^+$, 371.13, found 371.05. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 7.16-7.12 (m, 1H), 6.91-6.88 (m, 1H), 6.79-6.77 (m, 1H), 6.29-6.28 (m, 1H), 5.23 (br, 1H), 4.99-4.95 (m, 1H), 4.31-4.22 (m, 1H), 4.08-3.93 (m, 2H), 3.60-3.54 (m, 1H), 3.49-3.42 (m, 1H), 2.45-2.41 (m, 1H), 2.05 (s, 3H), 1.74-1.70 (m, 1H).

Step 4: (3*S*,4*R*)-4-{[7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00290] A solution of (3*S*,4*R*)-4-{[7-(3,3,3-trifluoroprop-1-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (1.23 g, 3.321 mmol), 2-nitrobenzenesulfonohydrazide (2.89 g, 13.284 mmol) and K_3PO_4 (1.41 g, 6.642 mmol) in CH_3CN (20 mL) was stirred for 16 h at room temperature. The reaction was quenched by the addition of water (100 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*S*,4*R*)-4-{[7-(1,1,1-trifluoropropan-2-

yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (0.43 g, 34%) as a light yellow solid. MS ESI calculated for $C_{16}H_{19}F_3N_4O_3$ $[M + H]^+$, 373.14, found 373.10. ^1H NMR (300 MHz, Chloroform-*d*) δ 8.63 (s, 1H), 7.20 (d, *J* = 4.8 Hz, 1H), 6.98 (d, *J* = 4.8 Hz, 1H), 5.10-5.06 (m, 1H), 4.53-4.44 (m, 1H), 4.06-4.01 (m, 3H), 3.73-3.69 (m, 1H), 3.59-3.51 (m, 1H), 2.40-2.35 (m, 1H), 2.08 (s, 3H), 1.89-1.86 (m, 1H), 1.62-1.58 (m, 3H).

Step 5: (3*S*,4*R*)-4-{[5-chloro-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00291] A solution of (3*S*,4*R*)-4-{[7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (400 mg, 1.074 mmol) and NCS (143 mg, 1.074 mmol) in DMF (5 mL) was stirred for 2 h at room temperature. The mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in Water (10 mM NH_4HCO_3), 40% to 65%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (430 mg, 98%) as a light yellow solid. MS ESI calculated for $C_{16}H_{18}ClF_3N_4O_3$ $[M + H]^+$, 407.11, found 407.05. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.64 (d, *J* = 2.0 Hz, 1H), 6.61 (s, 1H), 5.14-5.06 (m, 1H), 5.02-4.96 (m, 1H), 4.40-4.31 (m, 1H), 4.06-3.92 (m, 3H), 3.67-3.58 (m, 1H), 3.50-3.42 (m, 1H), 2.46-2.33 (m, 1H), 2.07 (d, *J* = 11.2 Hz, 3H), 1.69-1.62 (m, 1H), 1.54-1.48 (m, 3H).

Step 6: (3*S*,4*R*)-4-{[5-chloro-6-iodo-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00292] A solution of (3*S*,4*R*)-4-{[5-chloro-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (0.41 g, 1.008 mmol) and I_2 (1.02 g, 4.032 mmol) in DMF (5 mL) was stirred for 16 h at room temperature. The reaction was quenched by the addition of *sat.* sodium hyposulfite (50 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*S*,4*R*)-4-{[5-chloro-6-iodo-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (0.42 g, 78%) as a light yellow solid. MS ESI calculated for $C_{16}H_{17}ClF_3IN_4O_3$ $[M + H]^+$, 533.00, found 533.10. ^1H NMR (300 MHz, Chloroform-*d*) *δ* 8.63 (s, 1H), 5.18-5.15 (m, 1H), 4.98-4.93 (m, 1H), 4.47-4.17 (m, 1H), 4.07-3.85 (m, 3H), 3.63-3.39 (m, 2H), 2.42-2.37 (m, 1H), 2.10-2.02 (m, 3H), 1.82-1.73 (m, 3H), 1.68-1.64 (m, 1H).

Step 7: (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00293] A mixture of (3*S*,4*R*)-4-{[5-chloro-6-iodo-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (400 mg, 0.751 mmol), $Zn(CN)_2$ (98 mg, 1.502

mmol) and $Pd(PPh_3)_4$ (87 mg, 0.075 mmol) in DMF (5 mL) was irradiated with microwave radiation for 2 h at 120 °C under nitrogen atmosphere. The mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in Water (10 mM NH_4HCO_3), 30% to 60% gradient in 15 min; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (270 mg, 83%) as a light yellow solid. MS ESI calculated for $C_{17}H_{17}ClF_3N_5O_3$ $[M + H]^+$, 432.10, found 432.10.

Step 8: (3*S*,4*R*)-4-{[6-cyano-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00294] A mixture of (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (300 mg, 0.695 mmol), Et_3SiH (242 mg, 2.081 mmol), Et_3N (281 mg, 2.777 mmol), $Pd(dba)_2$ (40 mg, 0.070 mmol) and di-*tert*-butyl[2',4',6'-tris(propan-2-yl)-[1,1'-biphenyl]-2-yl]phosphane (59 mg, 0.139 mmol) in dioxane (5 mL) was stirred for 2 h at 100 °C under nitrogen atmosphere. The reaction was quenched by the addition of water (10 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[6-cyano-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (260 mg, 94%) as a yellow solid. MS ESI calculated for $C_{17}H_{18}F_3N_5O_3$ $[M + H]^+$, 398.14; found 398.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.71 (d, *J* = 2.0 Hz, 1H), 7.04 (d, *J* = 2.0 Hz, 1H), 5.32 (brs, 1H), 5.03-4.98 (m, 1H), 4.56-4.51 (m, 1H), 4.04-3.99 (m, 3H), 3.63-3.59 (m, 1H), 3.48-3.44 (m, 1H), 2.44-2.39 (m, 1H), 2.06 (d, *J* = 4.8 Hz, 3H), 1.83-1.78 (m, 3H), 1.71-1.66 (m, 1H).

Step 9: 2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00295] A mixture of (3*S*,4*R*)-4-{[6-cyano-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (260 mg, 0.654 mmol) and K_2CO_3 (271 mg, 1.961 mmol) in MeOH (3 mL) was stirred for 1 h at room temperature. The reaction was quenched by the addition of water (10 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-

f][1,2,4]triazine-6-carbonitrile (200 mg, 86%) as a yellow solid. MS ESI calculated for $C_{15}H_{16}FN_5O_2$ $[M + H]^+$, 356.13; found 356.05.

Example 17:

2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1,1,1-trifluoropropan-2-yl was not determined) (CHIRALPAK IG, Hexane/EtOH = 70/30, 1st peak)

Example 18:

2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1,1,1-trifluoropropan-2-yl was not determined) (CHIRALPAK IG, Hexane/EtOH = 70/30, 2nd peak)

[00296] 2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (100 mg) was purified by Prep-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hexane, Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: A:B = 70:30; Wave Length: 254/220 nm;

[00297] RT_1: 6.80 min to afford 2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1,1,1-trifluoropropan-2-yl was not determined) (CHIRALPAK IG, Hexane/EtOH = 70/30, 1st peak) (29.6 mg, 29%) as a white solid. MS ESI calculated for $C_{15}H_{16}FN_5O_2$ $[M + H]^+$, 356.13; found 356.15. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 (s, 1H), 7.39-7.35 (m, 2H), 4.95 (brs, 1H), 4.69-4.64 (m, 1H), 3.85-3.81 (m, 2H), 3.71-3.66 (m, 1H), 3.56-3.51 (m, 1H), 3.41-3.36 (m, 1H), 3.10-3.06 (m, 1H), 2.10-1.96 (m, 1H), 1.71-1.67 (m, 3H), 1.48-1.43 (m, 1H). ^{19}F NMR (377 MHz, DMSO-d_6) δ -69.74 (3F).

[00298] RT_2: 9.04 min to afford 2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1,1,1-trifluoropropan-2-yl was not determined) (CHIRALPAK IG, Hexane/EtOH = 70/30, 2nd peak) (29.1 mg, 28%) as a white solid. MS ESI calculated for $C_{15}H_{16}FN_5O_2$ $[M + H]^+$, 356.13; found 356.10. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 (s, 1H), 7.39-7.34 (m, 2H), 4.92 (brs, 1H), 4.69-4.64 (m, 1H), 3.85-3.81 (m, 2H), 3.71-3.66 (m, 1H), 3.56-3.51 (m, 1H), 3.41-3.36 (m, 1H), 3.10-3.06 (m, 1H), 2.10-2.00 (m, 1H), 1.72-1.67 (m, 3H), 1.48-1.43 (m, 1H). ^{19}F NMR (377 MHz, DMSO-d_6) δ -69.41 (3F).

Example 19:

2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-isopropyl-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: *tert*-butyl (3*R*,4*R*)-3-fluoro-4-({7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00299] To a stirred solution of 2-chloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine (7.4 g, 37.82 mmol) and *tert*-butyl (3*R*,4*R*)-4-amino-3-fluoropiperidine-1-carboxylate (93 mg, 0.43 mmol) in NMP (74 mL) was added DIEA (19.55 g, 151.29 mmol). The resulting mixture was stirred for 16 h at 150 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% $NH_3.H_2O$), 10% to 50%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-3-fluoro-4-({7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate as a yellow solid. MS ESI calculated for $C_{19}H_{28}FN_5O_2$ $[M + H]^+$, 378.22, found 378.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.53 (s, 1H), 6.68 (d, *J* = 4.8 Hz, 1H), 6.52 (d, *J* = 4.8 Hz, 1H), 4.94-4.88 (m, 1H), 4.72-4.69 (m, 1H), 4.60-4.57 (m, 1H), 4.15-4.10 (m, 1H), 3.73-3.69 (m, 1H), 3.47-3.44 (m, 1H), 3.36-3.33 (m, 1H), 2.41-2.37 (m, 1H), 1.53-1.48 (m, 9H), 1.38-1.35 (m, 6H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -189.50 (1F).

Step 2: *tert*-butyl (3*R*,4*R*)-4-({5-chloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate

[00300] A solution of *tert*-butyl (3*R*,4*R*)-3-fluoro-4-({7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (100 mg, 0.27 mmol) and NCS (6.37 g, 47.69 mmol) in DMF (120 mL) was stirred for 16 h at room temperature. The resulting mixture was diluted with EtOAc (400 mL), washed with brine (200 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% $NH_3.H_2O$), 80% to 90%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-4-({5-chloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate as a yellow solid. MS ESI calculated for $C_{19}H_{27}ClFN_5O_2$ $[M + H]^+$, 412.18, found 412.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.58 (s, 1H), 6.44 (s, 1H), 4.89-4.86 (m, 1H), 4.69-4.65 (m, 1H), 4.57-4.54 (m, 1H), 4.09-4.05 (m, 2H), 3.77-3.69 (m, 1H), 3.44-3.40 (m, 1H), 3.34-3.31 (m, 1H), 2.38-2.33 (m, 1H), 1.53-1.48 (m, 9H), 1.36-1.33 (m, 6H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -189.50 (1F).

Step 3: *tert*-butyl (3*R*,4*R*)-4-({5-chloro-6-iodo-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate

[00301] A solution of *tert*-butyl (3*R*,4*R*)-4-({5-chloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate (100 mg, 0.24 mmol) and I_2 (18.49 g, 72.83 mmol) in DMF (60 mL) was stirred for 3 h at room temperature.The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (50 mL). The resulting mixture was extracted with EtOAc (3 x

100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (8/1) to afford *tert*-butyl (3*R*,4*R*)-4-({5-chloro-6-iodo-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate (7.2 g, 91%) as a yellow solid. MS ESI calculated for $C_{19}H_{26}ClFIN_5O_2$ $[M + H]^+$, 538.08, found 538.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.56 (s, 1H), 4.95-4.91 (m, 1H), 4.66-4.62 (m, 1H), 4.53-4.49 (m, 1H), 4.05-4.01 (m, 2H), 3.59-3.56 (m, 1H), 3.44-3.40 (m, 1H), 3.33-3.30 (m, 1H), 2.38-2.33 (m, 1H), 1.52-1.43 (m, 9H), 1.31-1.26 (m 6H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -189.46 (1F).

Step 4: *tert*-butyl (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate

[00302] To a stirred solution of *tert*-butyl (3*R*,4*R*)-4-({5-chloro-6-iodo-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate (6.0 g, 11.157 mmol) and $Zn(CN)_2$ (0.44 g, 6.69 mmol) in DMF (60 mL) was added $Pd(PPh_3)_4$ (1.29 g, 1.12 mmol) under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 120 °C under nitrogen atmosphere. The resulting mixture was purified by silica gel column chromatography, eluted with PE/EtOAc (7/1) to afford *tert*-butyl (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate (4.4 g, 90%) as a yellow solid. MS ESI calculated for $C_{20}H_{26}ClFN_6O_2$ $[M + H]^+$, 437.18, found 437.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 5.18-5.16 (m, 1H), 4.63-4.59 (m, 1H), 4.49-4.46 (m, 1H), 4.06-4.02 (m, 1H), 3.89-3.79 (m, 1H), 3.67-3.64 (m, 1H), 3.29-3.25 (m, 1H), 3.23-3.19 (m, 1H), 2.39-2.26 (m, 1H), 1.48 (m, 15H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -189.28 (1F).

Step 5: *tert*-butyl (3*R*,4*R*)-4-({6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate

[00303] To a stirred solution of *tert*-butyl (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate (6.02 g, 13.78 mmol) and Et_3SiH (4.81 g, 41.33 mmol), TEA (6.97 g, 68.89 mmol) in dioxane (60 mL) was added $Pd(dba)_2$ (0.79 g, 1.38 mmol). The resulting mixture was stirred for 2 h at 80 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-4-({6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate (5.5 g, 99%) as a yellow solid. MS ESI calculated for $C_{20}H_{27}FN_6O_2$ $[M + H]^+$, 403.22, found 403.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.64 (s, 1H), 6.96 (s, 1H), 5.02-4.98 (m, 1H), 4.64-4.61 (m, 1H), 4.53-4.48 (m, 1H), 4.18-4.13 (m, 1H), 4.08-4.05 (m, 1H), 3.87-3.76 (m, 1H),

3.70-3.67 (m, 1H), 3.33-3.22 (m, 2H), 2.38-2.34 (m, 1H), 1.53-1.47 (m, 15H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -189.35 (1F).

Step 6: *tert*-butyl (3*R*,4*R*)-4-({6-cyano-5-iodo-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate

[00304] A solution of *tert*-butyl (3*R*,4*R*)-4-({6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate (5.5 g, 13.67 mmol) and I_2 (17.34 g, 68.33 mmol) in DMF (55 mL) was stirred for 16 h at room temperature. The resulting mixture was quenched with $Na_2S_2O_3$ (200 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford *tert*-butyl (3*R*,4*R*)-4-({6-cyano-5-iodo-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate (6.14 g, 85%) as a yellow solid. MS ESI calculated for $C_{20}H_{26}FIN_6O_2$ $[M + H]^+$, 529.11, found 529.25. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.49 (s, 1H), 5.10-5.08 (m, 1H), 4.62-4.57 (m, 1H), 4.49-4.45 (m, 1H), 4.08-4.03 (m, 1H), 3.89-3.78 (m, 1H), 3.68-3.65 (m, 1H), 3.32-3.28 (m, 1H), 3.23-3.18 (m, 1H), 2.39-2.28 (m, 1H), 1.51-1.46 (m, 15H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -189.28 (1F).

Step 7: *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-7-isopropyl-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00305] To a stirred solution of tert-butyl (3*R*,4*R*)-4-({6-cyano-5-iodo-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate (100 mg, 0.19 mmol) and KF (0.68 g, 11.68 mmol), CuI (1.84 g, 9.65 mmol) in DMF (51 mL) was added methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (9.27 g, 48.26 mmol,) under nitrogen atmosphere. The resulting mixture was stirred for 3h at 80°C under nitrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with EtOAc (200 mL). The resulting mixture was washed with brine (500 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-7-isopropyl-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (3.4 g, 74%) as a yellow solid. MS ESI calculated for $C_{21}H_{26}F_4N_6O_2$ $[M + H]^+$, 471.21, found 471.25. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.89 (d, *J* = 1.2 Hz, 1H), 5.21 (m, 1H), 4.62-4.57 (m, 1H), 4.49-4.45 (m, 1H), 4.21-4.19 (m, 1H), 4.06-4.03 (m, 1H), 3.94-3.84 (m, 1H), 3.72-3.69 (m, 1H), 3.20-3.15 (m, 1H), 2.39-2.27 (m, 1H), 1.61-1.59 (m, 1H), 1.52-1.49 (m, 15H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -54.96 (3F), -189.23 (1F).

Example 19:

2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-isopropyl-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00306] A solution of *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-7-isopropyl-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (3.4 g, 7.23 mmol) and HCl (gas) in 1,4-dioxane (60 mL) in DCM (34 mL) was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure. To this was added methanesulfonic anhydride (2.63 g, 15.12 mmol) in EtOAc (28 mL). The mixture was basified to pH 7 with saturated $NaHCO_3$ (aq.). The reaction mixture was stirred for 2 h at room temperature. The resulting mixture was diluted with EtOAc (100 mL), washed with brine (100 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% $NH_3.H_2O$), 40% to 70%; detector, UV 254 nm to afford 2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-isopropyl-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (2.96 g, 86%) as a white solid. MS ESI calculated for $C_{17}H_{20}F_4N_6O_2S$ $[M + H]^+$, 449.13, found 449.15. ^1H NMR (400 MHz, DMSO-d_6) δ 8.91 (d, J = 1.6 Hz, 1H), 5.19 (d, J = 7.2 Hz, 1H), 4.77-4.70 (m, 1H), 4.11-4.07 (m, 1H), 4.01-3.96 (m, 1H), 3.74-3.70 (m, 2H), 3.21-3.17 (m, 2H), 2.96-2.90 (m, 3H), 2.46-2.44 (m, 1H), 1.83-1.79 (m, 1H), 1.55-1.50 (m, 6H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -54.98 (3F), -188.55 (1F).

Example 20:

7-(3-fluoro-3-methylbutan-2-yl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH/DCM = 80/10/10, 1st peak)

Example 21:

7-(3-fluoro-3-methylbutan-2-yl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH/DCM = 80/10/10, 2nd peak)

Step 1: 7-(3-fluoro-3-methylbutan-2-yl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00307] A solution of (3*S*,4*R*)-4-{[6-cyano-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (180 mg, 0.462 mmol) and K_2CO_3 (96 mg, 0.693 mmol) in MeOH (2 mL) was stirred for 30 min at room temperature. The resulting mixture was purified by

reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford 7-(3-fluoro-3-methylbutan-2-yl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (110 mg, 68%) as an off-white solid. MS ESI calculated for $C_{17}H_{22}FN_5O_2$ $[M + H]^+$, 348.18, found 348.20.

Example 20:

7-(3-fluoro-3-methylbutan-2-yl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH/DCM = 80/10/10, 1st peak)

Example 21:

7-(3-fluoro-3-methylbutan-2-yl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH/DCM = 80/10/10, 2nd peak)

[00308] 7-(3-fluoro-3-methylbutan-2-yl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (110 mg) was purified by Chiral-HPLC with the following conditions (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μm; Mobile Phase A: Hexane, Mobile Phase B: EtOH/DCM (1/1); Flow rate: 20 mL/min; Gradient: A:B = 80;20; Wave Length: 254/220 nm;

[00309] RT_1: 14.06 min to afford 7-(3-fluoro-3-methylbutan-2-yl)-2-{[(3S,4R)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH/DCM = 80/10/10, 1st peak) (37.1 mg, 33%) as a white solid. MS ESI calculated for $C_{17}H_{22}FN_5O_2$ $[M + H]^+$, 348.18; found 348.05. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 7.07 (s, 1H), 5.06 (s, 1H), 4.12-4.09 (m, 1H), 4.02-3.94 (m, 2H), 3.85-3.83 (m, 1H), 3.71-3.66 (m, 1H), 3.56-3.47 (m, 1H), 3.31-3.25 (m, 1H), 2.16-2.12 (m, 1H), 1.77-1.66 (m, 1H), 1.65-1.61 (m, 3H), 1.47-1.44 (m, 6H). ^{19}F NMR (376 MHz, Chloroform -*d*) δ -138.64 (1F).

[00310] RT_2: 7-(3-fluoro-3-methylbutan-2-yl)-2-{[(3S,4R)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH/DCM = 80/10/10, 2nd peak) (37.8 mg, 34%) as a white solid. MS ESI calculated for $C_{17}H_{22}FN_5O_2$ $[M + H]^+$, 348.18; found 348.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 7.07 (s, 1H), 5.06 (s, 1H), 4.10 (m, 1H), 4.02-3.94 (m, 2H), 3.86-3.82 (m, 1H), 3.71-3.66 (m, 1H), 3.56-3.47 (m,

1H), 3.31-3.25 (m, 1H), 2.16-2.12 (m, 1H), 1.77-1.66 (m, 1H), 1.63 (m, 3H), 1.45 (m, 6H). ^{19}F NMR (376 MHz, Chloroform -*d*) δ -140.14 (1F).

Example 22:

(3*S*,4*R*)-4-((5-chloro-6-(2,2-difluoroethyl)-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IF, Hexane/EtOH = 90/10, 1st peak)

Example 23:

(3*S*,4*R*)-4-((5-chloro-6-(2,2-difluoroethyl)-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IF, Hexane/EtOH = 90/10, 2nd peak)

Step 1: (3*S*,4*R*)-4-{[5-chloro-6-(2,2-difluoroethyl)-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00311] To a stirred solution of (3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (500 mg, 0.953 mmol), nickel(II) iodide (30 mg, 0.095 mmol), dppf (105 mg, 0.191 mmol), dtbpy (51 mg, 0.191 mmol) and Mn (183 mg, 3.335 mmol) in DMA (5 mL) was added 1,1-difluoro-2-iodoethane (549 mg, 2.859 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 16 h at room temperature under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of water (50 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc/EtOH (18/5/1) to afford (3*S*,4*R*)-4-{[5-chloro-6-(2,2-difluoroethyl)-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (33 mg, 5 %) as a light yellow solid. MS ESI calculated for $C_{20}H_{26}ClF_3N_4O_3$ $[M + H]^+$, 463.16, found 463.20.

Step 2: (3*S*,4*R*)-4-{[5-chloro-6-(2,2-difluoroethyl)-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol

[00312] A solution of (3*S*,4*R*)-4-{[5-chloro-6-(2,2-difluoroethyl)-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (15 mg, 0.032 mmol) and K_2CO_3 (13 mg, 0.096 mmol) in MeOH (0.3 mL) was stirred for 30 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-6-(2,2-difluoroethyl)-7-(3-fluoro-3-methylbutan-2-

yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (13 mg, 95%) as a light yellow solid. MS ESI calculated for $C_{18}H_{24}ClF_3N_4O_2$ $[M + H]^+$, 421.15, found 421.15.

Example 22:

(3*S*,4*R*)-4-((5-chloro-6-(2,2-difluoroethyl)-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IF, Hexane/EtOH = 90/10, 1st peak)

Example 23:

(3*S*,4*R*)-4-((5-chloro-6-(2,2-difluoroethyl)-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IF, Hexane/EtOH = 90/10, 2nd peak)

[00313] (3*S*,4*R*)-4-{[5-chloro-6-(2,2-difluoroethyl)-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (13 mg) was purified by Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: hexane, Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: A:B = 90:10; Wave Length: 254/220 nm;

[00314] RT_1: 16.56 min to afford (3*S*,4*R*)-4-((5-chloro-6-(2,2-difluoroethyl)-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IF, Hexane/EtOH = 90/10, 1st peak) (2.7 mg, 20%) as a light yellow solid. MS ESI calculated for $C_{18}H_{24}ClF_3N_4O_2$ $[M + H]^+$, 421.15; found 421.30. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.59 (s, 1H), 6.03 (t, *J* = 56.8 Hz, 1H), 4.94-4.92 (m, 1H), 4.10-4.08 (m, 1H), 4.01-3.98 (m, 1H), 3.79-3.76 (m, 2H), 3.68-3.63 (m, 1H), 3.53-3.48 (m, 2H), 3.29-3.24 (m, 2H), 2.13-2.10 (m, 1H), 1.72-1.69 (m, 1H), 1.55-1.44 (m, 6H), 1.22 (m, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -113.01--114.73 (2F), -146.77 (1F).

[00315] RT_2: 20.60 min to afford (3*S*,4*R*)-4-((5-chloro-6-(2,2-difluoroethyl)-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IF, Hexane/EtOH = 90/10, 2nd peak) (2.2 mg, 16%) as a light yellow solid. MS ESI calculated for $C_{18}H_{24}ClF_3N_4O_2$ $[M + H]^+$, 421.15; found 421.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.59 (s, 1H), 6.03 (t, *J* = 56.8 Hz, 1H), 4.98-4.94 (m, 1H), 4.13-4.07 (m, 1H), 4.01-3.98 (m, 1H), 3.79-3.75 (m, 2H), 3.66-3.63 (m, 1H), 3.53-3.50 (m, 2H), 3.29-3.26 (m, 2H), 2.16-2.11 (m, 1H), 1.70-1.68 (m, 6H), 1.49-1.45 (m, 1H), 1.29-1.26 (m, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -113.02--114.57 (2F), -147.24 (1F).

Example 24:

5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*S*,4*R*)-4-{[5-chloro-7-(2-methylprop-1-en-1-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00316] To a stirred solution of (3*S*,4*R*)-4-({7-bromo-5-chloropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (1 g, 2.567 mmol) and 4,4,5,5-tetramethyl-2-(2-methylprop-1-en-1-yl)-1,3,2-dioxaborolane (560 mg, 3.080 mmol) in dioxane (20 mL) and H_2O (4 mL) were added Pd(dppf)Cl_2DCM (209 mg, 0.257 mmol) and Cs_2CO_3 (1.6 g, 5.134 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 4 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (100 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford (3*S*,4*R*)-4-{[5-chloro-7-(2-methylprop-1-en-1-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (770 mg, 82 %) as a yellow solid. MS ESI calculated for $C_{17}H_{21}ClN_4O_3$ $[M + H]^+$, 365.13, found 365.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.57 (s, 1H), 6.67 (s, 1H), 6.62 (s, 1H), 5.03-4.93 (m, 1H), 4.93-4.91 (m, 1H), 4.17-4.09 (m, 1H), 4.08-3.95 (m, 1H), 3.97-3.93 (m, 1H), 3.72-3.48 (m, 1H), 3.47-3.45 (m, 1H), 2.47-2.42 (m, 1H), 2.10-1.98 (m, 9H), 1.71-1.62 (m, 1H).

Step 2: (3*S*,4*R*)-4-{[5-chloro-7-(1,2-dihydroxy-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00317] To a stirred solution of (3*S*,4*R*)-4-{[5-chloro-7-(2-methylprop-1-en-1-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (770 mg, 2.111 mmol) and NMO (494 mg, 4.222 mmol) in acetone (10 mL) and H_2O (10 mL) was added $K_2OsO_4.2H_2O$ (77 mg, 0.211 mmol) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction was quenched with sat. $Na_2S_2O_3$ (aq.) (5 mL) at 0 °C. The resulting mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 10% to 40%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-7-(1,2-dihydroxy-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (600 mg, 71%) as a yellow solid. MS ESI calculated for $C_{17}H_{23}ClN_4O_5$ $[M + H]^+$, 399.14, found 399.10. ^1H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, *J* =

6.4, 1H), 6.65 (s, 1H), 5.35 (s, 1H), 5.01-4.82 (m, 1H), 4.87-4.71 (m, 1H), 4.48-4.24 (m, 1H), 4.24-4.08 (m, 1H), 4.02-3.79 (m, 3H), 3.51-3.40 (m, 1H), 3.30-3.22 (m, 1H), 2.12-2.00 (m, 1H), 1.95-1.91 (m, 3H), 1.72-1.71 (m, 1H), 1.70-1.59 (d, J = 8.9 Hz, 3H), 1.00-1.13 (m, 3H).

Step 3: *tert*-butyl (3*S*,4*R*)-4-{[5-chloro-7-(2-hydroxy-2-methylpropanoyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00318] A mixture of (3*S*,4*R*)-4-{[5-chloro-7-(1,2-dihydroxy-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (600 mg, 1.504 mmol) and IBX (842 mg, 3.008 mmol) in CH_3CN (10 mL) was stirred for 2 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (15 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[5-chloro-7-(2-hydroxy-2-methylpropanoyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (490 mg, 82%) as a yellow solid. MS ESI calculated for $C_{17}H_{21}ClN_4O_5$ $[M + H]^+$, 397.12, found 397.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.81 (d, J = 1.6 Hz, 1H), 7.31-7.28 (m, 2H), 5.53 (d, J = 8.0 Hz, 1H), 4.97-4.91 (m, 1H), 4.19-3.93 (m, 3H), 3.57-3.51 (m, 1H), 3.45-3.39 (m, 1H), 2.38-2.35 (m, 1H), 2.09-2.03 (m, 3H), 1.80-1.68 (m, 1H), 1.67-1.57 (m, 6H).

Step 4: (3*S*,4*R*)-4-{[5-chloro-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00319] A solution of (3*S*,4*R*)-4-{[5-chloro-7-(2-hydroxy-2-methylpropanoyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (500 mg, 1.260 mmol) in DAST (10 mL) was stirred for 16 h at room temperature under nitrogen atmosphere. The reaction was quenched with sat. $NaHCO_3$ (aq.) (100 mL) at 0 °C. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*S*,4*R*)-4-{[5-chloro-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (100 mg, 18%) as a yellow solid. MS ESI calculated for $C_{17}H_{20}ClF_3N_4O_3$ $[M + H]^+$, 421.12, found 421.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.72 (s, 1H), 6.79 (s, 1H), 5.22 (d, J = 6.8 Hz, 1H), 4.97-4.92 (m, 1H), 4.06-4.02 (m, 1H), 3.98-3.93 (m, 2H), 3.61-3.52 (m, 1H), 3.48-3.40 (m, 1H), 2.48-2.44 (m, 1H), 2.08-2.07 (m, 3H), 1.76-1.63 (m, 1H), 1.58-1.53 (m, 6H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -107.65--108.57 (2F), -152.87 (1F).

Step 5: (3*S*,4*R*)-4-{[5-chloro-6-iodo-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00320] A solution of (3*S*,4*R*)-4-{[5-chloro-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (100 mg, 0.238 mmol) and NIS (107 mg, 0.476 mmol) in DMF (2 mL) was stirred for 16 h at 120 °C. The mixture was allowed to cool down to room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: column, C18; mobile phase, CH_3CN in water (0.1% formic acid), 20% to 60%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-6-iodo-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (7 mg, 5%) as a yellow solid. MS ESI calculated for $C_{17}H_{19}ClF_3IN_4O_3$ $[M + H]^+$, 547.01, found 547.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 5.16 (d, *J* = 6.8 Hz, 1H), 4.95-4.91 (m, 1H), 4.07-3.86 (m, 3H), 3.55-3.52 (m, 1H), 3.49-3.38 (m, 1H), 2.47-2.44 (m, 1H), 2.07-2.05 (m, 3H), 1.68-1.65 (m, 1H), 1.64-1.62 (m, 3H), 1.61-1.55 (m, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -105.32 (2F), -152.85 (1F).

Step 6: (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00321] To a stirred solution of (3*S*,4*R*)-4-{[5-chloro-6-iodo-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (7 mg, 0.013 mmol) and $Zn(CN)_2$ (1.0 mg, 0.008 mmol) in DMF (0.5 mL) was added $Pd(PPh_3)_4$ (1.5 mg, 0.001 mmol) under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 130 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The residue was purified by reversed-phase chromatography with the following conditions: column, C18; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (2 mg, 35%) as a yellow solid. MS ESI calculated for $C_{18}H_{19}ClF_3N_5O_3$ $[M + H]^+$, 446.11, found 446.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.80 (s, 1H), 5.45 (d, *J* = 6.8 Hz, 1H), 4.96 (d, *J* = 4.8 Hz, 1H), 4.09-3.94 (m, 2H), 3.92-3.83 (m, 1H), 3.53-3.36 (m, 2H), 2.47-2.44 (m, 1H), 2.08-2.07 (m, 3H), 1.67-1.60 (m, 4H), 1.58-1.57 (m, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -106.66--107.72 (2F), -152.61 (1F).

Example 24:

5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00322] A solution of (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (2 mg, 0.004 mmol) and K_2CO_3 (1.8 mg, 0.012 mmol) in MeOH (0.3 mL) was stirred for 1 h at room temperature. The resulting mixture was

purified by reversed-phase chromatography with the following conditions: column, C18; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford 5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(1,1,2-trifluoro-2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (0.9 mg, 49%) as an off-white solid. MS ESI calculated for $C_{16}H_{17}ClF_3N_5O_2$ $[M + H]^+$, 404.10, found 404.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.83 (s, 1H), 5.18 (d, *J* = 6.9 Hz, 1H), 4.12-3.96 (m, 2H), 3.82-3.61 (m, 2H), 3.57-3.43 (m, 1H), 3.23-3.05 (m, 1H), 2.17-2.15 (m, 1H), 1.76-1.67 (m, 1H), 1.66-1.62 (m, 3H), 1.58-1.55 (m, 3H), 1.29-1.26 (m, 1H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ-106.72 (2F), -152.52(1F).

Example 25:

5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(2,3,3-trifluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 2,3,3-trifluorobutan-2-yl was not determined) (DAICEL DCpak® P4VP, CO_2/MeOH = 66/34, 1st peak)

Example 26:

5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(2,3,3-trifluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 2,3,3-trifluorobutan-2-yl was not determined) (DAICEL DCpak® P4VP, CO_2/MeOH = 66/34, 2nd peak)

Step 1: (3*S*,4*R*)-4-({7-[(2*E*)-but-2-en-2-yl]-5-chloropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00323] To a stirred solution of (3*S*,4*R*)-4-({7-bromo-5-chloropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (2 g, 5.133 mmol) and potassium (2*Z*)-but-2-en-2-yltrifluoroboranuide (498 mg, 3.080 mmol) in dioxane (20 mL) and H_2O (4 mL) were added Pd(dppf)Cl_2DCM (418 mg, 0.513 mmol) and Cs_2CO_3 (3.3 g, 10.266 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford (3*S*,4*R*)-4-({7-[(2*E*)-but-2-en-2-yl]-5-chloropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (1.4 g, 74%) as a yellow solid. MS ESI calculated for $C_{17}H_{21}ClN_4O_3$ $[M + H]^+$, 365.13, found 365.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.61 (s, 1H), 6.47 (s, 1H), 5.86-5.77 (m, 1H), 4.94-4.87 (m, 2H), 4.08-3.98 (m, 2H), 3.98-3.90 (m, 1H), 3.62-3.50 (m, 1H), 3.48-3.37 (m, 1H), 2.44-2.33 (m, 1H), 2.17-2.11 (m, 3H), 2.06-2.03 (s, 3H), 1.73-1.61 (m, 4H).

Step 2: (3*S*,4*R*)-4-{[5-chloro-7-(2,3-dihydroxybutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00324] To a stirred solution of (3*S*,4*R*)-4-({7-[(2*E*)-but-2-en-2-yl]-5-chloropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (1.4 g, 3.837 mmol) and NMO (899 mg, 7.674 mmol) in acetone (20 mL) and H_2O (20 mL) was added $K_2OsO_4.2H_2O$ (141 mg, 0.384 mmol) at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched with sat. $Na_2S_2O_3$ (aq.) (5 mL) at 0 °C. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: column, C18; mobile phase, CH_3CN in water (0.1% formic acid), 10% to 40%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-7-(2,3-dihydroxybutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (1.1 g, 71%) as a yellow solid. MS ESI calculated for $C_{17}H_{23}ClN_4O_5$ $[M + H]^+$, 399.14, found 399.15. ^1H NMR (400 MHz, DMSO-d_6) δ 8.74 (s, 1H), 7.18-7.11 (m, 1H), 6.61 (s, 1H), 5.12 (d, J = 14.3 Hz, 1H), 4.75-4.73 (m, 1H), 4.54-4.45 (m, 1H), 4.34-4.23 (m, 1H), 3.96-3.81 (m, 3H), 3.46-3.45 (m, 1H), 3.29-3.23 (m, 1H), 2.10-2.06 (m, 1H), 1.94-1.93 (m, 3H), 1.70-1.62 (m, 1H), 1.58-1.56 (m, 3H), 0.88-0.85 (m, 3H).

Step 3: (3*S*,4*R*)-4-{[5-chloro-7-(2-hydroxy-3-oxobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00325] A solution of (3*S*,4*R*)-4-{[5-chloro-7-(2,3-dihydroxybutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (1.1 g, 2.758 mmol) and IBX (1.5 g, 5.516 mmol) in CH_3CN (20 mL) was stirred for 2 h at 80 °C. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford (3*S*,4*R*)-4-{[5-chloro-7-(2-hydroxy-3-oxobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (750 mg, 68%) as a yellow solid. MS ESI calculated for $C_{17}H_{21}ClN_4O_5$ $[M + H]^+$, 397.12, found 397.12. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.66 (d, J = 1.2 Hz, 1H), 6.72 (s, 1H), 5.34-5.26 (m, 1H), 5.05-4.93 (m, 1H), 4.90-4.80 (m, 1H), 4.06-3.90 (m, 2H), 3.81-3.66 (m, 2H), 3.55-3.45 (m, 1H), 2.43-2.33 (m, 1H), 2.32-2.28 (m, 3H), 2.16-2.06 (m, 3H), 1.79-1.65 (m, 3H), 1.67-1.54 (m, 1H).

Step 4: (3*S*,4*R*)-4-{[5-chloro-7-(2,3,3-trifluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00326] A solution of (3*S*,4*R*)-4-{[5-chloro-7-(2-hydroxy-3-oxobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (400 mg, 1.008 mmol) in DAST (8 mL) was stirred for 16 h at room temperature under nitrogen atmosphere. The reaction was quenched with sat. $NaHCO_3$ (aq.) (100 mL) at 0 °C. The resulting mixture was extracted with DCM (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[5-chloro-7-(2,3,3-trifluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (150 mg, 35%) as a yellow solid. MS ESI calculated for $C_{17}H_{20}ClF_3N_4O_3$ $[M + H]^+$, 421.12, found 421.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 6.73 (s, 1H), 5.18 (s, 1H), 4.98-4.90 (m, 1H), 4.15-4.06 (m, 1H), 4.02-3.97 (m, 1H), 3.92-3.84 (m, 1H), 3.60-3.50 (m, 1H), 3.48-3.38 (m, 1H), 2.50-2.36 (m, 1H), 2.15-2.03 (m, 6H), 1.78-1.57 (m, 4H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -101.15--107.81 (2F), -153.68 (1F).

Step 5: (3*S*,4*R*)-4-{[5-chloro-6-iodo-7-(2,3,3-trifluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00327] A solution of (3*S*,4*R*)-4-{[5-chloro-7-(2,3,3-trifluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (150 mg, 0.356 mmol) and I_2 (452 mg, 1.780 mmol) in DMF (3 mL) was stirred for 48 h at 40 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched with sat. $Na_2S_2O_3$ (aq.) (5 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[5-chloro-6-iodo-7-(2,3,3-trifluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (80 mg, 41%) as a yellow solid. MS ESI calculated for $C_{17}H_{19}ClF_3IN_4O_3$ $[M + H]^+$, 547.01, found 547.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.65 (d, J = 5.6 Hz, 1H), 5.18 (d, J = 7.2 Hz, 1H), 4.97-4.87 (m, 1H), 4.09-3.93 (m, 2H), 3.90-3.79 (m, 1H), 3.64-3.28 (m, 2H), 2.52-2.28 (m, 1H), 2.25-2.06 (m, 3H), 2.09-2.04 (m, 3H), 1.85-1.56 (m, 4H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -100.64--103.24 (2F), -150.32(1F).

Step 6: (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(2,3,3-trifluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00328] To a stirred solution of (3*S*,4*R*)-4-{[5-chloro-6-iodo-7-(2,3,3-trifluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (70 mg, 0.128 mmol) and $Zn(CN)_2$ (9 mg, 0.077 mmol) in DMF (1 mL) was added $Pd(PPh_3)_4$ (14 mg, 0.013 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 130 °C under nitrogen

atmosphere. The mixture was allowed to cool down to room temperature. The residue was purified by reversed-phase chromatography with the following conditions: column, C18; mobile phase, CH_3CN in water (0.1% formic acid), 20% to 70%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(2,3,3-trifluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (25 mg, crude) as a yellow solid. MS ESI calculated for $C_{18}H_{19}ClF_3N_5O_3$ $[M + H]^+$, 446.11, found 446.15.

Step 7: 5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(2,3,3-trifluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00329] A solution of (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(2,3,3-trifluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (22 mg, 0.049 mmol) and K_2CO_3 (20 mg, 0.147 mmol) in MeOH (0.5 mL) was stirred for 30 min at room temperature. The residue was purified by reversed-phase chromatography with the following conditions: column, C18; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford 5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(2,3,3-trifluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (18 mg, crude) as a yellow solid. MS ESI calculated for $C_{16}H_{17}ClF_3N_5O_2$ $[M + H]^+$, 404.10, found 404.15.

Example 25:

5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(2,3,3-trifluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 2,3,3-trifluorobutan-2-yl was not determined) (DAICEL DCpak® P4VP, CO_2/MeOH = 66/34, 1st peak)

Example 26:

5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(2,3,3-trifluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 2,3,3-trifluorobutan-2-yl was not determined) (DAICEL DCpak® P4VP, CO_2/MeOH = 66/34, 2nd peak)

[00330] 5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(2,3,3-trifluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (15 mg) was purified by Prep-SFC with the following conditions (Column: DAICEL DCpak® P4VP 325 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MeOH; Flow rate: 65 mL/min; Gradient: A:B = 66:34;

[00331] RT_1: 6.76 min to afford 5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(2,3,3-trifluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 2,3,3-trifluorobutan-2-yl was not determined) (DAICEL DCpak® P4VP, CO_2/MeOH = 66/34, 1st peak) (3.1 mg, 20%) as a white solid. MS ESI calculated for $C_{16}H_{17}ClF_3N_5O_2$ $[M + H]^+$, 404.10, found 403.95. ^1H NMR (400 MHz,

Chloroform-*d*) δ 8.78 (s, 1H), 5.12 (d, *J* = 6.4 Hz, 1H), 4.09-4.06 (m, 1H), 4.01-3.93 (m, 1H), 3.72-3.67 (m, 2H), 3.55-3.48 (m, 1H), 3.33-3.28 (m, 1H), 2.30-2.23 (m, 1H), 2.15-2.01 (m, 3H), 1.98-1.90 (m, 3H), 1.68-1.53 (m, 1H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -100.60--103.11 (2F), -152.21 (1F).

[00332] RT_2: 7.53 min to afford 5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(2,3,3-trifluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 2,3,3-trifluorobutan-2-yl was not determined) (DAICEL DCpak® P4VP, CO_2/MeOH = 66/34, 2nd peak) (2.6 mg, 17%) as a white solid. MS ESI calculated for $C_{16}H_{17}ClF_3N_5O_2$ $[M + H]^+$, 404.10, found 403.90. ^{1}H NMR (400 MHz, Chloroform-*d*) 8.78 (s, 1H), 5.12 (d, *J* = 6.4 Hz, 1H), 4.09-4.06 (m, 1H), 4.01-3.93 (m, 1H), 3.72-3.67 (m, 2H), 3.55-3.48 (m, 1H), 3.33-3.28 (m, 1H), 2.30-2.23 (m, 1H), 2.15-2.01 (m, 3H), 1.98-1.90 (m, 3H), 1.68-1.53 (m, 1H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -100.60--103.01 (2F), -151.91 (1F).

Example 27:

(3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-(2,2,2-trifluoroethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol

Step 1: (3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-(2,2,2-trifluoroethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00333] To a stirred solution of (3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (400 mg, 0.762 mmol), nickel(II) iodide (24 mg, 0.076 mmol), dtbpy (41 mg, 0.152 mmol), dppf (84 mg, 0.152 mmol) and Mn (147 mg, 2.667 mmol) in DMA (4 mL) was added 1,1,1-trifluoro-2-iodoethane (480 mg, 2.286 mmol) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 24 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The mixture was allowed to cool down to room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-(2,2,2-trifluoroethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (25 mg, 6%) as a light yellow solid. MS ESI calculated for $C_{20}H_{25}ClF_4N_4O_3$ $[M + H]^+$, 481.16, found 481.35.

Example 27:

(3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-(2,2,2-trifluoroethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol

[00334] A solution of (3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-(2,2,2-trifluoroethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (25 mg, 0.052 mmol)

and K_2CO_3 (22 mg, 0.156 mmol) in MeOH (1 mL) was stirred for 30 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 50% to 70%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-(2,2,2-trifluoroethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (3.3 mg, 14%) as a light yellow solid. MS ESI calculated for $C_{18}H_{23}ClF_4N_4O_2$ $[M + H]^+$, 439.15; found 439.05. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.62 (s, 1H), 5.04 (brs, 1H), 4.11-4.07 (m, 1H), 4.01-3.97 (m, 1H), 3.80-3.65 (m, 3H), 3.57-3.46 (m, 3H), 3.32-3.21 (m, 1H), 2.16-2.12 (m, 1H), 1.99-1.87 (m, 1H), 1.76-1.03 (m, 9H). ^{19}F NMR (376 MHz, Chloroform -*d*) δ -62.63--65.52 (3F), -146.51 (1F).

Example 28:

5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(2-methoxyethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*S*,4*R*)-4-{[7-(2-methoxyethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00335] To a solution of (3*S*,4*R*)-4-({7-bromopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (400 mg, 1.126 mmol) and potassium trifluoro(2-methoxyethyl)boranuide (373 mg, 2.252 mmol) in dioxane (20 mL) and H_2O (2 mL) were added 3rd Gen RuPhos (94 mg, 0.113 mmol) and Cs_2CO_3 (1.10 g, 3.378 mmol). The reaction mixture was stirred for 2 h at 100 °C under nitrogen atmosphere. The reaction was quenched with water (30 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc/EtOH (6/5/1) to afford (3*S*,4*R*)-4-{[7-(2-methoxyethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (220 mg, 58%) as light yellow oil. MS ESI calculated for $C_{16}H_{22}N_4O_4$ $[M + H]^+$, 335.16, found 335.05. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.56 (s, 1H), 6.67 (d, *J* = 5.6 Hz, 1H), 6.55 (d, *J* = 4.6 Hz, 1H), 5.03-4.94 (m, 1H), 4.92-4.88 (m, 1H), 4.12-4.00 (m, 2H), 3.97-3.91 (m, 1H), 3.78-3.74 (m, 2H), 3.65-3.55 (m, 1H), 3.48-3.40 (m, 4H), 3.23-3.19 (m, 2H), 2.51-2.35 (m, 1H), 2.07 (s, 3H), 1.70-1.65 (m, 1H).

Step 2: (3*S*,4*R*)-4-{[5-chloro-7-(2-methoxyethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00336] A solution of (3*S*,4*R*)-4-{[7-(2-methoxyethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (220 mg, 0.658 mmol) and NCS (92.25 mg, 0.691 mmol) in DMF (4 mL) was stirred for 16 h at room temperature. The reaction mixture was stirred for additional 2 h at 50 °C. The mixture was allowed to cool down to room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: column, C18; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford (3*S*,4*R*)-

4-{[5-chloro-7-(2-methoxyethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (108 mg, 44%) as light yellow oil. MS ESI calculated for $C_{16}H_{21}ClN_4O_4$ [M + H]$^+$; 369.13, found 369.10. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.57 (s, 1H), 6.48 (s, 1H), 5.03-4.88 (m, 2H), 4.05-3.92 (m, 3H), 3.74-3.70 (m, 2H), 3.63-3.55 (m, 1H), 3.47-3.38 (m, 4H), 3.18-3.14 (m, 2H), 2.45-2.38 (m, 1H), 2.08-2.04 (m, 3H), 1.70-1.62 (m, 1H).

Step 3: (3*S*,4*R*)-4-{[5-chloro-6-iodo-7-(2-methoxyethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00337] A solution of (3*S*,4*R*)-4-{[5-chloro-7-(2-methoxyethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (108 mg, 0.293 mmol) and I_2 (446 mg, 1.758 mmol) in DMF (3 mL) was stirred for 16 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: column, C18; mobile phase, CH_3CN in water (0.1% formic acid), 30% to 50%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-6-iodo-7-(2-methoxyethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (120 mg, 82%) as yellow oil. MS ESI calculated for $C_{16}H_{20}ClIN_4O_4$ [M + H]$^+$; 495.02, found 495.00. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.56 (s, 1H), 5.02-4.94 (m, 2H), 4.08-3.91 (m, 3H), 3.70-3.66 (m, 2H), 3.65-3.55 (m, 1H), 3.47-3.39 (m, 4H), 3.29-3.25 (m, 2H), 2.43-2.38 (m, 1H), 2.09-2.05 (m, 3H), 1.70-1.66 (m, 1H).

Step 4: 5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(2-methoxyethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00338] To a stirred solution of 5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(2-methoxyethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (120 mg, 0.341 mmol)in DMF (3 mL) were added $Pd(PPh_3)_4$ (39 mg, 0.034 mmol) and $Zn(CN)_2$ (24 mg, 0.205 mmol) under nitrogen atmosphere. The reaction mixture was stirred for 2 h at 130 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: column, C18; mobile phase, CH_3CN in water (0.1% formic acid), 40% to 70%; detector, UV 254 nm to afford 5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(2-methoxyethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (25 mg, 20%) as a yellow solid. MS ESI calculated for $C_{17}H_{20}ClN_5O_4$ [M + H]$^+$, 394.12, found 394.10. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 5.23 (d, *J* = 7.6 Hz, 1H), 5.01-4.95 (m, 1H), 4.06-4.01 (m, 1H), 3.99-3.94 (m, 2H), 3.81-3.77 (m, 2H), 3.63-3.52 (m, 1H), 3.46-3.38 (m, 4H), 3.33-3.29 (m, 2H), 2.43-2.39 (m, 1H), 2.10-2.06 (m, 3H), 1.70-1.66 (m, 1H).

Example 28:

5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(2-methoxyethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00339] A solution mixture of (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(2-methoxyethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (25 mg, 0.063 mmol) and K_2CO_3 (26.32 mg, 0.189 mmol) in MeOH (2 mL) was stirred for 1 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: column, C18; mobile phase, CH_3CN in water (0.1% formic acid), 15% to 50%; detector, UV 254 nm to afford 5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(2-methoxyethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (4.1 mg, 16%) as a white solid. MS ESI calculated for $C_{15}H_{18}ClN_5O_3$ $[M + H]^+$, 352.11, found 352.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.64 (s, 1H), 5.00 (brs, 1H), 4.21-3.91 (m, 2H), 3.78-3.74 (m, 4H), 3.59-3.17 (m, 8H), 2.17-2.13 (m, 1H), 1.67-1.54 (m, 1H).

Example 29:

5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-hydroxy-3-methylbutan-2-yl was not determined) (CHIRALPAK IG, CO_2/MeOH = 54/46, 1st peak)

Example 30:

5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-hydroxy-3-methylbutan-2-yl was not determined) (CHIRALPAK IG, CO_2/MeOH = 54/46, 2nd peak)

Step 1: (3*S*,4*R*)-4-{[5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol

[00340] A mixture of 3-{2,5-dichloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl}-2-methylbutan-2-ol (100 mg, 0.365 mmol), (3*S*,4*R*)-4-aminooxan-3-ol hydrochloride (112 mg, 0.729 mmol) and DIEA (188 mg, 1.455 mmol) in NMP (2 mL) was stirred for 16 h at °C. The reaction was quenched by the addition of sat. H_2O (10 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (80 mg, 73%) as yellow oil. MS ESI calculated for $C_{16}H_{23}ClN_4O_3$ $[M + H]^+$, 355.15; found 355.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.59-8.55 (m, 1H), 6.62-6.44 (m, 1H), 5.02 (d, *J* = 43.1 Hz, 1H), 4.10-4.06 (m, 1H), 4.00-3.96 (m, 1H), 3.66-3.62 (m, 1H), 3.58-3.40 (m, 2H), 3.32-3.26 (m, 1H), 2.15-2.11 (m, 1H), 1.77-1.61 (m, 1H), 1.37-1.32 (m, 3H), 1.30-1.21 (m, 6H).

Step 2: (3*S*,4*R*)-4-{[5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00341] A mixture of (3*S*,4*R*)-4-{[5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (100 mg, 0.282 mmol), Ac_2O (43 mg, 0.421 mmol) and TEA (114 mg, 1.127 mmol) in DCM (2 mL) was stirred for 16 h at 50 °C. The mixture was allowed to cool down to room temperature. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (100 mg, 89%) as a yellow solid. MS ESI calculated for $C_{11}H_{13}ClN_3O$ $[M + H]^+$, 397.16; found 397.00. ^1H NMR (Chloroform-*d*) δ 8.57 (s, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 5.13-4.94 (m, 2H), 4.04-4.00 (m, 1H), 3.99-3.87 (m, 2H), 3.68-3.64 (m, 1H), 3.58-3.48 (m, 2H), 2.43-2.39 (m, 1H), 2.11-2.07 (m, 3H), 1.67-1.63 (m, 1H), 1.38-1.34 (m, 3H), 1.28-1.24 (m, 3H), 1.22-1.18 (m, 3H).

Step 3: (3*S*,4*R*)-4-{[5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00342] A mixture of (3*S*,4*R*)-4-{[5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (80 mg, 0.202 mmol) and I_2 (208 mg, 0.820 mmol) in DMF (2 mL) was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (10 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (70 mg, 66%) as a yellow solid. MS ESI calculated for $C_{18}H_{24}ClIN_4O_4$ $[M + H]^+$, 523.05; found 523.05. ^1H NMR (Chloroform-*d*) δ 8.59 (s, 1H), 4.90 (m, 1H), 4.06-3.92 (m, 3H), 3.84-3.80 (m, 1H), 3.65-3.58 (m, 1H), 3.51-3.42 (m, 1H), 2.30-2.10 (m, 1H), 2.09-2.05 (m, 3H), 1.70-1.60 (m, 1H), 1.47-1.43 (m, 3H), 1.41-1.37 (m, 3H), 1.08-1.04 (m, 3H).

Step 4: (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(3-hydroxy-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00343] A mixture of (3*S*,4*R*)-4-{[5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (65 mg, 0.124 mmol), $Zn(CN)_2$ (26 mg, 0.221 mmol) and $Pd(PPh_3)_4$ (13 mg, 0.011 mmol) in DMF (1 mL) was stirred for 2 h at 130 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: column, C18; mobile phase, CH_3CN in water (0.1% formic acid), 20% to 45%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(3-hydroxy-3-

methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (40 mg, 76%) as a yellow solid. MS ESI calculated for $C_{19}H_{24}ClN_5O_4$ $[M + H]^+$, 422.15; found 422.15.

Step 5: 5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00344] A mixture of (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(3-hydroxy-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (50 mg, 0.119 mmol) and K_2CO_3 (50 mg, 0.362 mmol) in MeOH (1 mL) was stirred for 30 min at room temperature. The resulting mixture was filtered, the filter cake was washed with EtOAc (3 x 10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (1/1) to afford 5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (20 mg, 44%) as a yellow solid. MS ESI calculated for $C_{17}H_{22}ClN_5O_3$ $[M + H]^+$, 380.14; found 380.20.

Example 29:

5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-hydroxy-3-methylbutan-2-yl was not determined) (CHIRALPAK IG, CO_2/MeOH = 54/46, 1st peak)

Example 30:

5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-hydroxy-3-methylbutan-2-yl was not determined) (CHIRALPAK IG, CO_2/MeOH = 54/46, 2nd peak)

[00345] 5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (20 mg) was purified by Prep-HPLC with the following conditions (Column: CHIRALPAK IG 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MeOH; Flow rate: 85 mL/min; Gradient: A:B = 54:46; Wave Length: 220 nm;

[00346] RT_1: 7.77 min to afford 5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-hydroxy-3-methylbutan-2-yl was not determined) (CHIRALPAK IG, CO_2/MeOH = 54/46, 1st peak) (2.7 mg, 13%) as a yellow solid. MS ESI calculated for $C_{17}H_{22}ClN_5O_3$ $[M + H]^+$, 380.14; found 380.15. ^1H NMR (Chloroform-*d*) δ 8.74 (s, 1H), 5.02 (brs, 1H), 4.12-4.08 (m, 1H), 4.03-3.99 (m, 1H), 3.81-3.77 (m, 1H), 3.73-3.69 (m, 1H), 3.58-3.48 (m, 1H), 3.30-3.26 (m, 1H), 3.18-2.14 (m, 1H), 2.18-2.14 (m, 1H), 1.74-1.70 (m, 1H), 1.56-1.52 (m, 3H), 1.39-1.31 (m, 6H).

[00347] RT_2: 10.6 min to afford 5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-hydroxy-3-methylbutan-2-yl was not determined) (CHIRALPAK IG, CO_2/MeOH = 54/46, 2nd peak) (2.8 mg, 13%) as a yellow solid. MS ESI calculated for $C_{17}H_{22}ClN_5O_3$ $[M + H]^+$, 380.14; found 380.15. ^1H NMR (Chloroform-*d*) δ 8.74 (s, 1H), 5.04 (brs, 1H), 4.12-4.08 (m, 1H), 4.03-3.99 (m, 1H), 3.81-3.77 (m, 1H), 3.73-3.69 (m, 1H), 3.58-3.48 (m, 1H), 3.30-3.20 (m, 2H), 2.18-2.12 (m, 1H), 1.74-1.68 (m, 1H), 1.56-1.52 (m, 3H), 1.39-1.31 (m, 6H).

Example 31:

(3*S*,4*R*)-4-{[7-(1-ethylcyclopent-3-en-1-yl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol

Step 1: 1-ethylcyclopent-3-ene-1-carboxylic acid

[00348] To a stirred solution of cyclopent-3-ene-1-carboxylic acid (10 g, 89.18 mmol) in THF (100 mL) was added ethyl iodide (27.82 g, 178.37 mmol) dropwise at room temperature under nitrogen atmosphere. To the above mixture was added LDA (2 M in THF) (89.2 mL, 178.37 mmol) dropwise at -10 °C. The resulting mixture was stirred for 16 h at room temperature. The reaction was quenched with sat. NH_4Cl (aq.) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 100 mL). The mixture was acidified to pH 2 with conc. HCl. The resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (1x50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 1-ethylcyclopent-3-ene-1-carboxylic acid (10.6 g, 85%) as a light yellow oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 5.63 (s, 2H), 2.97-2.91 (m, 2H), 2.37-2.32 (m, 2H), 1.77 (q, *J* = 7.2 Hz, 2H), 0.93 (t, *J* = 7.2 Hz, 3H).

Step 2: 2,4-dichloro-7-(1-ethylcyclopent-3-en-1-yl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazine

[00349] To a stirred solution of 1-ethylcyclopent-3-ene-1-carboxylic acid (408 mg, 2.91 mmol) and 2,4-dichloro-5-fluoropyrrolo[2,1-*f*][1,2,4]triazine (300 mg, 1.46 mmol) in CH_3CN was added $AgNO_3$ (990 mg, 5.82 mmol) at room temperature under nitrogen atmosphere. To this was added $(NH_4)_2S_2O_8$ (1661.58 mg, 7.28 mmol) in H_2O) at 50 °C. The resulting mixture was stirred for additional 2 h at 50 °C. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (6/1). The crude product was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% TFA), 10% to 50%;

detector, UV 254 nm to afford 2,4-dichloro-7-(1-ethylcyclopent-3-en-1-yl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazine (140 mg, 32%) as a light yellow oil. MS ESI calculated for $C_{13}H_{12}Cl_2FN_3$ [M + H]$^+$, 300.04, found 300.05. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.05 (s, 1H), 5.76-5.67 (m, 2H), 2.86-2.82 (m, 2H), 2.65-2.56 (m, 2H), 1.92 (q, *J* = 7.2 Hz, 2H), 0.61-0.57 (t, *J* = 7.2 Hz, 3H).^{19}F NMR (400 MHz, Chloroform-*d*) δ -153.81 (1F).

Step 3: 2-chloro-7-(1-ethylcyclopent-3-en-1-yl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazine

[00350] To a stirred solution of 2,4-dichloro-7-(1-ethylcyclopent-3-en-1-yl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazine (120 mg, 0.40 mmol) in THF (1.2 mL) and *i*-PrOH (0.6 mL) was added $NaBH_4$ (24 mg, 0.64 mmol) at 0 °C. The reaction was stirred for 2 h at 0 °C. The resulting mixture was quenched with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. To this was added DDQ (136.13 mg, 0.60 mmol) in DCM (6 mL) at room temperature. The resulting mixture was stirred for additional 2 h at room temperature. The mixture was to pH 8 with saturated $NaHCO_3$ (aq.). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 2-chloro-7-(1-ethylcyclopent-3-en-1-yl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazine (89 mg, 84%) as a light yellow oil. MS ESI calculated for $C_{13}H_{13}ClFN_3$ [M + H]$^+$, 266.08, found 266.15. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.76 (s, 1H), 6.49 (s, 1H), 5.74 (s, 2H), 2.88-2.84 (m, 2H), 2.80-2.74 (m, 2H), 2.05-2.01 (m, 2H), 0.67-0.63 (m, 3H); ^{19}F NMR (400 MHz, Chloroform-*d*) δ -158.41 (1F).

Example 31:

(3*S*,4*R*)-4-{[7-(1-ethylcyclopent-3-en-1-yl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol

[00351] To a stirred solution of (3*S*,4*R*)-4-aminooxan-3-ol hydrochloride (184.99 mg, 1.20 mmol) and 2-chloro-7-(1-ethylcyclopent-3-en-1-yl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazine (80 mg, 0.30 mmol) in NMP (5 mL) was added DIEA (233 mg, 1.81 mmol). The resulting mixture was stirred for additional 16 h at 80 °C. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% $NH_3.H_2O$), 10% to 50%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[7-(1-ethylcyclopent-3-en-1-yl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (58.5 mg, 56%) as a light yellow solid.

MS ESI calculated for $C_{18}H_{23}FN_4O_2$ $[M + H]^+$, 347.18, found 347.20. ^1H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1H), 6.66 (d, J = 4.4 Hz, 1H), 6.36 (s, 1H), 5.71 (s, 2H), 4.92-4.96 (m, 1H), 3.81-3.85 (m, 2H), 3.51-3.55 (m, 2H), 3.32-3.36 (m, 1H), 3.08-3.03 (m, 1H), 2.85-2.80 (m, 2H), 2.52-2.48 (m, 2H), 2.16-2.12 (m, 1H), 1.35-1.31 (m, 2H), 1.42-1.38 (m, 1H), 0.63-0.59 (m, 3H); ^{19}F NMR (400 MHz, DMSO-d_6) δ -163.20 (1F).

Example 32:

7-(1-(1-fluoroethyl)cyclopentyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1-fluoroethyl)cyclopentyl was not determined) (CHIRALPAK IG, Hexane/EtOH/DCM = 87/6.5/6.5, 1st peak)

Example 33:

7-(1-(1-fluoroethyl)cyclopentyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1-fluoroethyl)cyclopentyl was not determined) (CHIRALPAK IG, Hexane/EtOH/DCM = 87/6.5/6.5, 2nd peak)

Step 1: 2,4-dichloro-7-(1-(1-fluoroethyl)cyclopentyl)pyrrolo[2,1-*f*][1,2,4]triazine

[00352] A mixture of 1,3-dioxoisoindol-2-yl 1-(1-fluoroethyl)cyclopentane-1-carboxylate (2 g, 6.551 mmol) $Ir[dF(CF_3)PPy]_2(dtbpy)PF_6$ (147 mg, 0.131 mmol) TFA (1.5 mL, 19.653 mmol) and 2,4-dichloropyrrolo[2,1-*f*][1,2,4]triazine (2.46 g, 13.102 mmol) in DMA (30 mL) was irradiated with Blue LED for 16 h at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of water/ice (20 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 40% to 60%; detector, UV 254 nm to afford 2,4-dichloro-7-[1-(1-fluoroethyl)cyclopentyl]pyrrolo[2,1-*f*][1,2,4]triazine (200 mg, 10%) as yellow oil. MS ESI calculated for $C_{13}H_{14}Cl_2FN_3$ $[M + H]^+$, 301.05, found 301.90; ^1H NMR (400 MHz, Chloroform-d) δ 7.05 (d, J = 4.8 Hz, 1H), 6.92 (d, J = 4.8 Hz, 1H), 5.47 (d, J = 47.6 Hz, 1H), 2.41-2.13 (m, 4H), 1.58-1.54 (m, 4H), 1.15-1.11 (m, 3H).

Step 2: 2-chloro-7-(1-(1-fluoroethyl)cyclopentyl)pyrrolo[2,1-*f*][1,2,4]triazine

[00353] To a stirred mixture of 2,5-dichloro-7-[1-(1-fluoroethyl)cyclopentyl]pyrrolo[2,1-*f*][1,2,4]triazine (160 mg, 0.530 mmol) in THF (2 mL) and *i*-PrOH (0.1 mL) was added $NaBH_4$ (30 mg, 0.795 mmol) in portions at 0 °C. The resulting mixture was stirred for 3 h at room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (3 x 3 mL). The filtrate was

concentrated under reduced pressure. To this were added DCM (4 mL) and DDQ (317 mg, 1.398 mmol). The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of sat. NaHCO3 (aq.) (3 mL). The resulting mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (3 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 2-chloro-7-[1-(1-fluoroethyl)cyclopentyl]pyrrolo[2,1-*f*][1,2,4]triazine (120 mg, 64%) as yellow oil. MS ESI calculated for $C_{13}H_{15}ClFN_3$ $[M + H]^+$, 268.09; found 268.10.

Step 3: (3*S*,4*R*)-4-({7-[1-(1-fluoroethyl)cyclopentyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol

[00354] A mixture of 2-chloro-7-[1-(1-fluoroethyl)cyclopentyl]pyrrolo[2,1-*f*][1,2,4]triazine (120 mg, 0.448 mmol), DIEA (347 mg, 2.688 mmol) and (3*S*,4*R*)-4-aminooxan-3-ol hydrochloride (344 mg, 2.240 mmol) in NMP (2 mL) was stirred for 16 h at 80 °C. The residue was purified by reversed-phase chromatography with the following conditions: column, C18 silica gel; mobile phase, CH_3CN in water (0.1% formic acid), 10% to 50%; detector, UV 254 nm to afford (3*S*,4*R*)-4-({7-[1-(1-fluoroethyl)cyclopentyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol (150 mg, 96%) as yellow oil. MS ESI calculated for $C_{18}H_{25}FN_4O_2$ $[M + H]^+$, 349.20; found 349.30.

Step 4: (3*S*,4*R*)-4-((7-(1-(1-fluoroethyl)cyclopentyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-yl acetate

[00355] A mixture of (3*S*,4*R*)-4-({7-[1-(1-fluoroethyl)cyclopentyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol (120 mg, 0.344 mmol), TEA (174 mg, 1.720 mmol) and Ac_2O (53 mg, 0.516 mmol) in DCM (2 mL) was stirred for 16 h at 50 °C. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (2 mL) at room temperature. The resulting mixture was extracted with DCM (2 x 3 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford (3*S*,4*R*)-4-({7-[1-(1-fluoroethyl)cyclopentyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (110 mg, 81%) as yellow oil. MS ESI calculated for $C_{20}H_{27}FN_4O_3$ $[M + H]^+$, 390.21; found 391.00.

Step 5: (3*S*,4*R*)-4-((5-chloro-7-(1-(1-fluoroethyl)cyclopentyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-yl acetate

[00356] To a stirred mixture of (3*S*,4*R*)-4-({7-[1-(1-fluoroethyl)cyclopentyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (165 mg, 0.423 mmol) in DMF (1 mL) was added NCS (45 mg, 0.338 mmol). The resulting mixture was stirred for 16 h at 50 °C. The reaction was quenched by the addition of water/ice (2 mL). The resulting mixture was extracted with EtOAc (3 x 5 mL).

The combined organic layers were washed with brine (3 x 6 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford (3*S*,4*R*)-4-({5-chloro-7-[1-(1-fluoroethyl)cyclopentyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (166 mg, 92%) as yellow oil. MS ESI calculated for $C_{20}H_{26}ClFN_4O_3$ $[M + H]^+$, 425.17; found 425.10. δ ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.57 (s, 1H), 6.52 (d, *J* = 2.4 Hz, 1H), 5.62-5.37 (m, 1H), 5.13 (brs, 1H), 4.96-4.92 (m, 1H), 4.05-4.01 (m, 1H), 4.01-3.91 (m, 2H), 3.63-3.59 (m, 1H), 3.55-3.45 (m, 1H), 2.52-2.25 (m, 2H), 2.21-2.05 (m, 6H), 1.76-1.61 (m, 5H), 1.14-1.10 (m, 3H).

Step 6: (3*S*,4*R*)-4-((5-chloro-7-(1-(1-fluoroethyl)cyclopentyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-yl acetate

[00357] A mixture of (3*S*,4*R*)-4-({5-chloro-7-[1-(1-fluoroethyl)cyclopentyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (160 mg, 0.377 mmol) and I_2 (478 mg, 1.885 mmol) in DMF (3 mL) was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. NaS_2O_3 (aq.) (25 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-({5-chloro-7-[1-(1-fluoroethyl)cyclopentyl]-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (166 mg, 80%) as yellow oil. MS ESI calculated for $C_{20}H_{25}ClFIN_4O_3$ $[M + H]^+$, 551.06; found 551.15.

Step 7: (3*S*,4*R*)-4-((5-chloro-6-cyano-7-(1-(1-fluoroethyl)cyclopentyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-yl acetate

[00358] A mixture of (3*S*,4*R*)-4-({5-chloro-7-[1-(1-fluoroethyl)cyclopentyl]-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (100 mg, 0.182 mmol), $Pd(PPh_3)_4$ (21 mg, 0.018 mmol) and $Zn(CN)_2$ (32 mg, 0.273 mmol) in DMA (1.5 mL) was stirred for 2 h at 130 °C under nitrogen atmosphere. The reaction was quenched by the addition of water/ice (3 mL). The resulting mixture was extracted with EtOAc (3 x 4 mL). The combined organic layers were washed with brine (3 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (3/2) to afford (3*S*,4*R*)-4-({5-chloro-6-cyano-7-[1-(1-fluoroethyl)cyclopentyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (80 mg, 97%) as a yellow solid. MS ESI calculated for $C_{21}H_{25}ClFN_5O_3$ $[M + H]^+$, 450.16; found 450.35.

Step 8: (3*S*,4*R*)-4-((6-cyano-7-(1-(1-fluoroethyl)cyclopentyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-yl acetate

[00359] A mixture of (3*S*,4*R*)-4-({5-chloro-6-cyano-7-[1-(1-fluoroethyl)cyclopentyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (60 mg, 0.133 mmol), TEA (40 mg, 0.399 mmol), Pd(dba)2 (7.6 mg, 0.013 mmol), di-*tert*-butyl[2',4',6'-tris(propan-2-yl)-[1,1'-biphenyl]-2-yl]phosphane (11 mg, 0.027 mmol) and Et_3SiH (62 mg, 0.532 mmol) in dioxane (1 mL) was stirred for 2 h at 100 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of water/ice (3 mL). The resulting mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (3 x 7 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (2/1) to afford (3*S*,4*R*)-4-({6-cyano-7-[1-(1-fluoroethyl)cyclopentyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (53 mg, 95%) as a off-white solid. MS ESI calculated for $C_{21}H_{26}FN_5O_3$ $[M + H]^+$, 416.20; found 416.15.

Step 9: (3*S*,4*R*)-4-((6-cyano-7-(1-(1-fluoroethyl)cyclopentyl)-5-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-yl acetate

[00360] A mixture of (3*S*,4*R*)-4-({6-cyano-7-[1-(1-fluoroethyl)cyclopentyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (90 mg, 0.217 mmol) and I_2 (220 mg, 0.868 mmol) in DMF (1 mL) was stirred for 4 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (8 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-({6-cyano-7-[1-(1-fluoroethyl)cyclopentyl]-5-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (80 mg, 68%) as an off-white solid. MS ESI calculated for $C_{21}H_{25}FIN_5O_3$ $[M + H]^+$, 542.10; found 542.00.

Step 10: (3*S*,4*R*)-4-((6-cyano-7-(1-(1-fluoroethyl)cyclopentyl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-yl acetate

[00361] To a stirred mixture of (3*S*,4*R*)-4-({6-cyano-7-[1-(1-fluoroethyl)cyclopentyl]-5-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (60 mg, 0.111 mmol), KF (19 mg, 0.333 mmol) and CuI (21 mg, 0.111 mmol) in DMF (1.5 mL) was added methyl 2,2-difluoro-2-sulfoacetate (106 mg, 0.555 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of water/ice (5 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 8 mL). The combined organic layers were washed with brine (2 x 12 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with

PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-({6-cyano-7-[1-(1-fluoroethyl)cyclopentyl]-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (35 mg, 65%) as an off-white solid. MS ESI calculated for $C_{22}H_{25}F_4N_5O_3$ $[M + H]^+$, 484.19; found 484.35. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.57 (s, 1H), 7.20 (s, 1H), 5.02-4.98 (m, 1H), 4.24-4.09 (m, 4H), 4.08-4.01 (m, 1H), 4.04-3.91 (m, 1H), 2.10-2.06 (m, 4H), 1.84-1.50 (m, 9H), 1.30-1.26 (m, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -54.91 (3F), -170.10 (1F).

Step 11: 7-(1-(1-fluoroethyl)cyclopentyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00362] A mixture of (3*S*,4*R*)-4-({6-cyano-7-[1-(1-fluoroethyl)cyclopentyl]-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (27 mg, 0.056 mmol) and K_2CO_3 (15 mg, 0.112 mmol) in MeOH (1 mL) was stirred for 1 h at 0 °C. The resulting mixture was purified by Prep-TLC with PE/EtOAc (1/1) to afford 7-[1-(1-fluoroethyl)cyclopentyl]-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (20 mg, 81%) as an off-white solid. MS ESI calculated for $C_{20}H_{23}F_4N_5O_2$ $[M + H]^+$, 442.18; found 442.35.

Example 32:

7-(1-(1-fluoroethyl)cyclopentyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1-fluoroethyl)cyclopentyl was not determined) (CHIRALPAK IG, Hexane/EtOH/DCM = 87/6.5/6.5, 1st peak)

Example 33:

7-(1-(1-fluoroethyl)cyclopentyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1-fluoroethyl)cyclopentyl was not determined) (CHIRALPAK IG, Hexane/EtOH/DCM = 87/6.5/6.5, 2nd peak)

[00363] 7-[1-(1-fluoroethyl)cyclopentyl]-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (20 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: hexane, Mobile Phase B: EtOH/DCM (1/1); Flow rate: 20 mL/min; Gradient: A:B = 87:13; Wave Length: 254/220 nm;

[00364] RT_1: 16.21 min to afford 7-(1-(1-fluoroethyl)cyclopentyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1-fluoroethyl)cyclopentyl was not determined) (CHIRALPAK IG, Hexane/EtOH/DCM = 87/6.5/6.5, 1st peak) (8.4 mg, 42%) as a white solid and 7-{1-[(1*R*)-1-fluoroethyl]cyclopentyl}-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-5-

(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (5.4 mg, 27%) as a white solid.MS ESI calculated for $C_{20}H_{23}F_4N_5O_2$ [M + H]$^+$, 442.18; found 442.35. δ ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.92 (d, *J* = 1.2 Hz, 1H), 5.19-4.99 (m, 2H), 4.11-4.07 (m, 1H), 4.04-3.96 (m, 1H), 3.85-3.81 (m, 1H), 3.71-3.67 (m, 1H), 3.61-3.51 (m, 1H), 3.33-3.29 (m, 1H), 2.71-2.46 (m, 4H), 2.23-2.19 (m, 1H), 1.80-1.65 (m, 5H), 1.25-1.21 (m, 3H); ^{19}F NMR (377 MHz, Chloroform-*d*) δ -54.92 (3F).

[00365] RT_2: 21.57 min to afford 7-(1-(1-fluoroethyl)cyclopentyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1-fluoroethyl)cyclopentyl was not determined) (CHIRALPAK IG, Hexane/EtOH/DCM = 87/6.5/6.5, 2nd peak) (8.4 mg, 42%) as a white solid and 7-{1-[(1R)-1-fluoroethyl]cyclopentyl}-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (5.4 mg, 27%) as a white solid.MS ESI calculated for $C_{20}H_{23}F_4N_5O_2$ [M + H]$^+$, 442.18; found 442.30. δ ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.92 (d, *J* = 1.2 Hz, 1H), 5.19-4.99 (m, 2H), 4.11-4.07 (m, 1H), 4.04-3.96 (m, 1H), 3.85-3.81 (m, 1H), 3.71-3.67 (m, 1H), 3.61-3.51 (m, 1H), 3.33-3.29 (m, 1H), 2.73-2.67 (m, 1H), 2.54-2.46 (m, 3H), 2.23-2.19 (m, 1H), 1.85-1.65 (m, 5H), 1.25-1.21 (m, 3H); ^{19}F NMR (377 MHz, Chloroform-*d*) δ -54.93 (3F).

Example 34:

5-chloro-7-[1-(2,2-difluoroethyl)piperidin-4-yl]-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: *tert*-butyl 4-(2-{[(3*S*,4*R*)-3-(acetyloxy)oxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylate

[00366] To a stirred solution of (3*S*,4*R*)-4-({7-bromopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (1 g, 2.815 mmol) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylate (1.31 g, 4.223 mmol) in dioxane (20 mL) and water (4 mL) were added Pd(dppf)Cl_2.DCM (0.23 g, 0.282 mmol) and Cs_2CO_3 (1.83 g, 5.630 mmol) under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl 4-(2-{[(3*S*,4*R*)-3-(acetyloxy)oxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylate (1.2 g, 93%) as a yellow solid; MS ESI calculated for $C_{23}H_{31}N_5O_5$ [M + H]$^+$, 458.23, found 458.25; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.59 (s, 1H), 7.17 (s, 1H), 6.75-6.66 (m, 2H), 5.02-4.97 (m, 2H), 4.23-4.18 (m, 2H), 4.06-4.01 (m, 2H), 3.98-3.94 (m, 1H), 3.69-3.67

(m, 2H), 3.62-3.57 (m, 1H), 3.52-3.49 (m, 1H), 2.69-2.65 (m, 2H), 2.49-2.44 (m, 1H), 2.08-2.06 (m, 3H), 1.73-1.68 (m, 1H), 1.54-1.50 (m, 9H).

Step 2: *tert*-butyl 4-(2-(((3*S*,4*R*)-3-acetoxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)piperidine-1-carboxylate

[00367] A mixture of *tert*-butyl 4-(2-{[(3*S*,4*R*)-3-(acetyloxy)oxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (500 mg, 1.093 mmol) and Pd/C (500 mg, 4.698 mmol) in MeOH (5 mL) was stirred for 5 h at room temperature under hydrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with MeOH (3 x 10 mL). The filtrate was concentrated under reduced pressure. To this was added DDQ (372 mg, 1.639 mmol) in DCM (5 mL). The resulting mixture was stirred for additional 2 h at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (5 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford *tert*-butyl 4-(2-{[(3*S*,4*R*)-3-(acetyloxy)oxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)piperidine-1-carboxylate (200 mg, 39%) as yellow oil.MS ESI calculated for $C_{23}H_{33}N_5O_5$ $[M + H]^+$, 460.25, found 460.40. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.53 (s, 1H), 6.75 (d, $J = 4.8$ Hz, 1H), 6.53 (d, $J = 4.8$ Hz, 1H), 5.27 (s, 1H), 5.07-5.03 (m, 1H), 4.36-3.89 (m, 5H), 3.54-3.49 (m, 1H), 3.35-3.31 (m, 1H), 2.95-2.91 (m, 2H), 2.48-2.42 (m, 1H), 2.09-2.05 (m, 6H), 1.72-1.67 (m, 1H), 1.52-1.49 (m, 10 H), 1.28 (m, 1H).

Step 3: *tert*-butyl 4-(2-(((3*S*,4*R*)-3-acetoxytetrahydro-2*H*-pyran-4-yl)amino)-5-chloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl)piperidine-1-carboxylate

[00368] A mixture of *tert*-butyl 4-(2-{[(3*S*,4*R*)-3-(acetyloxy)oxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)piperidine-1-carboxylate (230 mg, 0.500 mmol) and NCS (53 mg, 0.400 mmol) in DMF (2 mL) was stirred for 16 h at 50 °C. The reaction was quenched by the addition of water/ice (3 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl 4-(2-{[(3*S*,4*R*)-3-(acetyloxy)oxan-4-yl]amino}-5-chloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl)piperidine-1-carboxylate (150 mg, 60%) as yellow oil. MS ESI calculated for $C_{23}H_{32}ClN_5O_5$, $[M + H]^+$, 494.21, found 494.40. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.59 (s, 1H), 6.41 (s, 1H), 5.10 (s, 1H), 5.05-5.01 (m, 1H), 4.27-4.22 (m, 2H), 4.15-4.12 (m, 1H), 4.05-3.92 (m, 2H),

3.65-3.59 (m, 1H), 3.50-3.47 (m, 1H), 3.32-3.26 (m, 1H), 2.92-2.89 (m, 2H), 2.44-2.40 (m, 1H), 2.08-2.06 (m, 6H), 1.73-1.65 (m, 2H), 1.60-1.58 (m, 9H).

Step 4: *tert*-butyl 4-(2-(((3*S*,4*R*)-3-acetoxytetrahydro-2*H*-pyran-4-yl)amino)-5-chloro-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)piperidine-1-carboxylate

[00369] A mixture of *tert*-butyl 4-(2-{[(3*S*,4*R*)-3-(acetyloxy)oxan-4-yl]amino}-5-chloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl)piperidine-1-carboxylate (157 mg, 0.318 mmol) and I_2 (403 mg, 1.590 mmol) in DMF (2 mL) was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. NaS_2O_3 (aq.) (7 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (3 x 12 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (1/1) to afford *tert*-butyl 4-(2-{[(3*S*,4*R*)-3-(acetyloxy)oxan-4-yl]amino}-5-chloro-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)piperidine-1-carboxylate (166 mg, 84%) as an off-white solid. MS ESI calculated for $C_{23}H_{31}ClIN_5O_5$ $[M + H]^+$, 620.11, found 620.40.

Step 5: *tert*-butyl 4-(2-{[(3*S*,4*R*)-3-(acetyloxy)oxan-4-yl]amino}-5-chloro-6-cyanopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)piperidine-1-carboxylate

[00370] A mixture of *tert*-butyl 4-(2-{[(3*S*,4*R*)-3-(acetyloxy)oxan-4-yl]amino}-5-chloro-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)piperidine-1-carboxylate (110 mg, 0.177 mmol), $Pd(PPh_3)_4$ (20 mg, 0.018 mmol) and $Zn(CN)_2$ (31 mg, 0.265 mmol) in DMA (1.5 mL) was stirred for 2 h at 130 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of water/ice (5 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 7 mL). The combined organic layers were washed with brine (3 x 9 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (1/1) to afford *tert*-butyl 4-(2-{[(3*S*,4*R*)-3-(acetyloxy)oxan-4-yl]amino}-5-chloro-6-cyanopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)piperidine-1-carboxylate (53 mg, 57%) as an off-white solid. MS ESI calculated for $C_{24}H_{31}ClN_6O_5$ $[M + H]^+$, 519.20, found 519.50. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 5.26 (d, *J* = 7.2 Hz, 1H), 5.03-4.98 (m, 1H), 4.35-4.31 (m, 2H), 4.08-3.96 (m, 1H), 3.98-3.95 (m, 2H), 3.60-3.57 (m, 1H), 3.48-3.42 (m, 2H), 2.86-2.83 (m, 2H), 2.42-2.38 (m, 1H), 2.19-2.12 (m, 3H), 2.08-2.05 (m, 3H), 1.87 (m, 2H), 1.60-1.58 (m, 9H).

Step 6: (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(piperidin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate trifluoroacetate

[00371] A mixture of *tert*-butyl 4-(2-{[(3*S*,4*R*)-3-(acetyloxy)oxan-4-yl]amino}-5-chloro-6-cyanopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)piperidine-1-carboxylate (50 mg, 0.096 mmol) and TFA (0.5 mL) in DCM (0.5 mL) was stirred for 1 h at room temperature. The resulting mixture was

concentrated under reduced pressure to afford (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(piperidin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate trifluoroacetate (40 mg, 80%) as a brown solid; MS ESI calculated for $C_{21}H_{24}ClF_3N_6O_5$ [M-CF_3COO]$^+$, 419.15, found 419.15.

Step 7: (3*S*,4*R*)-4-({5-chloro-6-cyano-7-[1-(2,2-difluoroethyl)piperidin-4-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00372] A mixture of (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(piperidin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate trifluoroacetate (40 mg, 0.077 mmol), K_2CO_3 (32 mg, 0.231 mmol) and 2,2-difluoroethyl trifluoromethanesulfonate (25 mg, 0.115 mmol) in DMF (1 mL) was stirred for 4 h at room temperature. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-({5-chloro-6-cyano-7-[1-(2,2-difluoroethyl)piperidin-4-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (23 mg, 61%) as an off-white solid. MS ESI calculated for $C_{21}H_{25}ClF_2N_6O_3$ [M + H]$^+$, 483.16, found 483.10. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 5.34-5.28 (m, 1H), 5.22-5.18 (m, 1H), 5.05-5.01 (m, 1H), 4.15-3.70 (m, 5H), 3.61-3.25 (m, 5H), 2.99-2.89 (m, 2H), 2.44-2.36 (m, 1H), 2.08-2.05 (m, 6H), 1.72-1.68 (m, 2H).

Example 34:

5-chloro-7-[1-(2,2-difluoroethyl)piperidin-4-yl]-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00373] To a stirred mixture of (3*S*,4*R*)-4-({5-chloro-6-cyano-7-[1-(2,2-difluoroethyl)piperidin-4-yl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (23 mg, 0.048 mmol) in MeOH (1 mL) was added K_2CO_3 (13 mg, 0.096 mmol) at room temperature. The reaction mixture was stirred for 1h at room. The resulting mixture was diluted with water (20 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/2) to afford 5-chloro-7-[1-(2,2-difluoroethyl)piperidin-4-yl]-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (5.3 mg, 25%) as an off-white solid. MS ESI calculated for $C_{19}H_{23}ClF_2N_6O_2$ [M + H]$^+$, 441.15, found 441.30; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.72 (s, 1H), 5.98 (t, *J* = 55.6 Hz, 1H), 5.11-5.08 (m, 1H), 4.08-4.05 (m, 1H), 4.01-3.96 (m, 1H), 3.87-3.82 (m, 1H), 3.75-3.70 (m, 1H), 3.59-3.56 (m, 1H), 3.38-3.33 (m, 1H), 3.22-3.18 (m, 3H), 2.89-2.85 (m, 2H), 2.45-2.42 (m, 4H), 2.28-2.20 (m, 1H), 1.90-1.85 (m, 2H), 1.76-1.62 (m, 2H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -118.13 (2F).

Example 35:

5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(3-methylbut-2-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: 4,4,5,5-tetramethyl-2-(3-methylbut-2-en-2-yl)-1,3,2-dioxaborolane

[00374] To a stirred solution of 2-bromo-3-methylbut-2-ene (2 g, 13.420 mmol) and dimethyl(phenyl)(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)silane (7.04 g, 26.840 mmol) in DME (20 mL) was added MeOK (1.13 g, 16.104 mmol) in portions at 30 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction was quenched with TBAF (30 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford 4,4,5,5-tetramethyl-2-(3-methylbut-2-en-2-yl)-1,3,2-dioxaborolane (2.2 g, 83%) as colorless oil; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.08-2.01 (m, 3H), 1.76-1.75 (m, 3H), 1.74-1.68 (m, 3H), 1.31-1.17 (m, 12H).

Step 2: (3*S*,4*R*)-4-{[7-(3-methylbut-2-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00375] To a stirred mixture of 4,4,5,5-tetramethyl-2-(3-methylbut-2-en-2-yl)-1,3,2-dioxaborolane (1.18 g, 2.534 mmol) and Pd(dppf)Cl_2.DCM (172.01 mg, 0.211 mmol) in dioxane (50 mL) were added (3*S*,4*R*)-4-({7-bromopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (750 mg, 2.112 mmol), and K_3PO_4 (896 mg, 4.224 mmol) in water (12.5 mL) under nitrogen atmosphere. The reaction mixture was stirred for 2 h at 100°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (30 mL).The aqueous layer was extracted with EtOAc (3 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[7-(3-methylbut-2-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (540 mg, 74%) as a yellow oil; MS ESI calculated for $C_{18}H_{24}N_4O_3$ $[M + H]^+$, 345.18, found 345.05; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.53 (s, 1H), 6.73 (d, *J* = 4.4 Hz, 1H), 6.52 (d, *J* = 4.4 Hz, 1H), 4.96-4.90 (m, 2H), 4.07-4.03 (m, 2H), 3.98-3.94 (m, 1H), 3.62-3.56 (m, 1H), 3.48-3.43 (m, 1H), 2.44-2.40 (m, 1H), 2.07-2.03 (m, 6H), 1.94-1.91 (m, 3H), 1.71-1.68 (m, 3H), 1.67-1.62 (m, 1H).

Step 3: (3*S*,4*R*)-4-{[5-chloro-7-(3-methylbut-2-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00376] To a stirred mixture of (3*S*,4*R*)-4-{[7-(3-methylbut-2-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (1.9 g, 5.517 mmol) in DMF (20 mL) was added NCS (0.74 g, 5.517

mmol) at room temperature. The reaction mixture was stirred for 16 h at room temperature. The resulting mixture was diluted with water (40 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*S*,4*R*)-4-{[5-chloro-7-(3-methylbut-2-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (930 mg, 44%) as a light yellow oil; MS ESI calculated for $C_{18}H_{23}ClN_4O_3$ $[M + H]^+$, 379.15, found 379.10; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.58 (s, 1H), 6.42 (s, 1H), 5.00-4.95 (m, 1H), 4.94-4.90 (m, 1H), 4.10-3.98 (m, 2H), 3.98-3.94 (m, 1H), 3.62-3.54 (m, 1H), 3.48-3.44 (m, 1H), 2.41-2.38 (m, 1H), 2.09-1.98 (m, 6H), 1.90-1.85 (m, 3H), 1.73-1.59 (m, 4H).

Step 4: (4*R*)-4-{[5-chloro-6-iodo-7-(3-methylbut-2-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol

[00377] To a stirred mixture of (3*S*,4*R*)-4-{[5-chloro-7-(3-methylbut-2-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (930 mg, 2.455 mmol) in DMF (10 mL) was added I_2 (2.49 g, 9.820 mmol) at room temperature. The reaction mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (20 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (4*R*)-4-{[5-chloro-6-iodo-7-(3-methylbut-2-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (910 mg, 80 %) as a light yellow solid; MS ESI calculated for $C_{18}H_{22}ClIN_4O_3$ $[M + H]^+$, 505.04, found 505.15; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.58 (s, 1H), 5.01-4.92 (m, 2H), 4.07-3.89 (m, 3H), 3.62-3.56 (m, 1H), 3.48-3.38 (m, 1H), 2.43-2.32 (m, 1H), 2.05-1.99 (m, 3H), 1.96-1.89 (m, 6H), 1.72-1.51 (m, 4H).

Step 5: (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbut-2-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00378] To a stirred mixture of (3*S*,4*R*)-4-{[5-chloro-6-iodo-7-(3-methylbut-2-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (900 mg, 1.783 mmol) and $Zn(CN)_2$ (126 mg, 1.070 mmol) in DMF (10 mL) was added $Pd(PPh_3)_4$ (206 mg, 0.178 mmol). The reaction mixture was stirred for 1.5 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was

concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbut-2-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (700 mg, 97%) as a light yellow solid. MS ESI calculated for $C_{19}H_{22}ClN_5O_3$ $[M + H]^+$, 404.14, found 404.15; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 5.21-5.18 (m, 1H), 4.96-4.92 (m, 1H), 4.04-3.96 (m, 3H), 3.58-3.52 (m, 1H), 3.45-3.40 (m, 1H), 2.38-2.34 (m, 1H), 2.09-2.05 (m, 3H), 2.04-1.97 (m, 3H), 1.95-1.90 (m, 3H), 1.77-1.68 (m, 4H).

Example 35:

5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(3-methylbut-2-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00379] To a stirred mixture of (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbut-2-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (730 mg, 1.808 mmol) in MeOH (10 mL) was added K_2CO_3 (499 mg, 3.616 mmol) at room temperature. The reaction mixture was stirred for 1.5 h at room temperature. The resulting mixture was concentrated under reduced pressure. The resulting mixture was diluted with water (20 mL), extracted with EtOAc (3 x 10 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/2) to afford 5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(3-methylbut-2-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (640 mg, 97%) as a light yellow solid; MS ESI calculated for $C_{17}H_{20}ClN_5O_2$ $[M + H]^+$, 362.13, found 362.15; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.73 (s, 1H), 5.03 (brs, 1H), 4.10-4.08 (m, 1H), 4.07-3.98 (m, 1H), 3.79-3.72 (m, 1H), 3.68-3.63 (m, 1H), 3.53-3.46 (m, 1H), 3.25-3.22 (m, 1H), 2.17-2.08 (m, 1H), 2.04-1.98 (m, 6H), 1.78-1.62 (m, 4H).

Example 36:

2-(5-fluoro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)cyclopentane-1-carbonitrile (single diastereoisomer, absolute chiral configuration of cyclopentane-1-carbonitrile was not determined) (CHIRALPAK IG, Hexane/EtOH/DCM = 50/25/25, 1st peak)

Example 37:

2-(5-fluoro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)cyclopentane-1-carbonitrile (single diastereoisomer, absolute chiral configuration of cyclopentane-1-carbonitrile was not determined) (CHIRALPAK IG, Hexane/EtOH/DCM = 50/25/25, 2nd peak)

Step 1: 2-cyanocyclopent-1-en-1-yl trifluoromethanesulfonate

[00380] To a stirred solution of 2-oxocyclopentane-1-carbonitrile (10 g, 91.636 mmol) and TEA (27.8 g, 274.908 mmol) in DCE (200 mL) was added Tf_2O (38.8 g, 137.454 mmol) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 0 °C under nitrogen atmosphere. The resulting mixture was diluted with water (300 mL). The resulting mixture was extracted with DCM (3 x 300 mL). The combined organic layers were washed with brine (3 x 300 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford 2-cyanocyclopent-1-en-1-yl trifluoromethanesulfonate (12.3 g, 55%) as yellow oil. MS EI calculated for $C_7H_6F_3NO_3S$ [M], 241.00, found 240.99. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.89-2.82 (m, 2H), 2.78-2.66 (m, 2H), 2.25-2.12 (m, 2H).

Step 2: 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-1-ene-1-carbonitrile

[00381] To a stirred solution of 2-cyanocyclopent-1-en-1-yl trifluoromethanesulfonate (11.5 g, 47.682 mmol) and bis(pinacolato)diboron (18.1 g, 71.523 mmol) in dioxane (200 mL) were added Pd(dppf)Cl_2.DCM (3.3 g, 4.768 mmol) and KOAc (14.0 g, 143.046 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 100 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered, the filter cake was washed with EtOAc (3 x 100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-1-ene-1-carbonitrile (10 g, 95%) as a yellow semi-solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.72-2.60 (m, 4H), 2.01-1.90 (m, 2H), 1.36-1.28 (m, 12H).

Step 3: (3*S*,4*R*)-4-{[7-(2-cyanocyclopent-1-en-1-yl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00382] To a stirred solution of (3*S*,4*R*)-4-({7-bromo-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (2 g, 5.359 mmol) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-1-ene-1-carbonitrile (2.3 g, 10.718 mmol) in dioxane (40 mL) and water (8 mL) were added Cs_2CO_3 (3.5 g, 10.718 mmol) and Pd(dppf)Cl_2.DCM (436 mg, 0.536 mmol) under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 100 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[7-(2-cyanocyclopent-1-en-1-yl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (1.5 g, 72%) as a yellow solid. MS ESI calculated for $C_{19}H_{20}FN_5O_3$ $[M + H]^+$, 386.16,

found 386.20. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 7.02 (s, 1H), 5.18-5.16 (m, 1H), 5.00-4.96 (m, 1H), 4.06-3.90 (m, 3H), 3.60-3.56 (m, 1H), 3.49-3.44 (m, 1H), 3.36-3.25 (m, 2H), 2.82-2.77 (m, 2H), 2.44-2.38 (m, 1H), 2.14-2.11 (m, 2H), 2.10-2.07 (m, 3H), 1.72-1.60 (m, 1H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -159.33 (1F).

Step 4: (3*S*,4*R*)-4-{[7-(2-cyanocyclopentyl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00383] To a solution of (3*S*,4*R*)-4-{[7-(2-cyanocyclopent-1-en-1-yl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (1.2 g, 3.114 mmol) in EtOAc (40 mL) was added Pd/C (10%, 600 mg) under nitrogen atmosphere. The mixture was stirred for 16 h at 50 °C under hydrogen atmosphere using a hydrogen balloon. The resulting mixture was filtered through a Celite pad and concentrated under reduced pressure. The residue was dissolved in DCM (20 mL). To this was added DDQ (699 mg, 3.082 mmol) at room temperature. The resulting mixture was stirred for additional 2 h at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq.) (20 mL) at 0 °C. The resulting mixture was extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[7-(2-cyanocyclopentyl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (160 mg, 16 %) as a yellow solid. MS ESI calculated for $C_{19}H_{22}FN_5O_3$ $[M + H]^+$, 388.17 found 388.20. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.62 (d, *J* = 3.2 Hz, 1H), 6.37 (d, *J* = 8.4 Hz, 1H), 5.22-5.01 (m, 2H), 4.03-4.00 (m, 1H), 3.99-3.89 (m, 1H), 3.93-3.75 (m, 1H), 3.73-3.48 (m, 3H), 2.42-2.37 (m, 1H), 2.30-2.16 (m, 3H), 2.16-2.06 (m, 5H), 1.95-1.85 (m, 1H), 1.76-1.63 (m, 1H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -159.20 (1F).

Step 5: 2-(5-fluoro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)cyclopentane-1-carbonitrile

[00384] A solution of (3*S*,4*R*)-4-{[7-(2-cyanocyclopentyl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (160 mg, 0.413 mmol) and K_2CO_3 (171 mg, 1.239 mmol) in MeOH (2 mL) was stirred for 1 h at room temperature. The residue was purified by reversed-phase chromatography with the following conditions: column, C18; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford 2-(5-fluoro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)cyclopentane-1-carbonitrile (110 mg, 77%) as a yellow solid. MS ESI calculated for $C_{17}H_{20}FN_5O_2$ $[M + H]^+$, 346.16, found 346.10.

Example 36:

2-(5-fluoro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)cyclopentane-1-carbonitrile (single diastereoisomer, absolute chiral

configuration of cyclopentane-1-carbonitrile was not determined) (CHIRALPAK IG, Hexane/EtOH/DCM = 50/25/25, 1st peak)

Example 37:

2-(5-fluoro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)cyclopentane-1-carbonitrile (single diastereoisomer, absolute chiral configuration of cyclopentane-1-carbonitrile was not determined) (CHIRALPAK IG, Hexane/EtOH/DCM = 50/25/25, 2nd peak)

[00385] (1*S*,2*R*)-2-(5-fluoro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)cyclopentane-1-carbonitrile (100 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hexane, Mobile Phase B: EtOH/DCM (1/1); Flow rate: 20 mL/min; Gradient: A; Wave Length: 254/220nm nm;

[00386] RT_1: 5.61 min to afford 2-(5-fluoro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)cyclopentane-1-carbonitrile (single diastereoisomer, absolute chiral configuration of cyclopentane-1-carbonitrile was not determined) (CHIRALPAK IG, Hexane/EtOH/DCM = 50/25/25, 1st peak) (31.7 mg, 31%) as a yellow solid, MS ESI calculated for $C_{17}H_{20}FN_5O_2$ $[M + H]^+$, 346.16, found 346.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.63 (s, 1H), 6.35 (s, 1H), 4.97-4.96 (m, 1H), 4.10-4.08 (m, 1H), 4.05-3.96 (m, 1H), 3.79-3.64 (m, 3H), 3.62-3.55 (m, 1H), 3.54-3.47 (m, 1H), 3.28-3.23 (m, 1H), 2.30-2.15 (m, 3H), 2.15-2.03 (m, 3H), 1.95-1.79 (m, 1H), 1.78-1.66 (m, 1H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -158.92 (1F).

[00387] RT_2: 7.17 min to afford 2-(5-fluoro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)cyclopentane-1-carbonitrile (single diastereoisomer, absolute chiral configuration of cyclopentane-1-carbonitrile was not determined) (CHIRALPAK IG, Hexane/EtOH/DCM = 50/25/25, 2nd peak) (19.3 mg, 19%) as a yellow solid. MS ESI calculated for $C_{17}H_{20}FN_5O_2$ $[M + H]^+$, 346.16, found 346.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.63 (s, 1H), 6.39 (s, 1H), 4.97-4.96 (m, 1H), 4.11-4.07 (m, 1H), 4.05-3.98 (m, 1H), 3.80-3.64 (m, 3H), 3.55-3.47 (m, 2H), 3.29-3.24 (m, 1H), 2.30-2.15 (m, 3H), 2.15-2.03 (m, 3H), 1.95-1.79 (m, 1H), 1.78-1.66 (m, 1H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -158.73 (1F).

Example 38:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-methanesulfonylpiperidin-3-yl acetate

[00388] To a stirred mixture of (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidin-3-yl acetate hydrochloride (60 mg, 0.145 mmol) in EtOAc (1 mL) was

added $NaHCO_3$ (1 mL). To this was added Methanesulfonic anhydride (38 mg, 0.217 mmol). The resulting mixture was stirred for 1 h at room temperature. The reaction was diluted with water (5 mL) at room temperature. The resulting mixture was extracted with DCM (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-methanesulfonylpiperidin-3-yl acetate (60 mg, 81%) as yellow oil. MS ESI calculated for $C_{18}H_{23}ClN_6O_4S$ $[M + H]^+$, 455.12, found 455.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 5.32 (s, 1H), 5.11-5.09 (m, 1H), 4.16-4.14 (m, 1H), 3.98-3.79 (m, 2H), 3.69-3.67 (m, 1H), 3.12-3.09 (m, 2H), 2.90 (s, 3H), 2.50-2.40 (m, 1H), 2.09 (s, 3H), 1.76-1.70 (m, 1H), 1.51-1.48 (m, 6H).

Example 38:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00389] A mixture of (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-methanesulfonylpiperidin-3-yl acetate (60 mg, 0.132 mmol) and K_2CO_3 (36 mg, 0.264 mmol) in MeOH (1 mL) was stirred for 30 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10mmol/L NH_4HCO_3), 10% to 80%; detector, UV 254 nm to afford 5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (30.6 mg, 55%) as a light yellow solid. MS ESI calculated for $C_{16}H_{21}ClN_6O_3S$ $[M + H]^+$, 413.11, found 413.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 5.19 (s, 1H), 4.00-3.96 (m, 1H), 3.85-3.79 (m, 3H), 3.67-3.63 (m, 1H), 2.99-2.93 (m, 1H), 2.89 (s, 3H), 2.84-2.79 (m, 1H), 2.34-2.30 (m, 1H), 1.80-1.70 (m, 1H), 1.52-148 (m, 6H).

Example 39:

5-chloro-7-(2,3-difluoro-3-methylbutan-2-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 2,3-difluoro-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH/DCM = 70/15/15, 1st peak)

Example 40:

5-chloro-7-(2,3-difluoro-3-methylbutan-2-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 2,3-difluoro-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH/DCM = 70/15/15, 2nd peak)

Example 40:

5-chloro-7-(2,3-difluoro-3-methylbutan-2-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 2,3-difluoro-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH/DCM = 70/15/15, 2nd peak)

[00390] To a stirred mixture of 5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(3-methylbut-2-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (100 mg, 0.276 mmol), 2-iodobenzoic acid (13.71 mg, 0.055 mmol) and Selectfluor (146.86 mg, 0.414 mmol) in DCE (0.75 mL) was added HF (0.75 mL, 8.324 mmol) at 0 °C. The reaction mixture was stirred for 16 h at room temperature. The resulting mixture was basified to pH 8 with saturated $NaHCO_3$ (aq.). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 3 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/2). The crude product was separated with Chrial-HPLC (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μm; Mobile Phase A: hexane, Mobile Phase B: EtOH/DCM (1/1); Flow rate: 20 mL/min; Gradient: A:B = 70:30; Wave Length: 254/220nm nm;

[00391] RT_1: 8.63 min to afford 5-chloro-7-(2,3-difluoro-3-methylbutan-2-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 2,3-difluoro-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH/DCM = 70/15/15, 1st peak) (23.9 mg, 20%) as an off-white solid. MS ESI calculated for $C_{17}H_{20}ClF_2N_5O_2$ $[M + H]^+$, 399.13, found 400.20; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.76 (s, 1H), 5.17 (brs, 1H), 4.10-4.06 (m, 1H), 3.99-3.94 (m, 1H), 3.73-3.67 (m, 2H), 3.55-3.50 (m, 1H), 3.34-3.29 (m, 1H), 2.25-2.20 (m, 1H), 2.11 (d, *J* = 24.8 Hz, 3H), 1.69-1.60 (m, 1H), 1.53-1.47 (m, 6H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -144.84--147.98 (2F).

[00392] RT_2: 11.20 min to afford 5-chloro-7-(2,3-difluoro-3-methylbutan-2-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 2,3-difluoro-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH/DCM = 70/15/15, 2nd peak) (24.5 mg, 21%) as an off-white solid; MS ESI calculated for $C_{17}H_{20}ClF_2N_5O_2$ $[M + H]^+$, 399.13, found 400.25; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.76 (s, 1H), 5.18 (brs, 1H), 4.10-4.06 (m, 1H), 4.01-3.97 (m, 1H), 3.77-3.72 (m, 1H), 3.68-3.63 (m, 1H), 3.55-3.49 (m, 1H), 3.28-3.23 (m, 1H), 2.17-2.07 (m, 4H), 1.72-1.66 (m, 1H), 1.54-1.48 (m, 6H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -144.67--147.83 (2F).

Example 41:

2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-isopropyl-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00393] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (190 mg, 0.398 mmol), Et_3N (166 uL, 1.194 mmol), $Pd(dba)_2$ (23 mg, 0.040 mmol) and di-*tert*-butyl[2',4',6'-tris(propan-2-yl)-[1,1'-biphenyl]-2-yl]phosphane (34 mg, 0.080 mmol) in dioxane (3 mL) was added Et_3SiH (258 uL, 1.592 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 100 °C under nitrogen atmosphere. The reaction was quenched by the addition of water (20 mL) at room temperature. The resulting mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (140 mg, 71%) as yellow oil. MS ESI calculated for $C_{22}H_{30}N_6O_4$ $[M + H]^+$, 443.23, found 443.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.63 (s, 1H), 6.98 (s, 1H), 5.30-5.20 (m, 1H), 4.94-4.80 (m, 1H), 4.15-3.71 (m, 3H), 3.69-3.68 (m, 1H), 3.22-3.16 (m, 2H), 2.35-2.25 (m, 1H), 2.09-2.05 (s, 3H), 1.90-1.80 (m, 1H), 1.59-1.49 (m, 15H).

Step 2: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({6-cyano-5-iodo-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00394] A mixture of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (140 mg, 0.316 mmol) and I_2 (321 mg, 1.264 mmol) in DMF (2 mL) was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (15 mL) at room temperature. The resulting mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (0~50%) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({6-cyano-5-iodo-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (170 mg, 85%) as a yellow solid. MS ESI calculated for $C_{22}H_{29}IN_6O_4$ $[M + H]^+$, 569.13, found 569.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.48 (s, 1H), 5.40-5.25 (m, 1H), 5.00-4.80 (m, 1H), 4.00-3.70 (m,

3H), 3.69-3.60 (m, 1H), 3.25-3.20 (m, 2H), 2.35-2.31 (m, 1H), 2.09-2.05 (m, 3H), 1.50-1.48 (m, 16H).

Step 3: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[6-cyano-7-isopropyl-5-(trifluoromethyl)-7a*H*-cyclopenta[*d*]pyrimidin-2-yl]amino}piperidine-1-carboxylate

[00395] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({6-cyano-5-iodo-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (170 mg, 0.299 mmol), CuI (57 mg, 0.299 mmol) and KF (52 mg, 0.897 mmol) in DMF (2 mL) was added methyl 2,2-difluoro-2-sulfoacetate (287 mg, 1.495 mmol) at room temperature. The resulting mixture was stirred for 3 h at 80 °C. The reaction was quenched by the addition of sat. NH_4Cl (aq.)/$NH_3.H_2O$ (9/1) (50 mL) at room temperature. The resulting mixture was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[6-cyano-7-isopropyl-5-(trifluoromethyl)-7a*H*-cyclopenta[*d*]pyrimidin-2-yl]amino}piperidine-1-carboxylate (140 mg, 87%) as colorless oil. MS ESI calculated for $C_{23}H_{29}F_3N_6O_4$ $[M + H]^+$, 511.22, found 511.45. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.87 (s, 1H), 4.94-4.92 (m, 1H), 4.16-4.14 (m, 1H), 3.99-3.95 (m, 2H), 3.74-3.69 (m, 1H), 3.15-3.09 (m, 2H), 2.34-2.25 (m, 1H), 2.08 (s, 3H), 1.53-1.50 (m, 16H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -54.94 (3F).

Step 4: (3*R*,4*R*)-4-{[6-cyano-7-isopropyl-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride

[00396] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[6-cyano-7-isopropyl-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (140 mg, 0.274 mmol) in DCM (2 mL) were added HCl (gas) in 1,4-dioxane (2 mL) at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford (3*R*,4*R*)-4-{[6-cyano-7-isopropyl-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (120 mg, 88%) as an off-white solid. MS ESI calculated for $C_{18}H_{22}ClF_3N_6O_2$ $[M - Cl]^+$, 411.17, found 411.20.

Step 5: (3*R*,4*R*)-4-{[6-cyano-7-isopropyl-5-(trifluoromethyl)-7a*H*-cyclopenta[d]pyrimidin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate

[00397] To a stirred mixture of (3*R*,4*R*)-4-{[6-cyano-7-isopropyl-5-(trifluoromethyl)-7a*H*-cyclopenta[d]pyrimidin-2-yl]amino}piperidin-3-yl acetate hydrochloride (120 mg, 0.269 mmol) in EtOAc (2 mL) was added sat. $NaHCO_3$ (2 mL). To this was added methanesulfonic anhydride (70 mg, 0.404 mmol). The resulting mixture was stirred for 16 h at room temperature. The reaction was diluted with water (5 mL). The resulting mixture was extracted with DCM (2 x 10

mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*R*,4*R*)-4-{[6-cyano-7-isopropyl-5-(trifluoromethyl)-7a*H*-cyclopenta[*d*]pyrimidin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (110 mg, 83%) as yellow oil. MS ESI calculated for $C_{19}H_{23}F_3N_6O_4S$ $[M + H]^+$, 489.15, found 489.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.89 (s, 1H), 5.32-5.10 (m, 1H), 3.93-3.90 (m, 2H), 3.74-3.72(m, 2H), 3.07-3.04 (m, 2H), 2.92-2.88 (m, 3H), 2.50-2.30 (m, 1H), 2.09-2.07 (m, 3H), 1.80-1.70 (m, 1H), 1.53-1.51 (m, 6H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -54.97 (3F).

Example 41:

2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-isopropyl-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00398] To a stirred mixture of (3*R*,4*R*)-4-{[6-cyano-7-isopropyl-5-(trifluoromethyl)-7a*H*-cyclopenta[*d*]pyrimidin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (115 mg, 0.236 mmol) in MeOH (2 mL) were added K_2CO_3 (65 mg, 0.472 mmol). The resulting mixture was stirred for 30 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 5% to 70%; detector, UV 254 nm to afford 2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-isopropyl-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (83.0 mg, 77%) as an off-white solid. MS ESI calculated for $C_{17}H_{21}F_3N_6O_3S$ $[M + H]^+$, 447.13, found 447.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.90 (s, 1H), 5.21-5.19 (m, 1H), 4.00-3.94 (m, 1H), 3.89-3.80 (m, 3H), 3.73-3.66 (m, 1H), 3.03-3.00 (m, 2H), 2.99-2.97 (m, 3H), 2.90-2.80 (m, 1H), 2.37-2.33 (m, 1H), 1.82-1.78 (m, 1H), 1.50-1.40 (m, 6H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -54.99 (3F).

Example 42:

7-(3,3-difluorobutan-2-yl)-2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3,3-difluorobutan-2-yl was not determined) (CHIRALPAK IE, Hexane/EtOH = 80/20, 1st peak)

Example 43:

7-(3,3-difluorobutan-2-yl)-2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3,3-difluorobutan-2-yl was not determined) (CHIRALPAK IE, Hexane/EtOH = 80/20, 2nd peak)

Step 1: *tert*-butyl (3*R*,4*R*)-3-fluoro-4-({7-[1-(2-methyl-1,3-dioxolan-2-yl)ethenyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00399] To a solution of *tert*-butyl (3*R*,4*R*)-4-({7-bromopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate (2 g, 4.828 mmol) and 4,4,5,5-tetramethyl-2-[1-(2-methyl-1,3-dioxolan-2-yl)ethenyl]-1,3,2-dioxaborolane (1.28 g, 5.311 mmol) in 1,4-dioxane (80 mL) and water (20 mL) were added Pd(dppf)Cl_2.DCM (0.39 g, 0.483 mmol) and K_3PO_4 (2.05 g, 9.656 mmol). The reaction mixture was stirred for 2 h at 100 °C under nitrogen atmosphere. The resulting mixture was diluted with water (150 mL) and extracted with EtOAc (2 x 150 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-3-fluoro-4-({7-[1-(2-methyl-1,3-dioxolan-2-yl)ethenyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (1.94 g, 62%) as a light yellow solid. MS ESI calculated for $C_{22}H_{30}FN_5O_4$ $[M + H]^+$, 448.23, found 448.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.63 (s, 1H), 7.13 (d, *J* = 4.8 Hz, 1H), 6.73 (d, *J* = 4.8 Hz, 1H), 6.64-6.63 (m, 1H), 6.03-6.02 (m, 1H), 4.92-4.90 (m, 1H), 4.63-4.59 (m, 1H), 4.08-4.00 (m, 4H), 3.99-3.92 (m, 2H), 3.73-3.72 (m, 1H), 3.31-3.29 (m, 2H), 2.39-2.38 (m, 1H), 2.04-2.03 (m, 1H), 1.51-1.49 (m, 12H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -189.45 (1F).

Step 2: *tert*-butyl (3*R*,4*R*)-3-fluoro-4-({7-[1-(2-methyl-1,3-dioxolan-2-yl)ethyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00400] To a stirred solution of *tert*-butyl (3*R*,4*R*)-3-fluoro-4-({7-[1-(2-methyl-1,3-dioxolan-2-yl)ethenyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (1.9 g, 4.246 mmol) and 2-nitrobenzenesulfonohydrazide (3.69 g, 16.984 mmol) in CH_3CN (40 mL) was added K_3PO_4 (1.80 g, 8.492 mmol) at room temperature. The resulting mixture was stirred for 16 h at 60 °C. The resulting mixture was diluted with water (200 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-3-fluoro-4-({7-[1-(2-methyl-1,3-dioxolan-2-yl)ethyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (1.2 g, 62%) as a light yellow solid. MS ESI calculated for $C_{22}H_{32}FN_5O_4$ $[M + H]^+$, 450.24, found 450.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.53 (s, 1H), 6.72-6.68 (m, 2H), 4.85-4.82 (m, 1H), 4.74-4.48 (m, 1H), 4.04-3.94 (m, 7H), 3.70-3.69 (m, 1H), 3.49-3.41 (m, 2H), 2.37-2.30 (m, 1H), 2.15-1.96 (m, 1H), 1.51-1.49 (m, 9H), 1.43-1.36 (m, 3H), 1.30-1.26 (m, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -189.53 (1F).

Step 3: 3-(2-{[(3*R*,4*R*)-3-fluoropiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)butan-2-one

[00401] A solution of *tert*-butyl (3*R*,4*R*)-3-fluoro-4-({7-[1-(2-methyl-1,3-dioxolan-2-yl)ethyl]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (1.49 g, 3.315 mmol) in HCOOH (15 mL) was stirred for 16 h at room temperature. The resulting mixture was concentrated under reduced pressure. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 5% to 30%; detector, UV 254 nm to afford 3-(2-{[(3*R*,4*R*)-3-fluoropiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)butan-2-one (1.0 g, 98%) as a light yellow solid. MS ESI calculated for $C_{15}H_{20}FN_5O$ $[M + H]^+$, 306.17, found 306.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.59 (s, 1H), 6.77 (d, *J* = 4.8 Hz, 1H), 6.62-6.53 (m, 1H), 5.59-5.57 (m, 1H), 5.01-4.84 (m, 1H), 4.26-4.23 (m, 1H), 4.11-4.10 (m, 1H), 3.59-3.42 (m, 1H), 3.28-3.27 (m, 1H), 3.19-3.14 (m, 1H), 2.45-2.43 (m, 1H), 2.21-2.19 (m, 1H), 2.11-3.10 (m, 3H), 1.86-1.85 (m, 1H), 1.56-1.54 (m, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -189.53 (1F).

Step 4: 3-(2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)butan-2-one

[00402] To a stirred solution of 3-(2-{[(3*R*,4*R*)-3-fluoropiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)butan-2-one (1.0 g, 3.275 mmol) in EtOAc (15 mL) was added Methanesulfonic anhydride (0.91 g, 5.240 mmol) at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was diluted with water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc/EtOH (8/3/1) to afford 3-(2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)butan-2-one (640 mg, 50%) as a light yellow solid. MS ESI calculated for $C_{16}H_{22}FN_5O_3S$ $[M + H]^+$, 384.14, found 384.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.61 (s, 1H), 6.78 (d, *J* = 4.8 Hz, 1H), 6.64 (d, *J* = 4.8 Hz, 1H), 5.02-5.00 (m, 1H), 4.80-4.62 (m, 1H), 4.20-4.16 (m, 1H), 4.01-3.83 (m, 2H), 3.69-3.57 (m, 1H), 3.30-3.25 (m, 2H), 2.92 (s, 3H), 2.45-2.38 (m, 1H), 2.08 (s, 3H), 1.73-1.71 (m, 1H), 1.57-1.54 (m, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -188.63 (1F).

Step 5: (3*R*,4*R*)-*N*-[7-(3,3-difluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]-3-fluoro-1-methanesulfonylpiperidin-4-amine

[00403] To a stirred solution of 3-(2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)butan-2-one (640 mg, 1.669 mmol) in DAST (13 mL) was added TEA.3HF (269 mg, 1.669 mmol) at room temperature. The resulting mixture was

stirred for 16 h at room temperature. The resulting mixture was diluted with DCM (100 mL). The reaction was quenched with sat. $NaHCO_3$ (aq.) (100 mL) at 0 °C. The resulting mixture was extracted with DCM (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc/EtOH (12/3/1) to afford (3*R*,4*R*)-*N*-[7-(3,3-difluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]-3-fluoro-1-methanesulfonylpiperidin-4-amine (130 mg, 19 %) as light yellow oil. MS ESI calculated for $C_{16}H_{22}F_3N_5O_2S$ $[M + H]^+$, 406.14, found 406.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.55 (s, 1H), 6.93 (d, *J* = 4.8 Hz, 1H), 6.82 (d, *J* = 4.8 Hz, 1H), 5.86 (s, 1H), 4.88-4.65 (m, 1H), 4.17-4.15 (m, 1H), 4.09-4.00 (m, 1H), 3.87-3.73 (m, 1H), 3.58-3.56 (m, 1H), 3.50-3.37 (m, 2H), 2.93 (s, 3H), 2.45-2.43 (m, 1H), 1.86-1.84 (m, 1H), 1.59-1.54 (m, 3H), 1.49 (d, *J* = 7.2 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -94.07--97.69 (2F), -188.33 (1F).

Step 6: (3*R*,4*R*)-*N*-[5-chloro-7-(3,3-difluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]-3-fluoro-1-methanesulfonylpiperidin-4-amine

[00404] To a stirred solution of (3*R*,4*R*)-*N*-[7-(3,3-difluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]-3-fluoro-1-methanesulfonylpiperidin-4-amine (130 mg, 0.321 mmol) in DMF (2 mL) was added NCS (43 mg, 0.321 mmol) at room temperature. The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford (3*R*,4*R*)-*N*-[5-chloro-7-(3,3-difluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]-3-fluoro-1-methanesulfonylpiperidin-4-amine (110 mg, 77%) as a light yellow solid. MS ESI calculated for $C_{16}H_{21}ClF_3N_6O_2S$ $[M + H]^+$, 440.11, found 440.10.

Step 7: (3*R*,4*R*)-*N*-[5-chloro-7-(3,3-difluorobutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]-3-fluoro-1-methanesulfonylpiperidin-4-amine

[00405] To a stirred solution of (3*R*,4*R*)-*N*-[5-chloro-7-(3,3-difluorobutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]-3-fluoro-1-methanesulfonylpiperidin-4-amine (110 mg, 0.250 mmol) in DMF (2 mL) was added I_2 (254 mg, 1.000 mmol) at room temperature. The resulting mixture was stirred for 20 h at 35 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 20% to 50%; detector, UV 254 nm to afford (3*R*,4*R*)-*N*-[5-chloro-7-(3,3-difluorobutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]-3-fluoro-1-methanesulfonylpiperidin-4-amine (110 mg, 77 %) as a light yellow solid. MS ESI calculated for $C_{16}H_{20}ClF_3IN_5O_2S$ $[M + H]^+$, 566.00, found 566.15. ^1H NMR (400 MHz, Chloroform-*d*) δ

8.61 (s, 1H), 5.22-5.20 (m, 1H), 4.89-4.72 (m, 1H), 4.04-4.01 (m, 1H), 3.91-3.87 (m, 1H), 3.63-3.60 (m, 1H), 3.49-3.48 (m, 2H), 3.26-3.21 (m, 2H), 2.92-2.91 (m, 3H), 2.45-2.43 (m, 1H), 1.72-1.67 (m, 3H), 1.57-1.56 (m, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -91.99--92.50 (2F).-188.43 (1F).

Step 8: 5-chloro-7-(3,3-difluorobutan-2-yl)-2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00406] To a stirred solution of (3*R*,4*R*)-*N*-[5-chloro-7-(3,3-difluorobutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]-3-fluoro-1-methanesulfonylpiperidin-4-amine (110 mg, 0.194 mmol) and $Zn(CN)_2$ (14 mg, 0.116 mmol) in DMF (2 mL) was added $Pd(PPh_3)_4$ (23 mg, 0.019 mmol) at room temperature. The resulting mixture was stirred for 2 h at 130 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 20% to 50%; detector, UV 254 nm to afford 5-chloro-7-(3,3-difluorobutan-2-yl)-2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (80 mg, 88 %) as a light yellow solid. MS ESI calculated for $C_{17}H_{20}ClF_3N_6O_2S$ $[M + H]^+$, 465.10, found 465.15.

Step 9: 7-(3,3-difluorobutan-2-yl)-2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00407] To a stirred solution of 5-chloro-7-(3,3-difluorobutan-2-yl)-2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (70 mg, 0.151 mmol) and Et_3SiH (53 mg, 0.453 mmol) in 1,4-dioxane (2 mL) were added TEA (61 mg, 0.604 mmol) and *t*-BuXPhos (13 mg, 0.030 mmol) at room temperature. The resulting mixture was stirred for 2 h at 100 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc/EtOH (18/5/1) to afford 7-(3,3-difluorobutan-2-yl)-2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (40 mg, 61%) as a light yellow solid. MS ESI calculated for $C_{17}H_{21}F_3N_6O_2S$ $[M + H]^+$, 431.14, found 431.15. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 7.12 (s, 1H), 5.34 (brs, 1H), 4.80-4.73 (m, 1H), 4.21-4.15 (m, 1H), 4.13-4.08 (m, 1H), 4.01-3.85 (m, 1H), 3.70-3.67 (m, 1H), 3.32-3.19 (m, 2H), 2.92 (s, 3H), 2.45-2.43 (m, 1H), 1.83-1.78 (m, 1H), 1.75-1.67 (m, 3H), 1.65-1.62 (m, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -93.05--93.78 (2F), -188.64 (1F).

Step 10: 7-(3,3-difluorobutan-2-yl)-2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-5-iodopyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00408] To a stirred solution of 7-(3,3-difluorobutan-2-yl)-2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (40 mg, 0.093 mmol) in DMF (1 mL) was added I_2 (94 mg, 0.372 mmol) at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc/EtOH (4/3/1) to afford 7-(3,3-difluorobutan-2-yl)-2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-5-iodopyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (40 mg, 77%) as a light yellow solid. MS ESI calculated for $C_{17}H_{20}F_3IN_6O_2S$ $[M + H]^+$, 557.04, found 557.05. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.56 (s, 1H), 5.36 (s, 1H), 4.79-4.69 (m, 1H), 4.22-4.14 (m, 1H), 4.10-3.88 (m, 2H), 3.71-3.67 (m, 1H), 3.25-3.16 (m, 2H), 2.93-2.92 (m, 3H), 2.42-2.40 (m, 1H), 1.82-1.78 (m, 1H), 1.72-1.41 (m, 6H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -92.75--93.64 (2F), -188.65 (1F).

Step 11: 7-(3,3-difluorobutan-2-yl)-2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00409] To a stirred solution of 7-(3,3-difluorobutan-2-yl)-2-{[(3*R*,4R)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-5-iodopyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (30 mg, 0.054 mmol) and methyl 2,2-difluoro-2-sulfoacetate (52 mg, 0.270 mmol) in DMF (0.5 mL) were added CuI (10 mg, 0.054 mmol) and KF (9 mg, 0.162 mmol) at room temperature. The resulting mixture was stirred for 2 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 20% to 50%; detector, UV 254 nm to afford 7-(3,3-difluorobutan-2-yl)-2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (20 mg, 74%) as a light yellow solid. MS ESI calculated for $C_{18}H_{20}F_6N_6O_2S$ $[M + H]^+$, 499.13, found 499.15.

Example 42:

7-(3,3-difluorobutan-2-yl)-2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3,3-difluorobutan-2-yl was not determined) (CHIRALPAK IE, Hexane/EtOH = 80/20, 1st peak)

Example 43:

7-(3,3-difluorobutan-2-yl)-2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3,3-difluorobutan-2-yl was not determined) (CHIRALPAK IE, Hexane/EtOH = 80/20, 2nd peak)

[00410] 7-(3,3-difluorobutan-2-yl)-2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (20 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IE, 2*25 cm, 5 μm; Mobile Phase A: hexane, Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: A:B = 80:20; Wave Length: 254/220 nm;

[00411] RT_1: 12.04 min to afford 7-(3,3-difluorobutan-2-yl)-2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3,3-difluorobutan-2-yl was not determined) (CHIRALPAK IE, Hexane/EtOH = 80/20, 1st peak) (5 mg, 26 %) as a white solid. MS ESI calculated for $C_{18}H_{20}F_6N_6O_2S$ $[M + H]^+$, 499.13, found 499.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.95 (s, 1H), 5.18 (d, *J* = 7.2 Hz, 1H), 4.79-4.65 (m, 1H), 4.26-4.21 (m, 1H), 4.09-3.94 (m, 2H), 3.74-3.71 (m, 1H), 3.22-3.12 (m, 2H), 2.93 (s, 3H), 2.43-2.37 (m, 1H), 1.88-1.81 (m, 1H), 1.75-1.59 (m, 6H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -55.04 (3F), -92.76--94.28 (2F), -188.69 (1F).

[00412] RT_2: 13.69 min to afford 7-(3,3-difluorobutan-2-yl)-2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3,3-difluorobutan-2-yl was not determined) (CHIRALPAK IE, Hexane/EtOH = 80/20, 2nd peak) (6 mg, 30%) as a white solid. MS ESI calculated for $C_{18}H_{20}F_6N_6O_2S$ $[M + H]^+$, 499.13, found 499.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.95 (s, 1H), 5.19 (d, *J* = 7.2 Hz, 1H), 4.79-4.66 (m, 1H), 4.26-4.21 (m, 1H), 4.08-4.00 (m, 2H), 3.76-3.72 (m, 1H), 3.22-3.12 (m, 2H), 2.93 (s, 3H), 2.43-2.37 (m, 1H), 1.85-1.79 (m, 1H), 1.78-1.57 (m, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -55.03 (3F), -91.66--93.81 (2F), -188.52 (1F).

Example 44:

2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-hydroxy-3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-hydroxy-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/MeOH/EtOH = 85/7.5/7.5, 1st peak)

Example 45:

2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-hydroxy-3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer,

absolute chiral configuration of 3-hydroxy-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/MeOH/EtOH = 85/7.5/7.5, 2nd peak)

Step 1: *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00413] A solution of 3-{2,5-dichloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl}-2-methylbutan-2-ol (353 mg, 1.288 mmol), *tert*-butyl (3*R*,4*R*)-4-amino-3-fluoropiperidine-1-carboxylate (843 mg, 3.864 mmol) and DIEA (1 g, 7.728 mmol) in NMP (4 mL) was stirred for 16 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (320 mg, 54%) as a light yellow solid. MS ESI calculated for $C_{21}H_{31}ClFN_5O_3$ $[M + H]^+$, 456.21, found 456.30. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.59 (d, *J* = 1.6 Hz, 1H), 6.49 (s, 1H), 4.87-4.85 (m, 1H), 4.65-4.40 (m, 1H), 4.08-3.98 (m, 2H), 3.83-3.76 (m, 1H), 3.53-3.46 (m, 1H), 3.32-3.23 (m, 2H), 2.34-2.28 (m, 1H), 1.50-1.49 (m, 10H), 1.38-1.36 (m, 3H), 1.24-1.21 (m, 6H).

Step 2: *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00414] A solution of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (300 mg, 0.658 mmol) and I_2 (668 mg, 2.632 mmol) in DMF (3 mL, 38.765 mmol) was stirred for 16 h at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (50 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (210 mg, 54%) as a light yellow solid. MS ESI calculated for $C_{21}H_{30}ClFIN_5O_3$ $[M + H]^+$, 582.11, found 582.15.

Step 3: *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-hydroxy-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00415] A solution of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(3-hydroxy-3-methylbutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (300 mg, 0.516 mmol), $Zn(CN)_2$ (36 mg, 0.310 mmol) and $Pd(PPh_3)_4$ (60 mg, 0.052 mmol) in DMF (3 mL) was stirred for 2 h at room temperature under nitrogen atmosphere. The mixture was allowed to cool

down to room temperature. The reaction was quenched by the addition of water (50 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-hydroxy-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (210 mg, 84%) as a light yellow solid. MS ESI calculated for $C_{22}H_{30}ClFN_6O_3$ $[M + H]^+$, 481.21, found 481.20.

Step 4: *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-7-(3-hydroxy-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00416] A solution of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-hydroxy-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (150 mg, 0.312 mmol), Et_3SiH (109 mg, 0.936 mmol), Et_3N (126 mg, 1.248 mmol), $Pd(dba)_2$ (18 mg, 0.031 mmol) and *t*-BuXPhos (26 mg, 0.062 mmol) in 1,4-dioxane (3 mL) was stirred for 2 h at 80 °C under nitrogen atmosphere. The reaction was quenched by the addition of water (50 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-7-(3-hydroxy-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (130 mg, 93%) as a light yellow solid. MS ESI calculated for $C_{22}H_{31}FN_6O_3$ $[M + H]^+$, 447.25, found 447.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.67 (d, *J* = 2.4 Hz, 1H), 7.05 (d, *J* = 4.0 Hz, 1H), 5.19 (brs, 1H), 4.52-4.38 (m, 1H), 3.98-3.90 (m, 2H), 3.62-3.54 (m, 1H), 3.20-3.13 (m, 3H), 2.38-2.18 (m, 1H), 1.58-1.49 (m, 13H), 1.37-1.36 (m, 3H), 1.20-1.17 (m, 3H).

Step 5: *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-7-(3-hydroxy-3-methylbutan-2-yl)-5-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00417] A solution of *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-7-(3-hydroxy-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (130 mg, 0.291 mmol) and I_2 (296 mg, 1.164 mmol) in DMF (2 mL) was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (50 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-

7-(3-hydroxy-3-methylbutan-2-yl)-5-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (130 mg, 78%) as a light yellow solid. MS ESI calculated for $C_{22}H_{30}FIN_6O_3$ $[M + H]^+$, 573.14, found 573.30.

Step 6: *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-7-(3-hydroxy-3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00418] A solution of *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-7-(3-hydroxy-3-methylbutan-2-yl)-5-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (120 mg, 0.210 mmol), methyl 2,2-difluoro-2-sulfoacetate (201 mg, 1.050 mmol), KF (37 mg, 0.630 mmol) and CuI (40 mg, 0.210 mmol) in DMF (2 mL) was stirred for 2 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (30 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-7-(3-hydroxy-3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (56 mg, 51%) as a light yellow solid. MS ESI calculated for $C_{23}H_{30}F_4N_6O_3$ $[M + H]^+$, 515.23, found 515.30.

Step 7: 2-{[(3*R*,4*R*)-3-fluoropiperidin-4-yl]amino}-7-(3-hydroxy-3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride

[00419] A solution of *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-7-(3-hydroxy-3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (56 mg, 0.109 mmol) in HCl (gas) in 1,4-dioxane (1 mL) and DCM (1 mL) was stirred for 2 h at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to afford 2-{[(3*R*,4*R*)-3-fluoropiperidin-4-yl]amino}-7-(3-hydroxy-3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (35 mg, 71%) as a light yellow solid. MS ESI calculated for $C_{18}H_{23}ClF_4N_6O$ $[M - Cl]^+$, 415.18, found 415.20.

Step 8: 2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-hydroxy-3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00420] A solution of 2-{[(3*R*,4*R*)-3-fluoropiperidin-4-yl]amino}-7-(3-hydroxy-3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (30 mg, 0.072 mmol), $NaHCO_3$ (61 mg, 0.720 mmol) and methanesulfonic anhydride (25 mg, 0.144 mmol) in EtOAc (1 mL) and water (2 mL) was stirred for 30 min at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of water (20 mL) at room temperature. The resulting

mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-hydroxy-3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (30 mg, 84%) as a light yellow solid. MS ESI calculated for $C_{19}H_{24}F_4N_6O_3S$ $[M + H]^+$, 493.16, found 493.20.

Example 44:

2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-hydroxy-3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-hydroxy-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/MeOH/EtOH = 85/7.5/7.5, 1st peak)

Example 45:

2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-hydroxy-3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-hydroxy-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/MeOH/EtOH = 85/7.5/7.5, 2nd peak)

[00421] 2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-hydroxy-3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (18 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μm; Mobile Phase A: hexane, Mobile Phase B: MeOH/EtOH (1/1); Flow rate: 20 mL/min; Gradient: A:B = 85:15; Wave Length: 254/220nm nm;

[00422] RT_1: 18.59 min to afford 2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-hydroxy-3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-hydroxy-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/MeOH/EtOH = 85/7.5/7.5, 1st peak) (1.9 mg, 10%) %) as a white solid. MS ESI calculated for $C_{19}H_{24}F_4N_6O_3S$ $[M + H]^+$, 493.16; found 493.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 9.04 (s, 1H), 5.20 (d, *J* = 7.2 Hz, 1H), 4.82-4.69 (m, 1H), 4.11-4.10 (m, 1H), 4.01-3.93 (m, 1H), 3.73-3.70 (m, 1H), 3.32-3.17 (m, 3H), 2.93 (s, 3H), 2.42-2.38 (m, 1H), 1.93-1.84 (m, 1H), 1.61-1.60 (m, 3H), 1.43-1.42 (m, 3H), 1.36-1.34 (m, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -53.88--54.06 (3F),-188.50 (1F).

[00423] RT_2: 24.22 min afford 2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-hydroxy-3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-hydroxy-3-methylbutan-2-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/MeOH/EtOH = 85/7.5/7.5, 2nd peak) (1.7

mg, 9%) as a white solid. MS ESI calculated for $C_{19}H_{24}F_4N_6O_3S$ $[M + H]^+$, 493.16; found 493.20. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.04 (s, 1H), 5.25 (d, *J* = 7.0 Hz, 1H), 4.87-4.70 (m, 1H), 4.10-3.96 (m, 2H), 3.73-3.70 (m, 1H), 3.32-3.28 (m, 1H), 3.26-3.15 (m, 2H), 2.93 (s, 3H), 2.43-2.39 (m, 1H), 1.90-1.82 (m, 1H), 1.61-1.60 (m, 3H), 1.43-1.42 (m, 3H), 1.36-1.34 (m, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ 53.81--54.61 (3F),-188.32 (1F).

Example 46:

2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1,1,1-trifluoropropan-2-yl was not determined) (CHIRAL ART Cellulose-SC, Hexane/^{i}PrOH = 75/25, 1st peak)

Example 47:

2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1,1,1-trifluoropropan-2-yl was not determined) (CHIRAL ART Cellulose-SC, Hexane/^{i}PrOH = 75/25, 2nd peak)

Step 1: *tert*-butyl (3*R*,4*R*)-3-fluoro-4-{[7-(3,3,3-trifluoroprop-1-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00424] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-4-({7-bromopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate (1 g, 2.41 mmol), Cs_2CO_3 (1.57 g, 4.83 mmol) and water (2 mL) in dioxane (8 mL) was added Pd(dppf)Cl_2·DCM (0.20 g, 0.24 mmol) at room temperature. The reaction mixture was degassed with nitrogen for three times. To the above mixture was added 4,4,6-trimethyl-2-(3,3,3-trifluoroprop-1-en-2-yl)-1,3,2-dioxaborinane (0.80 g, 3.62 mmol) at room temperature. The resulting mixture was stirred for additional 2 h at 80 °C. The resulting mixture was allowed to cool down to room temperature. The resulting mixture was quenched with water (100 mL) and extracted with ethyl acetate (3 x 70 mL). The combined organic layers were washed with saturated brine (50 mL), dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: C18 column; mobile phase, acetonitrile in water (Plus 10 mM NH_4HCO_3), 20% to 60%; detector, UV 254 nm. The fractions contained desired product were combined and concentrated to afford *tert*-butyl (3*R*,4*R*)-3-fluoro-4-{[7-(3,3,3-trifluoroprop-1-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (1.1 g, 96%) as a light brown solid. MS ESI calculated for $C_{19}H_{23}F_4N_5O_2$ $[M + H]^+$, 430.18, found 430.30. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.97 (s, 1H), 7.42 (s, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 7.87 (d, *J* = 4.8 Hz, 1H), 6.81-6.78 (m, 1H), 6.32 (d, *J* = 1.2 Hz, 1H), 4.69-4.52 (m, 1H), 4.19-

4.00 (m, 1H), 3.93-3.85 (m, 2H), 3.69-3.65 (m, 1H), 3.23-3.16 (m, 1H), 2.04-1.99 (m, 1H), 1.57-1.49 (m, 1H), 1.45-1.40 (m, 9H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -63.81 (3F), -186.97 (1F).

Step 2: *tert*-butyl (3*R*,4*R*)-3-fluoro-4-{[7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00425] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-3-fluoro-4-{[7-(3,3,3-trifluoroprop-1-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (1.1 g, 2.56 mmol) and K_3PO_4 (1.09 g, 5.12 mmol) in CH_3CN (11 mL) was added 2-nitrobenzenesulfonohydrazide (2.23 g, 10.25 mmol) at room temperature. The resulting mixture was stirred for 3 h at 60 °C. The resulting mixture was allowed to cool down to room temperature. The resulting mixture was quenched with water (100 mL) and extracted with ethyl acetate (3 x 70 mL). The combined organic layers were washed with saturated brine (50 mL), dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: C18 column; mobile phase, acetonitrile in water (Plus 10 mM NH_4HCO_3), 30% to 70%; detector, UV 254 nm. The fractions contained desired product were combined and concentrated to afford *tert*-butyl (3*R*,4*R*)-3-fluoro-4-{[7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (340 mg, 31%) as a light yellow solid. MS ESI calculated for $C_{19}H_{25}F_4N_5O_2$ [M + H]$^+$, 432.19, found 432.30. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (s, 1H), 7.16 (d, J = 7.6 Hz, 1H), 6.78 (d, J = 4.8 Hz, 1H), 6.72 (dd, J = 4.8, 2.8 Hz, 1H), 4.71-4.53 (m, 1H), 4.42-4.34 (m, 1H), 4.08-4.03 (m, 1H), 3.94-3.82 (m, 2H), 3.67-3.63 (m, 1H), 3.25-3.15 (m, 1H), 2.01-1.98 (m, 1H), 1.59-1.48 (m, 4H), 1.45-1.40 (m, 9H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -70.16 (3F), -187.05 (1F).

Step 3: *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00426] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-3-fluoro-4-{[7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (340 mg, 0.79 mmol) in THF (4 mL) was added NCS (111 mg, 0.83 mmol) at room temperature. The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was quenched with water (70 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with saturated brine (50 mL), dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: C18 column; mobile phase, acetonitrile in water (Plus 10 mM NH_4HCO_3), 30% to 70%; detector, UV 254 nm. The fractions contained desired product were combined and concentrated to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-

f][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (290 mg, 79%) as a light yellow solid. MS ESI calculated for $C_{19}H_{24}ClF_4N_5O_2$ $[M + H]^+$, 466.16, found 466.20.

Step 4: *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-iodo-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00427] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (290 mg, 0.62 mmol) in DMF (5 mL) was added I_2 (632 mg, 2.49 mmol) at room temperature. The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was quenched with saturated aqueous $Na_2S_2O_3$ (150 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with saturated brine (70 mL), dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with petroleum ether/ethyl acetate (3/1). The fractions contained desired product were combined and concentrated to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-iodo-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (230 mg, 62%) as a light yellow solid. MS ESI calculated for $C_{19}H_{23}ClF_4IN_5O_2$ $[M + H]^+$, 592.05, found 592.20.

Step 5: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00428] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-iodo-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (220 mg, 0.37 mmol) and $Zn(CN)_2$ (87 mg, 0.74 mmol) in DMF (3 mL) was added $Pd(PPh_3)_4$ (43 mg, 0.04 mmol) at room temperature. The reaction mixture was degassed with nitrogen for three times and irradiated with microwave radiation for 2 h at 140 °C. The resulting mixture was allowed to cool down to room temperature. The resulting mixture was quenched with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with saturated brine (50 mL), dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: C18 column; mobile phase, acetonitrile in water (10 mM NH_4HCO_3), 30% to 70%; detector, UV 254 nm. The fractions contained desired product were combined and concentrated to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (190 mg, 81%, Purity 77.6%) as a light yellow solid. MS ESI calculated for $C_{20}H_{23}ClF_4N_6O_2$ $[M + H]^+$, 491.15, found 491.15.

Step 6: *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00429] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (190 mg, 0.30 mmol), TEA (182 mg, 1.80 mmol) and *t*BuXPhos (51 mg, 0.12 mmol) in dioxane (2 mL) were added $Pd(dba)_2$ (35 mg, 0.06 mmol) and Et_3SiH (175 mg, 1.50 mmol) at room temperature. The resulting mixture was stirred for additional 7 h at 100 °C under nitrogen atmosphere. The resulting mixture was quenched with water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with saturated brine (50 mL), dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (120 mg, 81%) as a light yellow solid. MS ESI calculated for $C_{20}H_{24}F_4N_6O_2$ $[M + H]^+$, 457.19, found 457.30. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.73 (s, 1H), 7.05 (s, 1H), 5.11-5.07 (m, 1H), 4.62-4.42 (m, 2H), 4.07-4.02 (m, 2H), 3.90-9.79 (m, 1H), 3.25-3.13 (m, 2H), 2.35-2.30 (m, 1H), 1.85-1.80 (m, 3H), 1.53-1.51(m, 1H), 1.45-1.40 (m, 9H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -70.45 (3F), -189.54 (1F).

Step 7: *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-5-iodo-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00430] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (120 mg, 0.24 mmol) in DMF (2 mL) was added I_2 (247mg, 0.97 mmol) at room temperature. The resulting mixture was stirred for 7 h at 40 °C. The resulting mixture was allowed to cool down to room temperature. The resulting mixture was quenched with saturated aqueous $Na_2S_2O_3$ (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with saturated brine (50 mL), dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: C18 column; mobile phase, acetonitrile in water (10 mM NH_4HCO_3), 30% to 70%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-5-iodo-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (110 mg, 73%, Purity 94.3%) as a light yellow solid.. MS ESI calculated for $C_{20}H_{23}F_4IN_6O_2$ $[M + H]^+$, 583.09, found 583.10.

Step 8: *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-5-(trifluoromethyl)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00431] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-5-iodo-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (110 mg, 0.18 mmol, 94.3%) and KF (31 mg, 0.53 mmol) in DMF (2 mL) were added CuI (34 mg, 0.18 mmol)

at room temperature and methyl 2,2-difluoro-2-sulfoacetate (171 mg, 0.89 mmol) under nitrogen atmosphere. The resulting mixture was stirred for additional 3 h at 80 °C under nitrogen atmosphere. The resulting mixture was allowed to cool down to room temperature. The resulting mixture was quenched with saturated aqueous NH_4Cl (100 mL) and extracted with ethyl acetate (3 x 70 mL). The combined organic layers were washed with saturated brine (60 mL), dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: C18 column; mobile phase, acetonitrile in water (10 mM NH_4HCO_3), 30% to 70%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-5-(trifluoromethyl)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (90 mg, 94%) as a light yellow solid. MS ESI calculated for $C_{21}H_{23}F_7N_6O_2$ $[M + H]^+$, 525.18, found 525.20.

Step 9: 2-{[(3*R*,4*R*)-3-fluoropiperidin-4-yl]amino}-5-(trifluoromethyl)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride

[00432] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-5-(trifluoromethyl)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (90 mg, 0.17 mmol) in DCM (2 mL) was added HCl (gas) in 1,4-dioxane (2 mL) at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford 2-{[(3*R*,4*R*)-3-fluoropiperidin-4-yl]amino}-5-(trifluoromethyl)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (110 mg, crude) as a light yellow solid. MS ESI calculated for $C_{16}H_{16}ClF_7N_6$ $[M - Cl]^+$, 425.12, found 425.20.

Step 10: 2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-5-(trifluoromethyl)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00433] To a stirred mixture of 2-{[(3*R*,4*R*)-3-fluoropiperidin-4-yl]amino}-5-(trifluoromethyl)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (100 mg, 0.22 mmol) in EtOAc (1.5 mL) was added sat. $NaHCO_3$ (1.5 mL) at 0 °C. To this was added methanesulfonic anhydride (56 mg, 0.33 mmol) at 0 °C. The resulting mixture was stirred for additional 1 h at room temperature. The resulting mixture was quenched with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with saturated brine (20 mL), dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc/EtOH (4/3/1). The crude product was purified by reverse flash chromatography with the following conditions: C18 column; mobile phase, acetonitrile in water (10 mM NH_4HCO_3), 30% to 70%; detector, UV 254 nm to afford 2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-5-(trifluoromethyl)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-

carbonitrile (55 mg, 49%) as a light yellow solid. MS ESI calculated for $C_{17}H_{17}F_7N_6O_2S$ [M + H]$^+$, 503.10, found 503.15.

Example 46:

2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1,1,1-trifluoropropan-2-yl was not determined) (CHIRAL ART Cellulose-SC, Hexane/^{i}PrOH = 75/25, 1st peak)

Example 47:

2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1,1,1-trifluoropropan-2-yl was not determined) (CHIRAL ART Cellulose-SC, Hexane/^{i}PrOH = 75/25, 2nd peak)

[00434] (2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-5-(trifluoromethyl)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (55 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Cellulose-SC, 2*25 cm, 5 μm; Mobile Phase A: Hexane, Mobile Phase B: ^{i}PrOH; Flow rate: 20 mL/min; Gradient: A:B = 75:25; Wave Length: 254/220 nm nm;

[00435] RT$_1$: 18.00 min to afford 2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1,1,1-trifluoropropan-2-yl was not determined) (CHIRAL ART Cellulose-SC, Hexane/^{i}PrOH = 75/25, 1st peak) (18.3 mg, 32%) as an off-white solid. MS ESI calculated for $C_{17}H_{17}F_7N_6O_2S$ [M + H]$^+$, 503.10, found 503.15. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.98 (s, 1H), 5.22 (brs, 1H), 4.78-4.60 (m, 1H), 4.55-4.47 (m, 1H), 4.10-4.03 (m, 2H), 3.78-3.75 (m, 1H), 3.16-3.06 (m, 2H), 2.93 (s, 3H), 2.44-2.39 (m, 1H), 1.86-1.72 (m, 4H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -55.13 (3F), -70.20 (3F), -188.45 (1F).

[00436] RT$_2$: 21.73 min to afford 2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)-7-(1,1,1-trifluoropropan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 1,1,1-trifluoropropan-2-yl was not determined) (CHIRAL ART Cellulose-SC, Hexane/^{i}PrOH = 75/25, 2nd peak) (16.9 mg, 30%) as an off-white solid. MS ESI calculated for $C_{17}H_{17}F_7N_6O_2S$ [M + H]$^+$, 503.10, found 503.10. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.98 (s, 1H), 5.22 (brs, 1H), 4.75-4.60 (m, 1H), 4.55-4.47 (m, 1H), 4.12-4.00 (m, 2H), 3.78-3.75 (m, 1H), 3.16-3.06 (m, 2H), 2.93 (s, 3H), 2.44-2.39 (m, 1H), 1.86-1.81 (m, 4H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -55.13 (3F), -70.00 (3F), -188.75 (1F).

Example 48:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: *tert*-butyl (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-hydroxypiperidine-1-carboxylate

[00437] To a stirred solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (50 mg, 0.105 mmol) in MeOH (2 mL) was added K_2CO_3 (29 mg, 0.210 mmol) at room temperature. The resulting mixture was stirred for 30 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-hydroxypiperidine-1-carboxylate (37 mg, 81%) as a light yellow solid. MS ESI calculated for $C_{20}H_{27}ClN_6O_3$ $[M + H]^+$, 435.18, found 435.20.

Step 2: 5-chloro-2-{[(3*R*,4*R*)-3-hydroxypiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride

[00438] A solution of *tert*-butyl (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-hydroxypiperidine-1-carboxylate (37 mg, 0.085 mmol) and HCl (gas) in 1,4-dioxane (2 mL) in DCM (2 mL) was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford 5-chloro-2-{[(3*R*,4*R*)-3-hydroxypiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (28 mg, 88%) as a light yellow solid. MS ESI calculated for $C_{15}H_{20}Cl_2N_6O$ $[M - Cl]^+$, 335.13, found 335.10.

Example 48:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00439] To a stirred solution of 5-chloro-2-{[(3*R*,4*R*)-3-hydroxypiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (28 mg, 0.084 mmol) and DIEA (54 mg, 0.420 mmol) in DCM (2 mL) was added TFAA (87 mg, 0.420 mmol) at room temperature. The resulting mixture was stirred for 40 min at room temperature. The resulting mixture was diluted with water (20 mL) and extracted with DCM (2 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 20% to 55%; detector, UV 254 nm to afford 5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-

6-carbonitrile (21 mg, 59%) as a light yellow solid. MS ESI calculated for $C_{17}H_{18}ClF_3N_6O_2$ [M + H]$^+$, 431.11, found 431.10. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.72 (s, 1H), 5.35-5.20 (m, 1H), 4.60-4.51 (m, 1H), 4.20-3.97 (m, 1H), 3.90-3.82 (m, 1H), 3.77-3.61 (m, 2H), 3.37-3.11 (m, 1H), 3.01-2.95 (m, 1H), 2.38-2.25 (m, 1H), 1.71-1.61 (m, 1H), 1.50-1.44 (m, 6H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -68.94 (3F).

Example 49:

5-chloro-2-{[(3*R*,4*R*)-1-(cyclopropanesulfonyl)-3-hydroxypiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-(cyclopropanesulfonyl)piperidin-3-yl acetate

[00440] The (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidin-3-yl acetate hydrochloride (70 mg, 0.169 mmol) was acidified to pH 8-9 with sat. $NaHCO_3$ (aq.). To this was added cyclopropanesulfonyl chloride (71 mg, 0.507 mmol) in EtOAc (2 mL) at 0 °C. The resulting mixture was stirred for additional 16 h at room temperature. The resulting mixture was diluted with water (5 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (1/1) to afford (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-(cyclopropanesulfonyl)piperidin-3-yl acetate (40 mg, 49%) as a light yellow solid. MS ESI calculated for $C_{20}H_{25}ClN_6O_4S$ [M + H]$^+$, 481.13, found 481.15.

Example 49:

5-chloro-2-{[(3*R*,4*R*)-1-(cyclopropanesulfonyl)-3-hydroxypiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00441] A solution of (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-(cyclopropanesulfonyl)piperidin-3-yl acetate (35 mg, 0.073 mmol) and K_2CO_3 (30.17 mg, 0.219 mmol) in MeOH (2 mL) was stirred for 1 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: column, C18; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford 5-chloro-2-{[(3*R*,4*R*)-1-(cyclopropanesulfonyl)-3-hydroxypiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (19.7 mg, 61%) as an off-white solid. MS ESI calculated for $C_{18}H_{23}ClN_6O_3S$ [M + H]$^+$, 439.12 found 439.25. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 (s, 1H), 7.43 (brs, 1H), 5.23 (brs, 1H), 3.69-3.46 (m, 5H), 2.99-2.93 (m, 1H), 2.79-2.75 (m, 1H), 2.66-2.59 (m, 1H), 2.15-2.10 (m, 1H), 1.53-1.49 (m, 1H), 1.42-1.39 (m, 6H), 1.05-0.92 (m, 4H).

Example 50:

5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-difluoromethanesulfonylpiperidin-3-yl acetate

[00442] (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidin-3-yl acetate (80 mg, 0.212 mmol) was acidified to pH 8-9 with saturated $NaHCO_3$ (aq.). To this was added difluoromethanesulfonyl chloride (96 mg, 0.636 mmol) in EtOAc (2 mL) at 0 °C. The resulting mixture was stirred for additional 16 h at room temperature. The resulting mixture was diluted with water (5 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (1/1) to afford (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-difluoromethanesulfonylpiperidin-3-yl acetate (40 mg, 38%) as a light yellow solid. MS ESI calculated for $C_{18}H_{21}ClF_2N_6O_4S$ $[M + H]^+$, 491.10, found 491.20.

Example 50:

5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00443] A solution of (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-difluoromethanesulfonylpiperidin-3-yl acetate (40 mg, 0.081 mmol) in MeOH (2 mL) was treated with K_2CO_3 (33 mg, 0.243 mmol) for 1 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: column, C18; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford 5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (17.9 mg, 48%) as an off-white solid. MS ESI calculated for $C_{16}H_{19}ClF_2N_6O_3S$ $[M + H]^+$, 449.09, found 449.10. ^1H NMR (400 MHz, DMSO-d_6) δ 8.97 (s, 1H), 7.53 (d, J = 6.8 Hz, 1H), 7.10 (t, J = 52.8 Hz, 1H), 5.37 (brs, 1H), 3.80-3.51 (m, 5H), 3.31-3.22 (m, 1H), 3.09-3.04 (m, 1H), 2.17-2.05 (m, 1H), 1.61-1.54 (m, 1H), 1.43-1.35 (m, 6H). ^{19}F NMR (377 MHz, DMSO-d_6) δ -123.04 (2F).

Example 51:

7-(3-ethyltetrahydrofuran-3-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-ethyltetrahydrofuran-3-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH/DCM = 70/15/15, 1st peak)

Example 52:

7-(3-ethyltetrahydrofuran-3-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-ethyltetrahydrofuran-3-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH/DCM = 70/15/15, 2nd peak)

Step 1: methyl 3-ethyloxolane-3-carboxylate

[00444] To a stirred solution of methyl oxolane-3-carboxylate (10 g, 76.83 mmol) and ethyl iodide (12.1 g, 77.60 mmol) in THF (100 mL) was added KHMDS (238 mL, 119.10 mmol) at -78 °C under nitrogen atmosphere. The resulting mixture was stirred for 4 h at room temperature under nitrogen atmosphere. The reaction was quenched with sat. NH_4Cl (800 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 500 mL). The combined organic layers were washed with brine (500 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford methyl 3-ethyloxolane-3-carboxylate (8.7 g, 71%) as yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.24-4.11 (m, 3H), 3.95-3.81 (m, 2H), 3.59 (d, *J* = 8.8 Hz, 1H), 2.51-2.43 (m, 1H),1.90-1.63 (m, 3H), 1.32-1.25 (m, 3H), 0.93-0.87 (m, 3H).

Step 2: 3-ethyloxolane-3-carboxylic acid

[00445] To a stirred solution of ethyl 3-ethyloxolane-3-carboxylate (7.5 g, 43.548 mmol) and MeOH (80 mL) in water (80 mL) was added $LiOH.H_2O$ (3.6 g, 87.096 mmol) at room temperature. The resulting mixture was stirred for 16 h at room temperature. The mixture was acidified to pH 2 with conc. HCl. The resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (3 x 200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 3-ethyloxolane-3-carboxylic acid (5.6 g, 89%) as yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.22-4.16 (m, 1H), 3.95-3.88 (m, 2H), 3.63-3.58 (m, 1H), 2.54-2.44 (m, 1H), 1.93-1.69 (m, 3H), 1.01-0.92 (m, 3H).

Step 3: 1,3-dioxoisoindol-2-yl 3-ethyloxolane-3-carboxylate

[00446] To a stirred solution of N-hydroxyphthalimide (5 g, 30.65 mmol) and 3-ethyloxolane-3-carboxylic acid (4.4 g, 30.65 mmol) in DCM (55 mL) was added DIC (4.2 g, 33.71 mmol) at 0 °C. The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (3 x 100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford 1,3-dioxoisoindol-2-yl 3-ethyloxolane-3-carboxylate (5.2 g, 58%) as colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93-7.89 (m, 2H), 7.84-7.80 (m, 2H), 4.37-

4.32 (m, 1H), 4.01-3.91 (m, 2H), 3.80-3.76 (m, 1H), 2.71-2.62 (m, 1H), 2.10-1.90 (m, 3H), 1.16-1.10 (m, 3H).

Step 4: 2,4-dichloro-7-(3-ethyloxolan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine

[00447] To a stirred solution of 1,3-dioxoisoindol-2-yl 3-ethyloxolane-3-carboxylate (150 mg, 0.51 mmol) and 2,4-dichloropyrrolo[2,1-*f*][1,2,4]triazine (195 mg, 1.03 mmol) and TFA (118 mg, 1.03 mmol) in DMA (2 mL) was added $Ir[dF(CF_3)PPy]_2(dtbpy)PF_6$ (11.6 mg, 0.01 mmol) under nitrogen atmosphere. The reaction mixture was irradiated with Blue LED for 16 h at room temperature under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% TFA), 70% to 90%; detector, UV 254 nm to afford 2,4-dichloro-7-(3-ethyloxolan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine (66 mg, 44%) as yellow oil. MS ESI calculated for $C_{12}H_{13}Cl_2N_3O$ $[M + H]^+$, 286.04, found 286.05 ^1H NMR (400 MHz, Chloroform-*d*) δ 7.06 (d, *J* = 4.8 Hz, 1H), 6.85 (d, *J* = 4.8 Hz, 1H), 4.23 (d, *J* = 8.8 Hz, 1H), 4.11 (d, *J* = 8.8 Hz, 1H), 4.08-4.00 (m, 1H), 3.94-3.85 (m, 1H), 2.55-2.46 (m, 1H), 2.36-2.27 (m, 1H), 2.17-2.02 (m, 2H), 0.69-0.61 (m, 3H).

Step 5: 2-chloro-7-(3-ethyloxolan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine

[00448] To a stirred mixture of 2,4-dichloro-7-(3-ethyloxolan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine (320 mg, 1.11 mmol) and *i*-PrOH (200 uL) in THF (4 mL) was added $NaBH_4$ (67 mg, 1.78 mmol) in portions at room temperature. The resulting mixture was stirred for 3 h at room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (3 x 10 mL). The filtrate was concentrated under reduced pressure. To this was added DDQ (380 mg, 1.677 mmol) in in DCM (10 mL) at 0 °C. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (60 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 2-chloro-7-(3-ethyloxolan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine (250 mg, 88%) as yellow oil. MS ESI calculated for $C_{12}H_{14}ClN_3O$ $[M + H]^+$, 252.08 found 252.35 ^1H NMR (400 MHz, Chloroform-*d*) δ 8.76 (s, 1H), 6.95 (d, *J* = 4.8 Hz, 1H), 6.85 (d, *J* = 4.8 Hz, 1H), 4.26-4.22 (m, 1H), 4.17-4.09 (m, 1H), 4.07-4.00 (m, 1H), 3.92-3.85 (m, 1H), 2.56-2.48 (m, 1H), 2.35-2.27 (m, 1H), 2.14-2.11 (m, 2H), 0.66-0.61 (m, 3H).

Step 6: (3*S*,4*R*)-4-{[7-(3-ethyloxolan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol

[00449] To a stirred mixture of 2-chloro-7-(3-ethyloxolan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine (250 mg, 0.99 mmol) and (3*S*,4*R*)-4-aminooxan-3-ol hydrochloride (763 mg, 4.96 mmol) in NMP (3 mL) was added DIEA (1.0 mL, 5.95 mmol). The resulting mixture was stirred for 4 h at 120 °C. The

resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% TFA), 30% to 50%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[7-(3-ethyloxolan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (320 mg, 96%) as yellow oil. MS ESI calculated for $C_{17}H_{24}N_4O_3$ $[M + H]^+$, 333.18 found 333.15.

Step 7: (3*S*,4*R*)-4-{[7-(3-ethyloxolan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00450] To a stirred mixture of (3*S*,4*R*)-4-{[7-(3-ethyloxolan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (300 mg, 0.90 mmol) and Ac_2O (170 uL, 1.80 mmol) in DCM (5 mL) was added TEA (251 uL, 1.80 mmol) at room temperature. The resulting mixture was stirred for 16 h at 50 °C. The reaction was quenched with water (50 mL). The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford (3*S*,4*R*)-4-{[7-(3-ethyloxolan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (320 mg, 94%) as yellow oil. MS ESI calculated for $C_{19}H_{26}N_4O_4$ $[M + H]^+$, 375.20 found 375.20 ^1H NMR (400 MHz, Chloroform-*d*) δ 8.53 (s, 1H), 6.75 (d, *J* = 4.8 Hz, 1H), 6.57 (d, *J* = 4.8 Hz, 1H), 5.30 (brs, 1H), 4.99-4.92 (m, 1H), 4.24-3.84 (m, 7H), 3.66-3.56 (m, 1H), 3.54-3.44 (m, 1H), 2.51-2.39 (m, 2H), 2.30-2.19 (m, 1H), 2.19-2.05 (m, 4H), 2.05-1.91 (m, 1H), 1.77-1.64 (m, 1H), 0.70-0.63 (m, 3H).

Step 8: (3*S*,4*R*)-4-{[5-chloro-7-(3-ethyloxolan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00451] To a stirred mixture of (3*S*,4*R*)-4-{[7-(3-ethyloxolan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (300 mg, 0.80 mmol) in DMF (4 mL) was added NCS (128 mg, 0.96 mmol) at room temperature. The reaction mixture was stirred for 16 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% TFA), 10% to 50%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-7-(3-ethyloxolan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (104 mg, 31%) as yellow oil. MS ESI calculated for $C_{19}H_{25}ClN_4O_4$ $[M + H]^+$, 409.16 found 409.15.

Step 9: (3*S*,4*R*)-4-{[5-chloro-7-(3-ethyloxolan-3-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00452] To a stirred mixture of (3*S*,4*R*)-4-{[5-chloro-7-(3-ethyloxolan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (300 mg, 0.73 mmol) in DMF (3 mL) was added I_2 (745 mg, 2.93 mmol) at room temperature. The resulting mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. Nas_2O_3 (aq.) (30 mL) at room temperature. The

resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% TFA), 10% to 50%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-7-(3-ethyloxolan-3-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (300 mg, 76%) as yellow oil. MS ESI calculated for $C_{19}H_{24}ClIN_4O_4$ $[M + H]^+$, 535.05 found 535.10

Step 10: (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(3-ethyloxolan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00453] To a stirred mixture of (3*S*,4*R*)-4-{[5-chloro-7-(3-ethyloxolan-3-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (130 mg, 0.24 mmol) and $Zn(CN)_2$ (57 mg, 0.48 mmol) in DMF (2 mL) was added $Pd(PPh_3)_4$ (56 mg, 0.04 mmol) under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(3-ethyloxolan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (100 mg, 94%) as yellow oil. MS ESI calculated for $C_{20}H_{24}ClN_5O_4$ $[M + H]^+$, 434.15 found 434.20 ^1H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 5.34 (brs, 1H), 4.99-4.90 (m, 1H), 4.47-4.39 (m, 1H), 4.20-4.11 (m, 1H), 4.09-3.94 (m, 4H), 3.91-3.82 (m, 1H), 3.62-3.52 (m, 1H), 3.49-3.40 (m, 1H), 2.65-2.57 (m, 2H), 2.41-2.33 (m, 1H), 2.16-2.01 (m, 5H), 1.93-1.82 (m, 1H), 0.84-0.75 (m, 3H).

Step 11: (3*S*,4*R*)-4-{[6-cyano-7-(3-ethyloxolan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00454] To a stirred mixture of (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(3-ethyloxolan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (100 mg, 0.23 mmol) and Et_3N (96 uL, 0.69 mmol) and *t*-BuXPhos (19 mg, 0.04 mmol) and $Pd(dba)_2$ (13 mg, 0.02 mmol) in dioxane (3 mL) was added Et_3SiH (145 uL, 0.92 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 100 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was quenchedwith water (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[6-cyano-7-(3-ethyloxolan-3-yl)pyrrolo[2,1-

f][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (75 mg, 81%) as yellow oil. MS ESI calculated for $C_{20}H_{25}N_5O_4$ $[M + H]^+$, 400.19 found 400.15.

Step 12: (3*S*,4*R*)-4-{[6-cyano-7-(3-ethyloxolan-3-yl)-5-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00455] To a stirred mixture of (3*S*,4*R*)-4-{[6-cyano-7-(3-ethyloxolan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (80 mg, 0.20 mmol) in DMF (2 mL) was added I_2 (203.33 mg, 0.80 mmol) at room temperature. The reaction mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (20 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[6-cyano-7-(3-ethyloxolan-3-yl)-5-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (80 mg, 76%) as yellow oil. MS ESI calculated for $C_{20}H_{24}IN_5O_4$ $[M + H]^+$, 526.09, found 526.15.

Step 13: (3*S*,4*R*)-4-{[6-cyano-7-(3-ethyloxolan-3-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00456] To a stirred mixture of (3*S*,4*R*)-4-{[6-cyano-7-(3-ethyloxolan-3-yl)-5-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (80 mg, 0.15 mmol) and methyl 2,2-difluoro-2-sulfoacetate (58 mg, 0.30 mmol) in DMF (2 mL) were added CuI (29 mg, 0.15 mmol) and KF (8.8 mg, 0.15 mmol) at room temperature. The resulting mixture was stirred for 4 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched with water (50 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[6-cyano-7-(3-ethyloxolan-3-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (62 mg, 87%) as yellow oil. MS ESI calculated for $C_{21}H_{24}F_3N_5O_4$ $[M + H]^+$, 468.18, found 468.15 ^1H NMR (400 MHz, Chloroform-*d*) δ 8.92 (s, 1H), 5.42 (brs, 1H), 4.99-4.91 (m, 1H), 4.53-4.45 (m, 1H), 4.21-4.10 (m, 1H), 4.09-3.95 (m, 4H), 3.92-3.82 (m, 1H), 3.61-3.49 (m, 1H), 3.47-3.39 (m, 1H), 2.72-2.57 (m, 2H), 2.41-2.32 (m, 1H), 2.16-1.98 (m, 4H), 1.96-1.83 (m, 1H), 1.75-1.62 (m, 1H), 0.84-0.76 (m, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -54.96 (3F).

Step 14: 7-(3-ethyloxolan-3-yl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00457] To a stirred mixture of (3*S*,4*R*)-4-{[6-cyano-7-(3-ethyloxolan-3-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (65 mg, 0.19 mmol) in MeOH (2 mL) was added K_2CO_3 (38 mg, 0.27 mmol) at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford 7-(3-ethyloxolan-3-yl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (50 mg, 84%) as a white solid. MS ESI calculated for $C_{19}H_{22}F_3N_5O_3$ $[M + H]^+$, 426.17, found 426.20.

Example 51:

7-(3-ethyltetrahydrofuran-3-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-ethyltetrahydrofuran-3-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH/DCM = 70/15/15, 1st peak)

Example 52:

7-(3-ethyltetrahydrofuran-3-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-ethyltetrahydrofuran-3-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH/DCM = 70/15/15, 2nd peak)

[00458] 7-(3-ethyloxolan-3-yl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (40 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μm; Mobile Phase A: hexane, Mobile Phase B: EtOH/DCM (1/1); Flow rate: 20 mL/min; Gradient: A:B = 70:30; Wave Length: 254/220 nm;

[00459] RT_1: 8.16 min to afford 7-(3-ethyltetrahydrofuran-3-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-ethyltetrahydrofuran-3-yl was not determined) (CHIRAL ART Amylose-SA, Hexane/EtOH/DCM = 70/15/15, 1st peak) (13.0 mg, 30%) as a white solid. MS ESI calculated for $C_{19}H_{22}F_3N_5O_3$ $[M + H]^+$, 426.17, found 426.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.93 (s, 1H), 5.14 (d, *J* = 7.2 Hz, 1H), 4.53-4.48 (m, 1H), 4.21-4.18 (m, 1H), 4.13-3.94 (m, 4H), 3.83-3.74 (m, 1H), 3.74-3.66 (m, 1H), 3.61-3.52 (m, 1H), 3.38-3.31 (m, 1H), 2.74-2.56 (m, 2H), 2.30-2.22 (m, 1H), 2.10-2.00 (m, 1H), 1.99-1.90 (m, 1H), 1.74-1.59 (m, 1H), 0.83-0.78 (m, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -54.97 (3F).

[00460] RT_2: 10.35 min to afford 7-(3-ethyltetrahydrofuran-3-yl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-ethyltetrahydrofuran-3-yl was not

determined) (CHIRAL ART Amylose-SA, Hexane/EtOH/DCM = 70/15/15, 2nd peak) (14.3 mg, 31%) as a white solid.

[00461] MS ESI calculated for $C_{19}H_{22}F_3N_5O_3$ $[M + H]^+$, 426.17, found 426.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.93 (s, 1H), 5.14 (d, *J* = 7.2 Hz, 1H), 4.53-4.48 (m, 1H), 4.18-4.15 (m, 1H), 4.13-3.94 (m, 4H), 3.83-3.74 (m, 1H), 3.74-3.66 (m, 1H), 3.61-3.52 (m, 1H), 3.38-3.31 (m, 1H), 2.74-2.56 (m, 2H), 2.25-2.20 (m, 1H), 2.14-2.08 (m, 1H), 1.96-1.87 (m, 1H), 1.74-1.59 (m, 1H), 0.83-0.78 (m, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -54.98 (3F).

Example 53:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfinylpiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-methanesulfinylpiperidin-3-yl acetate

[00462] To a stirred solution of (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidin-3-yl acetate hydrochloride (50 mg, 0.121 mmol) and TEA (61 mg, 0.605 mmol) in DCM (2 mL) was added methanesulfinyl chloride (60 mg, 0.605 mmol) at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The solution was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-methanesulfinylpiperidin-3-yl acetate (46 mg, 86%) as a light yellow solid. MS ESI calculated for $C_{18}H_{23}ClN_6O_3S$ $[M + H]^+$, 439.12, found 439.15.

Example 53:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfinylpiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00463] A solution of (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-methanesulfinylpiperidin-3-yl acetate (36 mg, 0.082 mmol) and K_2CO_3 (34 mg, 0.246 mmol) in MeOH (2 mL) was stirred for 1 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford 5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfinylpiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (16.7 mg, 50 %) as a light yellow solid. MS ESI calculated for $C_{16}H_{21}ClN_6O_2S$ $[M + H]^+$, 397.11; found 397.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 5.13-5.03 (m, 1H), 3.88-3.40 (m, 6H), 3.30-2.95 (m, 2H), 2.67 (s, 3H), 2.33-2.24 (m, 1H), 1.80-1.71 (m, 1H), 1.51-1.42 (m, 6H).

Example 54:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-trifluoromethanesulfonylpiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-trifluoromethanesulfonylpiperidin-3-yl acetate

[00464] To a mixture of (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidin-3-yl acetate (90 mg, 0.239 mmol) and sat. $NaHCO_3$ (2 mL) was added trifluoromethanesulfonyl chloride (120.73 mg, 0.717 mmol) in EtOAc (2 mL) at 0 °C. The resulting mixture was stirred for additional 16 h at room temperature. The resulting mixture was diluted with water (5 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (1/1) to afford (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-trifluoromethanesulfonylpiperidin-3-yl acetate (40 mg, 27%) as a light yellow solid. MS ESI calculated for $C_{18}H_{20}ClF_3N_6O_4S$ $[M + H]^+$, 509.09, found 509.10.

Example 54:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-trifluoromethanesulfonylpiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00465] A solution of (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-trifluoromethanesulfonylpiperidin-3-yl acetate (40 mg, 0.067 mmol) and K_2CO_3 (27.70 mg, 0.201 mmol) in MeOH (2 mL, 49.398 mmol) was stirred for 1 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford 5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-trifluoromethanesulfonylpiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (13.9 mg, 43%) as a white solid. MS ESI calculated for $C_{16}H_{18}ClF_3N_6O_3S$ $[M + H]^+$, 467.08, found 467.30. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 5.02 (brs, 1H), 4.17-4.12 (m, 1H), 4.01-3.97 (m, 1H), 3.84-3.80 (m, 2H), 3.73-3.53 (m, 1H), 3.28-3.22 (m, 1H), 3.10-3.05 (m, 1H), 2.35-2.30 (m, 1H), 1.82-1.75 (m, 1H), 1.50-1.47 (m, 6H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -75.60 (3F).

Example 55:

7-(*sec*-butyl)-2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer,

absolute chiral configuration of *sec*-butyl was not determined) (Lux 5um Cellulose-3, Hexane/MeOH/EtOH = 90/5/5, 1st peak)

Example 56:

7-(*sec*-butyl)-2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (Lux 5um Cellulose-3, Hexane/MeOH/EtOH = 90/5/5, 2nd peak)

Step 1: (3*R*,4*R*)-4-{[5-chloro-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00466] To a stirred mixture of 2,5-dichloro-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazine (520 mg, 2.130 mmol) and DIEA (1.37 g, 10.650 mmol) in NMP (8 mL) was added *tert*-butyl (3*R*,4*R*)-4-amino-3-fluoropiperidine-1-carboxylate (1.39 g, 6.390 mmol). The reaction mixture was stirred for 16 h at 100 °C. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (4/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (600 mg, 66%) as a yellow oil; MS ESI calculated for $C_{20}H_{29}ClFN_5O_2$ $[M + H]^+$, 425.20, found 426.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.56 (s, 1H), 6.44 (s, 1H), 5.00 (brs, 1H), 4.70-4.52 (m, 1H), 4.08-4.02 (m, 2H), 3.76-3.70 (m, 1H), 3.41-3.24 (m, 3H), 2.39-2.36 (m, 1H), 1.81-1.76 (m, 1H), 1.72-1.55 (m, 2H), 1.51-1.47 (m, 9H), 1.33-1.29 (m, 3H), 0.93-0.86 (m, 3H).

Step 2: *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-iodo-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00467] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (590 mg, 1.385 mmol) in DMF (8 mL) was added I_2 (1.40 g, 5.540 mmol) at room temperature. The reaction mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (10 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-iodo-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (630 mg, 82%) as a yellow solid; MS ESI calculated for $C_{20}H_{28}ClFIN_5O_2$ $[M + H]^+$, 551.10, found 552.10.

Step 3: *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00468] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-iodo-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (570 mg, 1.033 mmol) and $Pd(PPh_3)_4$ (119 mg, 0.103 mmol) in DMF (7 mL) was added $Zn(CN)_2$ (73 mg, 0.620 mmol) at room temperature. The reaction mixture was stirred for 2 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (450 mg, 96%) as a light yellow solid; MS ESI calculated for $C_{21}H_{28}ClFN_6O_2$ [M + H]$^+$, 450.19, found 451.30.

Step 4: (3*R*,4*R*)-4-{[6-cyano-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00469] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (420 mg, 0.931 mmol), $Pd(PPh_3)_4$ (107 mg, 0.093 mmol) and di-*tert*-butyl({2-[2,4,6-tris(propan-2-yl)phenyl]phenyl})phosphane (79 mg, 0.186 mmol) in dioxane (5 mL) was added Et_3N (377 mg, 3.724 mmol) and Et_3SiH (325 mg, 2.793 mmol) at room temperature. The reaction mixture was stirred for 2 h at 100 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (8 mL). The resulting mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (380 mg, 97%) as a light yellow solid.MS ESI calculated for $C_{21}H_{29}FN_6O_2$ [M + H]$^+$, 417.23, found 417.40; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.64 (s, 1H), 7.04 (s, 1H), 5.26 (brs, 1H), 4.67-4.46 (m, 1H), 4.21-3.99 (m, 2H), 3.86-3.76 (m, 1H), 3.51-3.44 (m, 1H), 3.34-3.25 (m, 2H), 2.39-2.30 (m, 1H), 2.11-1.95 (m, 1H), 1.92-1.77 (m, 1H), 1.67-1.54 (m, 1H), 1.51-1.46 (m, 12H), 0.88 (t, J = 7.2 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -189.33 (1F).

Step 5: (3*R*,4*R*)-4-{[6-cyano-5-iodo-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00470] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (400 mg, 0.960 mmol) in DMF (5 mL) was added I_2 (975 mg, 3.840 mmol) at room temperature. The reaction mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of $Na_2S_2O_3$ solution (10 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (4/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-5-iodo-7-(sec-butyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (410 mg, 78%) as a yellow solid; MS ESI calculated for $C_{21}H_{28}FIN_6O_2$ $[M + H]^+$, 543.13, found 543.20.

Step 6: (3*R*,4*R*)-4-{[6-cyano-7-(*sec*-butyl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00471] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-5-iodo-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (320 mg, 0.590 mmol), methyl 2,2-difluoro-2-sulfoacetate (566 mg, 2.950 mmol) and CuI (112 mg, 0.590 mmol) in DMF (4 mL) was added KF (103 mg, 1.770 mmol) at room temperature. The reaction mixture was stirred for 2 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-7-(*sec*-butyl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (280 mg, 97%) as an off-white solid. MS ESI calculated for $C_{22}H_{28}F_4N_6O_2$ $[M + H]^+$, 485.22, found 485.30.

Step 7: 2-{[(3*R*,4*R*)-3-fluoropiperidin-4-yl]amino}-7-(*sec*-butyl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride

[00472] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-7-(*sec*-butyl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (290 mg, 0.599 mmol) in DCM (3 mL) was added HCl (gas) in 1,4-dioxane (3 mL, 98.738 mmol) at 0 °C. The reaction mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford 2-{[(3*R*,4*R*)-3-fluoropiperidin-4-yl]amino}-7-(*sec*-butyl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (210 mg, crude) as an off-white solid; MS ESI calculated for $C_{17}H_{21}ClF_4N_6$ $[M - Cl]^+$, 385.17, found 385.10.

Example 55:

7-(*sec*-butyl)-2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (Lux 5um Cellulose-3, Hexane/MeOH/EtOH = 90/5/5, 1st peak)

Example 56:

7-(*sec*-butyl)-2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (Lux 5um Cellulose-3, Hexane/MeOH/EtOH = 90/5/5, 2nd peak)

[00473] To a stirred mixture of 2-{[(3*R*,4*R*)-3-fluoropiperidin-4-yl]amino}-7-(*sec*-butyl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (100 mg, 0.238 mmol) in EtOAc (2 mL) was added sat. $NaHCO_3$ (1 mL) and methanesulfonic anhydride (74 mg, 0.428 mmol) at room temperature. The reaction mixture was stirred for 1.5 h at room temperature. The resulting mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified with Prep-Chiral-HPLC (Column: Lux 5um Cellulose-3 2.12*25 cm, 5 μm; Mobile Phase A: hexane, Mobile Phase B: MeOH/EtOH (1/1); Flow rate: 20 mL/min; Gradient: A:B = 90:10; Wave Length: 254/220 nm;

[00474] RT_1: 31.35 min to afford 7-(*sec*-butyl)-2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (Lux 5um Cellulose-3, Hexane/MeOH/EtOH = 90/5/5, 1st peak) (29.9 mg, 25 %) as an off white solid. MS ESI calculated for $C_{18}H_{22}F_4N_6O_2S$ $[M + H]^+$, 462.15, found 463.35; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.89 (s, 1H), 5.11 (d, *J* = 7.2 Hz, 1H), 4.76-4.62 (m, 1H), 4.12-3.93 (m, 2H), 3.71-3.65 (m, 1H), 3.56-3.49 (m, 1H), 3.27-3.12 (m, 2H), 2.91 (s, 3H), 2.47-2.42 (m, 1H), 2.11-1.95 (m, 1H), 1.94-1.74 (m, 2H), 1.54-1.51 (m, 3H), 0.93-0.89 (m, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -54.98 (3F), -189.59 (1F).

[00475] RT_2: 34.31 min to afford 7-(*sec*-butyl)-2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (Lux 5um Cellulose-3, Hexane/MeOH/EtOH = 90/5/5, 2nd peak) (29.9 mg, 26%) as an off white solid; MS ESI calculated for $C_{18}H_{22}F_4N_6O_2S$ $[M + H]^+$, 462.15, found 463.30; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.91 (s, 1H), 5.14 (d, *J* = 6.8 Hz, 1H), 4.82-4.64 (m, 1H), 4.10-3.95 (m, 2H), 3.76-3.66 (m, 1H), 3.57-3.44 (m, 1H), 3.27-3.11 (m, 2H), 2.91 (s, 3H), 2.45-2.40 (m, 1H), 2.12-

1.96 (m, 1H), 1.89-1.78 (m, 2H), 1.51 (m, 3H), 0.90 (m, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -54.98 (3F), -189.59 (1F).

Example 57:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({7-bromopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00476] To a stirred solution of *tert*-butyl (3*R*,4*R*)-4-({7-bromopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-hydroxypiperidine-1-carboxylate (1.9 g, 4.608 mmol) in DCM (20 mL) were added Ac_2O (0.71 g, 6.912 mmol) and TEA (2.33 g, 23.040 mmol) at room temperature. The resulting mixture was stirred for 16 h at 50 °C. The mixture was allowed to cool down to room temperature. The resulting mixture was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({7-bromopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (1.9 g, 90%) as an off-white solid. MS ESI calculated for $C_{18}H_{24}BrN_5O_4$ $[M + H]^+$, 454.10, 456.10, found 454.15, 456.15.

Step 2: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[7-(2-methylprop-1-en-1-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00477] To a solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({7-bromopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (2 g, 4.402 mmol) and 4,4,5,5-tetramethyl-2-(2-methylprop-1-en-1-yl)-1,3,2-dioxaborolane (1.20 g, 6.603 mmol) in dioxane (20 mL) and water (2 mL) were added Cs_2CO_3 (4.30 g, 13.206 mmol) and $Pd(dppf)_2Cl_2$.DCM (0.36 g, 0.440 mmol). The reaction mixture was stirred for 2 h at 100 °C under a nitrogen atmosphere. The resulting mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[7-(2-methylprop-1-en-1-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (1.65 g, 87%) as orange oil. MS ESI calculated for $C_{22}H_{31}N_5O_4$ $[M + H]^+$, 430.24, found 430.25. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.53-8.48 (s, 1H), 6.76 (d, *J* = 4.8 Hz, 1H), 6.72 (d, *J* = 4.8 Hz, 1H), 6.69-6.64 (m, 1H), 5.13-4.77 (m, 2H), 4.09-3.88 (m, 2H), 4.05-3.93 (m, 1H), 3.30-3.25 (m, 2H), 2.38-2.32 (m, 1H), 2.07-2.03 (m, 9H), 1.52-1.47 (m, 10H).

Step 3: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00478] To a solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[7-(2-methylprop-1-en-1-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (1.2 g, 2.263 mmol) in EtOAc (24 mL) was added Pd/C (0.96 g, 0.905 mmol) under nitrogen atmosphere. The mixture was hydrogenated at 50 °C for 2 h under hydrogen atmosphere using a hydrogen balloon. The resulting mixture was filtered through a Celite pad and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1). The crude product was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (802 mg, 58%) as a light yellow solid. MS ESI calculated for $C_{22}H_{33}N_5O_4$ $[M + H]^+$, 432.25 found 432.40. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.55-8.50 (d, *J* = 4.0 Hz, 1H), 6.67 (d, *J* = 4.8 Hz, 1H), 6.48 (d, *J* = 4.8 Hz, 1H), 4.98 (brs, 1H), 4.82-4.77 (m, 1H), 4.02-3.97 (m, 2H), 3.78-3.74 (m, 1H), 3.33-3.27 (m, 2H), 2.80-2.76 (m, 2H), 2.41-2.34 (m, 1H), 2.17-2.11 (m, 1H), 2.06 (s, 3H), 1.52-1.47 (m, 10H), 1.00-0.93 (m, 6H).

Step 4: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00479] A solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (805 mg, 1.324 mmol) and NCS (185 mg, 1.390 mmol) in DMF (14 mL) was stirred for 16 h at room temperature. The resulting mixture was stirred for additional 16 h at 50 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% TFA), 50% to 70%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (590 mg, 87%) as a yellow solid. MS ESI calculated for $C_{22}H_{32}ClN_5O$ $[M + H]^+$, 466.21, found 466.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.47 (s, 1H), 6.57 (s, 1H), 5.01 (brs, 1H), 4.22-4.19 (m, 1H), 3.95-3.91 (m, 1H), 3.82-3.77 (m, 1H), 3.70-3.64 (m, 1H), 3.51-3.45 (m, 2H), 2.87-2.74 (m, 2H), 2.31-2.20 (m, 1H), 2.15-2.03 (m, 4H), 1.73-1.64 (m, 1H), 1.51-1.46 (m, 9H), 1.00-0.95 (m, 6H).

Step 5: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00480] A solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (560 mg, 1.202 mmol) and I_2 (1.22 g, 4.808 mmol) in DMF (5 mL) was stirred for 16 h at room temperature. The reaction was quenched with sat. $Na_2S_2O_3$ (aq.)(10 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous

Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (534 mg, 75%) as a yellow solid. MS ESI calculated for $C_{22}H_{31}ClIN_5O_4$ $[M + H]^+$, 592.11, found 592.20.

Step 6: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00481] To a stirred solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (530 mg, 0.895 mmol) and $Zn(CN)_2$ (210 mg, 1.790 mmol) in DMF (5 mL) was added $Pd(PPh_3)_4$ (103 mg, 0.090 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 130 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (5 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% TFA), 40% to 60%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (240 mg, 54%) as a yellow solid. MS ESI calculated for $C_{23}H_{31}ClN_6O_4$ $[M + H]^+$, 491.21, found 491.30. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 5.60 (brs, 1H), 4.99-4.93 (m, 1H), 3.97-3.76 (m, 3H), 3.30-3.25 (m, 2H), 2.98-2.82 (m, 2H), 2.34-2.29 (m, 1H), 2.24-2.18 (m, 1H), 2.08 (s, 3H), 1.61-1.48 (m, 10H), 1.03-0.98 (m, 6H).

Step 7: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate

[00482] A solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (50 mg, 0.102 mmol) in DCM (1 mL) was added HCl (gas) in 1,4-dioxane (1 mL, 4.000 mmol) at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure. To this were added sat. $NaHCO_3$ (1 mL) and methanesulfonic anhydride (53.22 mg, 0.306 mmol) in EtOAc (1 mL) at 0 °C. The reaction mixture was stirred for additional 1 h at room temperature. The resulting mixture was diluted with water (3 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by

Prep-TLC with PE/EtOAc/EtOH (6/1/5) to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (30 mg, 62%) as a light yellow oil. MS ESI calculated for $C_{19}H_{25}ClN_6O_4S$ $[M + H]^+$, 469.13, found 469.15.

Example 57:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00483] To a stirred solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (30 mg, 0.064 mmol) in MeOH (1 mL) was added K_2CO_3 (26.52 mg, 0.192 mmol) at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH4HCO3), 30% to 50%; detector, UV 254 nm to afford 5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (11.4 mg, 41%) as a white solid. MS ESI calculated for $C_{17}H_{23}ClN_6O_3S$ $[M + H]^+$, 427.12, found 427.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 5.08 (d, *J* = 6.8 Hz, 1H), 4.01-3.96 (m, 1H), 3.86-3.80 (m, 2H), 3.78-3.69 (m, 1H), 2.96-2.84 (m, 6H), 2.78-2.73 (m, 1H), 2.32-2.28 (m, 1H), 2.24-2.14 (m, 1H), 1.80-1.71 (m, 1H),1.02.-0.97 (m, 6H).

Example 58:

2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(2-methylpropyl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00484] To a stirred solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (190 mg, 0.387 mmol) in dioxane (4 mL) were added $Pd(dba)_2$ (22 mg, 0.039 mmol), *t*-BuXPhos (33 mg, 0.077 mmol), TEA (117.48 mg, 1.161 mmol) and Et_3SiH (180 mg, 1.548 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 100 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-

yl]amino}piperidine-1-carboxylate (150 mg, 76%) as yellow oil. MS ESI calculated for $C_{23}H_{32}N_6O_4$ $[M + H]^+$, 457.25, found 457.20.

Step 2: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[6-cyano-5-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00485] A solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (150 mg, 0.329 mmol) and I_2 (333 mg, 1.316 mmol) in DMF (3 mL) was stirred for 16 h at room temperature. The reaction was quenched with sat.$Na_2S_2O_3$ (aq.) (5 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[6-cyano-5-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (100 mg, 52%) as a light yellow solid. MS ESI calculated for $C_{23}H_{31}IN_6O_4$ $[M + H]^+$, 583.15, found 583.45.

Step 3: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[6-cyano-7-(2-methylpropyl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00486] To a stirred solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[6-cyano-5-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (70 mg, 0.120 mmol) and methyl 2,2-difluoro-2-sulfoacetate (115 mg, 0.600 mmol) in DMF (2 mL) were added CuI (23 mg, 0.120 mmol) and KF (21 mg, 0.360 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 80 °C under nitrogen atmosphere. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[6-cyano-7-(2-methylpropyl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (40 mg, 63%) as light yellow oil. MS ESI calculated for $C_{24}H_{31}F_3N_6O_4$ $[M + H]^+$, 525.24, found 525.30. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.87 (d, *J* = 1.1 Hz, 1H), 5.32 (brs, 1H), 4.98-4.93 (m, 1H), 4.13-4.08 (m, 1H), 3.95-3.84 (m, 2H), 3.21-3.07 (m, 2H), 3.03-2.88 (m, 2H), 2.41-2.32 (m, 1H), 2.25-2.18 (m, 1H), 2.08 (s, 3H), 1.59-1.46 (m, 10H), 1.03-0.98 (m, 6H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -54.95 (3F).

Step 4: (3*R*,4*R*)-4-{[6-cyano-7-(2-methylpropyl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate

[00487] A solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[6-cyano-7-(2-methylpropyl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (40 mg, 0.076

mmol) in DCM (1.5 mL) was added HCl (gas) in 1,4-dioxane (0.7 mL, 2.848 mmol) at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure. To this was added sat. $NaHCO_3$ (1 mL) and methanesulfonic anhydride (40 mg, 0.228 mmol) in EtOAc (0.5 mL) at 0 °C. The reaction mixture was stirred for additional 40 min at room temperature. The resulting mixture was diluted with water (5 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 50% to 70%; detector, UV 254 nm to afford (3*R*,4*R*)-4-{[6-cyano-7-(2-methylpropyl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (22 mg, 57%) as light yellow oil. MS ESI calculated for $C_{20}H_{25}F_3N_6O_4S$ $[M + H]^+$, 503.16, found 503.20.

Example 58:

2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(2-methylpropyl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00488] A solution of (3*R*,4*R*)-4-{[6-cyano-7-(2-methylpropyl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (20 mg, 0.040 mmol) and K_2CO_3 (16 mg, 0.120 mmol) in MeOH (1 mL) was stirred for 1 h at room temperature. The resulting mixture was diluted with water (5 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 50% to 70%; detector, UV 254 nm to afford 2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(2-methylpropyl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (3.0 mg, 15%) as a white solid. MS ESI calculated for $C_{18}H_{23}F_3N_6O_3S$ $[M + H]^+$, 461.15, found 461.30. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.91 (s, 1H), 5.18 (brs, 1H), 4.01-3.98 (m, 1H), 3.90-3.75 (m, 3H), 2.97-2.89 (m, 6H), 2.83-2.77 (m, 1H), 2.38-2.33 (m, 1H), 2.25-2.18 (m, 1H), 1.81-1.73 (m, 1H), 1.05-0.99 (m, 6H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -55.02 (3F).

Example 59:

5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) ((*R*,*R*)-WHELK-O1-Kromasil, Hexane/EtOH/DCM = 90/5/5, 1st peak)

Example 60:

5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) ((*R*,*R*)-WHELK-O1-Kromasil, Hexane/EtOH/DCM = 90/5/5, 2nd peak)

Step 1: (3*S*,4*R*)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol

[00489] To a stirred mixture of 2,5-dichloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (110 mg, 0.42 mmol) and (3*S*,4*R*)-4-aminooxan-3-ol hydrochloride (327 mg, 2.13 mmol) in NMP (2 mL) was added DIEA (330 mg, 2.55 mmol) at room temperature. The resulting mixture was stirred for 16 h at 100 °C. The mixture was allowed to cool down to room temperature. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% TFA), 10% to 50%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (150 mg, 98%) as a yellow solid. MS ESI calculated for $C_{16}H_{23}ClN_4O_2$ [M + H]$^+$, 339.15 found 339.15. ^{1}H-NMR (400 MHz, Chloroform-*d*) δ 8.44 (s, 1H), 6.73 (s, 1H), 4.13-4.08 (m, 1H), 4.42-3.96 (m, 1H), 3.87-3.69 (m, 2H), 3.55-3.50 (m, 1H), 3.37-3.21 (m, 2H), 2.35-2.23 (m, 1H), 2.12-1.99 (m, 1H), 1.79-1.64 (m, 1H), 1.31 (d, *J* = 7.2 Hz, 3H), 1.01-0.87 (m, 6H).

Step 2: (3*S*,4*R*)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00490] To a stirred mixture of (3*S*,4*R*)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (160 mg, 0.47 mmol) and Ac_2O (89 uL, 0.94 mmol) in DCM (3 mL) was added TEA (131 uL, 0.94 mmol) at room temperature. The resulting mixture was stirred for 16 h at 50 °C. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of water/ice (10 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (150 mg, 83%) as a yellow solid. MS ESI calculated for $C_{18}H_{25}ClN_4O_3$ [M + H]$^+$, 381.16 found 381.20. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.57 (s, 1H), 6.44 (s, 1H), 5.17 (brs, 1H), 5.01-4.96 (m, 1H), 4.03-3.91 (m, 3H), 3.63-3.58 (m, 1H), 3.50-3.45 (m, 1H), 3.30-3.25 (m, 1H), 2.50-2.37 (m, 1H), 2.15-1.98 (m, 4H), 1.73-1.67 (m, 1H), 1.33-1.23 (m, 3H), 1.03-0.86 (m, 6H).x

Step 3: (3*S*,4*R*)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00491] To a stirred mixture of (3*S*,4*R*)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (150 mg, 0.394 mmol) in DMF (3 mL) was added I_2 (400 mg, 1.576 mmol) at room temperature. The reaction mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of water (20 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*S*,4*R*)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (180 mg, 90%) as a yellow solid. MS ESI calculated for $C_{18}H_{24}ClIN_4O_3$ $[M + H]^+$, 507.06 found 507.15.

Step 4: (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00492] To a stirred mixture of (3*S*,4*R*)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (155 mg, 0.306 mmol) and $Zn(CN)_2$ (43 mg, 0.36 mmol) in DMA (3 mL) was added $Pd(PPh_3)_4$ (71 mg, 0.06 mmol). The resulting mixture was stirred for 2 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (20 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (86 mg, 69%) as a yellow solid. MS ESI calculated for $C_{19}H_{24}ClN_5O_3$ $[M + H]^+$, 406.16 found 406.15.

Step 4: 5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00493] To a stirred mixture of (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (85 mg, 0.20 mmol) in MeOH (2 mL) was added K_2CO_3 (58 mg, 0.41 mmol) in portions at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford 5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(3-

methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (70 mg, 91%) as a yellow solid. MS ESI calculated for $C_{17}H_{22}ClN_5O_2$ $[M + H]^+$, 364.15 found 364.15.

Example 59:

5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) ((*R*,*R*)-WHELK-O1-Kromasil, Hexane/EtOH/DCM = 90/5/5, 1st peak)

Example 60:

5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) ((*R*,*R*)-WHELK-O1-Kromasil, Hexane/EtOH/DCM = 90/5/5, 2nd peak)

[00494] 5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (70 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: (*R*,*R*)-WHELK-O1-Kromasil, 2.12*25 cm, 5 μm; Mobile Phase A: Hexane, Mobile Phase B: EtOH/DCM (1/1); Flow rate: 20 mL/min; Gradient: A:B = 90:10; Wave Length: 254/220 nm;

[00495] RT_1: 19.94 min to afford 5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) ((*R*,*R*)-WHELK-O1-Kromasil, Hexane/EtOH/DCM = 90/5/5, 1st peak) (26.4 mg, 37%) as a yellow solid. MS ESI calculated for $C_{17}H_{22}ClN_5O_2$ $[M + H]^+$, 364.15 found 364.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 5.30 (brs, 1H), 4.14-4.05 (m, 1H), 4.03-3.97 (m, 1H), 3.83-3.77 (m, 1H), 3.73-3.78 (m, 1H), 3.56-3.50 (m, 1H), 3.35-3.20 (m, 2H), 2.29-2.14 (m, 2H), 1.73-1.67 (m, 1H), 1.47 (d, J = 7.2 Hz, 3H), 1.08 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 6.4 Hz, 3H).

[00496] RT_2: 21.71 min to afford 5-chloro-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) ((*R*,*R*)-WHELK-O1-Kromasil, Hexane/EtOH/DCM = 90/5/5, 2nd peak) (24 mg, 34%)as a yellow solid. MS ESI calculated for $C_{17}H_{22}ClN_5O_2$ $[M + H]^+$, 364.15 found 364.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 5.13 (brs, 1H), 4.14-4.05 (m, 1H), 4.03-3.97 (m, 1H), 3.83-3.77 (m, 1H), 3.73-3.78 (m, 1H), 3.56-3.50 (m, 1H), 3.35-3.20 (m, 2H), 2.29-2.14 (m, 2H), 1.73-1.67 (m, 1H), 1.47 (d, J = 7.2 Hz, 3H), 1.07 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H).

Example 61:

5-chloro-2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 85/15, 2nd peak)

Example 62:

5-chloro-2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 85/15, 1st peak)

Step 1: *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00497] To a stirred solution of 2,5-dichloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (300 mg, 1.16 mmol,) and *tert*-butyl (3R,4R)-4-amino-3-fluoropiperidine-1-carboxylate (761 mg, 3.49 mmol) in NMP (3 mL) was added DIEA (600 mg, 4.65 mmol) at room temperature.The resulting mixture was stirred for 16 h at 120 °C under nitrogen atmosphere. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% $NH_3.H_2O$), 40 % to 50 %; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (400 mg, 78%) as a yellow solid. MS ESI calculated for $C_{21}H_{31}ClFN_5O_2$ $[M + H]^+$, 440.22, found 440.30. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.56 (s, 1H), 6.44 (s, 1H), 4.96 (brs, 1H), 4.69-4.53 (m, 1H), 4.04-3.97 (m, 2H), 3.70-3.69 (m, 1H), 3.345-3.22 (m, 3H), 2.40-2.35 (m, 1H), 2.10-2.02 (m, 1H), 1.60-1.47 (m, 10H), 1.34-1.26 (m, 3H), 0.92-0.89 (m, 6H).^{19}F NMR (377 MHz, Chloroform-*d*) δ -189.54 (1F).

Step 2: *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00498] A solution of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (270 mg, 0.61 mmol) and I2 (778 mg, 3.07 mmol) in DMF (3 mL) was stirred for 16 h at room temperature. The resulting mixture was stirred for 16 h at room temperature under nitrogen atmosphere. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% $NH_3.H_2O$), 10% to 50%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (310 mg, 89%) as a yellow solid. MS ESI calculated for $C_{21}H_{30}ClFIN_5O_2$ $[M + H]^+$, 566.11, found 566.20.

Step 3: *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00499] To a stirred solution of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (300 mg, 0.68 mmol) and $Zn(CN)_2$ (43.58 mg, 0.37 mmol) in DMF (2 mL) was added $Pd(PPh_3)_4$ (43 mg, 0.04 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 120 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% $NH_3.H_2O$), 10% to 50%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (170 mg, 98%) as a yellow solid. MS ESI calculated for $C_{22}H_{30}ClFN_6O_2$ $[M + H]^+$, 465.21, found 465.25.

Step 4: 5-chloro-2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00500] A solution of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (230 mg, 0.50 mmol) and HCl (gas) in 1,4-dioxane (4 mL) in DCM (2 mL) was stirred for 40 min at room temperature. The resulting mixture was concentrated under reduced pressure. To this was added methanesulfonic anhydride (190 mg, 1.10 mmol) in EtOAc (4 mL, 40.87 mmol) and sat. $NaHCO_3$ (2 mL). The reaction mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford 5-chloro-2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (100 mg, 41%) as a yellow solid. MS ESI calculated for $C_{18}H_{24}ClFN_6O_2S$ $[M + H]^+$, 443.14, found 443.10.

Example 61:

5-chloro-2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 85/15, 2nd peak)

Example 62:

5-chloro-2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 85/15, 1st peak)

[00501] 5-chloro-2-{[(3R,4R)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (100 mg, 0.23 mmol) was purified by Prep-Chiral-

HPLC with the following conditions (Column: CHIRALPAK AD-H, 2*25 cm, 5 μm; Mobile Phase A: Hexane, Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: A:B = 85:15; Wave Length: 254/220 nm;

[00502] RT_1: 15.66 min to afford 5-chloro-2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 85/15, 1st peak) (28 mg, 28%) as a white solid. $C_{18}H_{24}ClFN_6O_2S$ $[M + H]^+$, 443.14, found 443.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 5.17-5.12 (m, 1H), 4.78-4.65 (m, 1H), 4.08-4.03 (m, 1H), 3.95-3.87 (m, 1H), 3.67-3.63 (m, 1H), 3.32-3.19 (m, 3H), 2.93 (s, 3H), 2.46-2.40 (m, 1H), 2.26-2.21 (m, 1H), 1.84-1.78 (m, 1H), 1.48 (d, *J* = 7.2 Hz, 3H), 1.07 (d, *J* = 6.4 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -188.53 (1F).

[00503] RT_2: 20.23 min to afford 5-chloro-2-(((3*R*,4*R*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 85/15, 2nd peak) (28 mg, 28%) as a white solid. $C_{18}H_{24}ClFN_6O_2S$ $[M + H]^+$, 443.14, found 443.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 5.15 (brs, 1H), 4.80-4.67 (m, 1H), 4.04-3.90 (m, 2H), 3.68-3.65 (m, 1H), 3.30-3.17 (m, 3H), 2.93 (s, 3H), 2.47-2.41 (m, 1H), 2.27-2.21 (m, 1H), 1.81-1.76 (m, 1H), 1.48 (d, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -188.53 (1F).

Example 63:

(3*R*,4*R*)-4-((5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)-1-(methylsulfonyl)piperidin-3-ol (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/MeOH/EtOH = 85/7.5/7.5, 2nd peak)

Example 64:

(3*R*,4*R*)-4-((5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)-1-(methylsulfonyl)piperidin-3-ol (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/MeOH/EtOH = 85/7.5/7.5, 1st peak)

Step 1: *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate

[00504] To a stirred mixture of 2,5-dichloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (310 mg, 1.21 mmol) and *tert*-butyl (3*R*,4*R*)-4-amino-3-hydroxypiperidine-1-carboxylate (1.3 g, 6.00

mmol) in NMP (8 mL) was added DIEA (931 mg, 7.20 mmol). The resulting mixture was stirred for 16 h at 100 °C. The mixture was allowed to cool down to room temperature. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% TFA), 10% to 50%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (450 mg, 85%) as a yellow solid. MS ESI calculated for $C_{21}H_{32}ClN_5O_3$ $[M + H]^+$, 438.22 found 438.30.

Step 2: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00505] To a stirred solution of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (500 mg, 1.14 mmol) and Ac_2O (216 uL, 2.28 mmol) in DCM (8 mL) was added TEA (317 uL, 2.28 mmol) at room temperature. The resulting mixture was stirred for 16 h at 50 °C. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of water (20 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (460 mg, 83%) as a yellow solid. MS ESI calculated for $C_{23}H_{34}ClN_5O_4$ $[M + H]^+$, 480.23 found 480.30.

Step 3: (3*R*,4*R*)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride

[00506] To a stirred mixture of *tert*-butyl (3R,4R)-3-(acetyloxy)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (100 mg, 0.20 mmol) in DCM (2 mL) was added HCl (gas) in 1,4-dioxane (2 mL) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford (3*R*,4*R*)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (85 mg, 98%) as a yellow solid. MS ESI calculated for $C_{18}H_{27}Cl_2N_5O_2$ $[M - Cl]^+$, 380.18 found 380.20.

Step 4: (3*R*,4*R*)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate

[00507] To a stirred mixture of (3*R*,4*R*)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (85 mg, 0.20 mmol) in EtOAc (2 mL) was added methanesulfonic anhydride (64 mg, 0.36 mmol) at 0 °C. The resulting mixture was stirred

for 2 h at room temperature. The reaction was quenched by the addition of water (20 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*R*,4*R*)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (90 mg, 96%) as a yellow solid. MS ESI calculated for $C_{19}H_{28}ClN_5O_4S$ $[M + H]^+$, 458.16, found 458.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.49 (s, 1H), 6.55 (s, 1H), 5.17-5.07 (m, 1H), 4.33-3.94 (m, 1H), 3.72-3.67 (m, 1H), 3.58-3.53 (m, 1H), 3.37-3.26 (m, 3H), 2.89 (s, 3H), 2.57-2.44 (m, 1H), 2.11-2.02 (m, 4H), 1.85-1.81 (m, 1H), 1.29-1.27 (m, 3H), 0.99-0.89 (m, 6H).

Step 5: (3*R*,4*R*)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-ol

[00508] To a stirred mixture of (3*R*,4*R*)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (90 mg, 0.19 mmol) in MeOH (2 mL) was added K_2CO_3 (54 mg, 0.39 mmol)at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The reaction was quenched by the addition of water (20 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford (3*R*,4*R*)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-ol (80 mg, 97%) as a yellow solid. MS ESI calculated for $C_{17}H_{26}ClN_5O_3S$ $[M + H]^+$, 416.14, found 416.25.

Example 63:

(3R,4R)-4-((5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-f][1,2,4]triazin-2-yl)amino)-1-(methylsulfonyl)piperidin-3-ol (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/MeOH/EtOH = 85/7.5/7.5, 2nd peak)

Example 64:

(3R,4R)-4-((5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-f][1,2,4]triazin-2-yl)amino)-1-(methylsulfonyl)piperidin-3-ol (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/MeOH/EtOH = 85/7.5/7.5, 1st peak)

[00509] (3*R*,4*R*)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-ol (80 mg) was purified by Chiral-HPLC with the following conditions (Column: CHIRALPAK AD-H, 2*25 cm, 5 μm; Mobile Phase A: hexane, Mobile

Phase B: MeOH/EtOH (1/1); Flow rate: 20 mL/min; Gradient: A:B = 85:15; Wave Length: 254/220 nm;

[00510] RT_1: 16.85 min to afford (3*R*,4*R*)-4-((5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)-1-(methylsulfonyl)piperidin-3-ol (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/MeOH/EtOH = 85/7.5/7.5, 1st peak) (27.5 mg, 34%) as a light yellow solid. MS ESI calculated for $C_{17}H_{26}ClN_5O_3S$ $[M + H]^+$, 416.14 found 416.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.51 (s, 1H), 6.57 (s, 1H), 5.81 (brs, 1H), 3.95-3.91 (m, 1H), 3.87-3.74 (m, 3H), 3.26-3.22 (m, 1H), 3.06-3.00 (m, 1H), 2.91-2.87 (m, 4H), 2.31-2.25 (m, 1H), 2.02-1.98 (m, 1H), 1.82-1.76 (m, 1H), 1.27-1.24 (m, 3H), 0.98-0.90 (m, 6H).

[00511] RT_2: 20.44 min to afford (3*R*,4*R*)-4-((5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)-1-(methylsulfonyl)piperidin-3-ol (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/MeOH/EtOH = 85/7.5/7.5, 2nd peak) (25.1 mg, 31%) as a light yellow solid.

[00512] MS ESI calculated for $C_{17}H_{26}ClN_5O_3S$ $[M + H]^+$, 416.14 found 416.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.53 (s, 1H), 6.54 (s, 1H), 5.81 (brs, 1H), 3.99-3.94 (m, 1H), 3.87-3.74 (m, 3H), 3.25-3.21 (m, 1H), 3.01-2.98 (m, 1H), 2.91-2.87 (m, 4H), 2.28-2.24 (m, 1H), 2.09-2.02 (m, 1H), 1.82-1.76 (m, 1H), 1.27-1.24 (m, 3H), 0.97-0.92 (m, 6H).

Example 66:

5-chloro-7-isopropyl-2-[(1-methanesulfonylpiperidin-4-yl)amino]pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: *N*-{5-chloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}-1-methanesulfonylpiperidin-4-amine

[00513] A mixture of 2,5-dichloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine (180 mg, 0.782 mmol), 1-methanesulfonylpiperidin-4-amine (697 mg, 3.910 mmol) and DIEA (0.80 mL, 4.692 mmol) in NMP (2 mL) was stirred for 2 h at 100 °C. The mixture was allowed to cool down to room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 10% to 95%; detector, UV 254 nm to afford *N*-{5-chloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}-1-methanesulfonylpiperidin-4-amine (270 mg, 88%) as a yellow solid. MS ESI calculated for $C_{15}H_{22}ClN_5O_2S$ $[M + H]^+$, 372.12, found 372.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.56 (s, 1H), 6.44 (s, 1H), 4.83 (brs, 1H), 3.90-3.84 (m, 1H), 3.77-3.70 (m, 2H), 3.41-3.40 (m, 1H), 3.07-3.01 (m, 2H), 2.85 (s, 3H), 2.27-2.22 (m, 2H), 1.76-1.71 (m, 2H), 1.34 (d, J = 6.8 Hz, 6H).

Step 2: *N*-{5-chloro-6-iodo-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}-1-methanesulfonylpiperidin-4-amine

[00514] A mixture of *N*-{5-chloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}-1-methanesulfonylpiperidin-4-amine (200 mg, 0.538 mmol) and I_2 (546 mg, 2.152 mmol) in DMF (1 mL) was stirred for 2 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (15 mL) at room temperature. The resulting mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (0~60%) to afford *N*-{5-chloro-6-iodo-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}-1-methanesulfonylpiperidin-4-amine (260 mg, 92%) as a yellow solid. MS ESI calculated for $C_{15}H_{21}ClIN_5O_2S$ $[M + H]^+$, 498.01, found 498.05.

Example 66:

5-chloro-7-isopropyl-2-[(1-methanesulfonylpiperidin-4-yl)amino]pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00515] A mixture of *N*-{5-chloro-6-iodo-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}-1-methanesulfonylpiperidin-4-amine (100 mg, 0.201 mmol), $Zn(CN)_2$ (14 mg, 0.121 mmol) and $Pd(PPh_3)_4$ (23 mg, 0.020 mmol) in DMA (1 mL) was stirred for 2 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of water (15 mL) at room temperature. The resulting mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (0~70%) to afford 5-chloro-7-isopropyl-2-[(1-methanesulfonylpiperidin-4-yl)amino]pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (40 mg, 50%) as an off-white solid. MS ESI calculated for $C_{16}H_{21}ClN_6O_2S$ $[M + H]^+$, 397.11, found 397.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 5.23 (brs, 1H), 3.87-3.84 (m, 1H), 3.77-3.72 (m, 2H), 3.70-3.62 (m, 1H), 3.08-3.01 (m, 2H), 2.86 (s, 3H), 2.25-2.21 (m, 2H), 1.79-1.76 (m, 2H), 1.53-1.48 (m, 6H).

Example 67:

(3*S*,4*R*)-4-{[6-cyano-7-(2-ethyloxolan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (single diastereoisomer, absolute chiral configuration of 2-ethyltetrahydrofuran-2-yl was not determined) (CHIRALPAK IG, CO_2/EtOH = 80/20, 1st peak)

Example 68:

(3*S*,4*R*)-4-{[6-cyano-7-(2-ethyloxolan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (single diastereoisomer, absolute chiral configuration of 2-

ethyltetrahydrofuran-2-yl was not determined) (CHIRALPAK IG, CO_2/EtOH = 80/20, 2nd peak)

Step 1: 2-ethyloxolane-2-carboxylic acid

[00516] To a stirred mixture of bis(propan-2-yl)amine (67.98 g, 671.741 mmol) in THF (300 mL) was added *n*-BuLi (258.4 mL, 645.905 mmol) dropwise at -78 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0 °C under nitrogen atmosphere. To this was added tetrahydro-2-furoic acid (30 g, 258.362 mmol) and THF (300 mL) dropwise at 0 °C. The resulting mixture was stirred for additional 1 h at 0 °C. To this was added ethyl iodide (120.89 g, 775.086 mmol) dropwise over 40 min at 0 °C. The resulting mixture was stirred for additional 16 h at room temperature. The reaction was quenched with sat. NH_4Cl (1 L). The resulting mixture was acidified to pH 2 with *conc.* HCl. The resulting mixture was extracted with EtOAc (3 x 1 L). The combined organic layers were washed with brine (3 x 1 L), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 2-ethyloxolane-2-carboxylic acid (28.9 g, 77%) as yellow oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 9.70 (br, 1H), 4.10-3.92 (m, 2H), 2.43-2.29 (m, 1H), 2.06-1.86 (m, 4H), 1.77-1.68 (m, 1H), 0.97 (t, *J* = 7.2 Hz, 3H).

Step 2: 1,3-dioxoisoindol-2-yl 2-ethyloxolane-2-carboxylate

[00517] To a stirred mixture of 2-ethyloxolane-2-carboxylic acid (3.00 g, 20.809 mmol) and DMAP (0.25 g, 2.081 mmol) and *N*-hydroxyphthalimide (3.73 g, 22.890 mmol) in DCM (30 mL) was added DIC (2.89 g, 22.890 mmol) at 0 °C. The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (3 x 15 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (9/1) to afford 1,3-dioxoisoindol-2-yl 2-ethyloxolane-2-carboxylate (4.8 g, 80%) as a white solid. MS ESI calculated for $C_{15}H_{15}NO_5$ [M + H]$^+$, 290.10, found, 290.10; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.93-7.89 (m, 2H), 7.84-7.79 (m, 2H), 4.11-4.05 (m, 2H), 2.66-2.51 (m, 1H), 2.23-1.86 (m, 5H), 1.15 (t, *J* = 7.2 Hz, 3H).

Step 3: 2,4-dichloro-7-(2-ethyloxolan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine

[00518] To a stirred mixture of 1,3-dioxoisoindol-2-yl 2-ethyloxolane-2-carboxylate (200 mg, 0.691 mmol) and 2,4-dichloropyrrolo[2,1-*f*][1,2,4]triazine (260 mg, 1.382 mmol) in DMA (6 mL) was added TFA (158 mg, 1.382 mmol) and $Ir[dF(CF_3)PPy]_2(dtbpy)PF_6$ (16 mg, 0.014 mmol) under nitrogen atmosphere. The reaction mixture was irradiated with Blue LED for 24 h at room temperature under nitrogen atmosphere. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 8 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was

concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 20% to 80%; detector, UV 254 nm to afford 2,4-dichloro-7-(2-ethyloxolan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (17 mg, 8%) as a yellow oil; MS ESI calculated for $C_{12}H_{13}Cl_2N_3O$ $[M + H]^+$, 286.04, found 286.15; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.05-7.02 (m, 2H), 4.10-3.94 (m, 2H), 2.53-2.47 (m, 1H), 2.35-2.17 (m, 2H), 2.06-1.94 (m, 2H), 1.86-1.78 (m, 1H), 0.75 (t, *J* = 7.2 Hz, 3H).

Step 4: 2-chloro-7-(2-ethyloxolan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine

[00519] To a mixture of 2,4-dichloro-7-(2-ethyloxolan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (260 mg, 0.909 mmol) in *i*-PrOH (0.2 mL) and THF (4 mL) was added $NaBH_4$ (52 mg, 1.364 mmol) in portions at 0 °C. The reaction mixture was stirred for 1.5 h at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (2 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 4 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced. To this were added DCM (5 mL) and DDQ (429 mg, 1.891 mmol). The reaction mixture was stirred for 1 h at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (5 mL) at 0°C. The aqueous layer was extracted with EtOAc (3 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford 2-chloro-7-(2-ethyloxolan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (220 mg, 69%) as a light yellow solid; MS ESI calculated for $C_{12}H_{14}ClN_3O$ $[M + H]^+$, 252.08, found 252.05; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.74 (s, 1H), 7.03 (d, *J* = 4.8 Hz, 1H), 6.93 (d, *J* = 4.8 Hz, 1H), 4.10-3.95 (m, 2H), 2.57-2.50 (m, 1H), 2.36-2.33 (m, 1H), 2.26-2.18 (m, 1H), 2.08-1.92 (m, 2H), 1.84-1.80 (m, 1H), 0.75 (t, *J* = 7.2 Hz, 3H).

Step 5: (3*S*,4*R*)-4-{[7-(2-ethyloxolan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol

[00520] To a stirred mixture of 2-chloro-7-(2-ethyloxolan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (175 mg, 0.695 mmol) and (3*S*,4*R*)-4-aminooxan-3-ol hydrochloride (534 mg, 3.475 mmol) in NMP (3 mL) was added DIEA (539 mg, 4.170 mmol) at room temperature. The reaction mixture was stirred for 16 h at 80 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 15% to 60%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[7-(2-ethyloxolan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (230 mg, 99%) as a light yellow solid; MS ESI calculated for $C_{17}H_{24}N_4O_3$ $[M + H]^+$, 333.18, found 333.20; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.54 (s, 1H), 6.78-6.69 (m, 2H), 4.94 (brs, 1H), 4.16-4.09 (m, 1H), 4.05-3.98 (m, 2H), 3.89-3.85 (m, 1H), 3.73-3.66 (m, 2H), 3.54-3.51 (m, 1H), 3.29-3.26 (m, 1H), 2.60-2.56 (m, 1H), 2.40-2.36 (m,

1H), 2.23-2.05 (m, 3H), 2.03-1.95 (m, 1H), 1.87-1.84 (m, 1H), 1.75-1.71 (m, 1H), 0.78-0.74 (m, 3H).

Step 6: (3*S*,4*R*)-4-{[7-(2-ethyloxolan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00521] To a stirred mixture of (3*S*,4*R*)-4-{[7-(2-ethyloxolan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (230 mg, 0.692 mmol) and TEA (140 mg, 1.384 mmol) in DCM (2 mL) was added Ac_2O (141 mg, 1.384 mmol) at 0 °C. The reaction mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[7-(2-ethyloxolan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (220 mg, 84%) as a yellow solid; MS ESI calculated for $C_{19}H_{26}N_4O_4$ $[M + H]^+$, 375.20, found 375.25.

Step 7: (3*S*,4*R*)-4-{[5-chloro-7-(2-ethyloxolan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00522] To a stirred mixture of (3*S*,4*R*)-4-{[7-(2-ethyloxolan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (220 mg, 0.588 mmol) in DMF (2 mL) was added NCS (71 mg, 0.529 mmol) at room temperature. The reaction mixture was stirred for 16 h at room temperature. The resulting mixture was diluted with water (10 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL). After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford (3*S*,4*R*)-4-{[5-chloro-7-(2-ethyloxolan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (190 mg, 79%) as yellow oil; MS ESI calculated for $C_{19}H_{25}ClN_4O_4$ $[M + H]^+$, 409.16, found 409.30; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.57 (s, 1H), 6.65 (s, 1H), 5.18 (brs, 1H), 5.00-4.96 (m, 1H), 4.09-3.86 (m, 5H), 3.61-3.58 (m, 1H), 3.49-3.44 (m, 1H), 2.62-2.46 (m, 1H), 2.46-2.36 (m, 1H), 2.36-2.20 (m, 1H), 2.10-2.05 (m, 4H), 1.99-1.79 (m, 3H), 1.79-1.64 (m, 1H), 0.78-0.74 (m, 3H).

Step 8: (3*S*,4*R*)-4-{[5-chloro-7-(2-ethyloxolan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00523] To a stirred mixture of (3*S*,4*R*)-4-{[5-chloro-7-(2-ethyloxolan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (190 mg, 0.465 mmol) in DMF (3 mL) was added I_2 (472 mg, 1.860 mmol) at room temperature. The reaction mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (10 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (3 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*S*,4*R*)-4-{[5-chloro-7-(2-ethyloxolan-2-

yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (220 mg, 88%) as a yellow solid; MS ESI calculated for $C_{19}H_{24}ClIN_4O_4$ $[M + H]^+$, 535.05, found 535.35.

Step 9: (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(2-ethyloxolan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00524] To a stirred mixture of (3*S*,4*R*)-4-{[5-chloro-7-(2-ethyloxolan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (220 mg, 0.411 mmol) and $Pd(PPh_3)_4$ (48 mg, 0.041 mmol) in DMF (3 mL) was added $Zn(CN)_2$ (29 mg, 0.247 mmol). The reaction mixture was stirred for 2 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (10 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (2 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(2-ethyloxolan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (160 mg, 89%) as a light yellow solid; MS ESI calculated for $C_{20}H_{24}ClN_5O_4$ $[M + H]^+$, 434.15, found 434.35; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 5.34-5.23 (m, 1H), 5.02-4.92 (m, 1H), 4.20-3.94 (m, 4H), 3.90-3.86 (m, 1H), 3.58-3.54 (m, 1H), 3.48-3.42 (m, 1H), 2.62-2.26 (m, 3H), 2.19-2.07 (m, 4H), 2.04-1.79 (m, 3H), 1.79-1.63 (m, 1H), 0.86-0.80 (m, 3H).

Step 10: (3*S*,4*R*)-4-{[6-cyano-7-(2-ethyloxolan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00525] To a stirred mixture of (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(2-ethyloxolan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (160 mg, 0.369 mmol),di-tert-butyl({2-[2,4,6-tris(propan-2-yl)phenyl]phenyl})phosphane (31.32 mg, 0.074 mmol) and Et_3N (149 mg, 1.476 mmol) in dioxane (3 mL) was added $Pd(dba)_2$ (21 mg, 0.037 mmol) and Et_3SiH (129 mg, 1.107 mmol) at room temperature. The reaction mixture was stirred for 2 h at 100 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (10 mL). The aqueous layer was extracted with EtOAc (3 x 3 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*S*,4*R*)-4-{[6-cyano-7-(2-ethyloxolan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (100 mg, 67%) as an off-white solid; MS ESI calculated for $C_{20}H_{25}N_5O_4$ $[M + H]^+$, 400.19, found 400.35; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.65 (s, 1H), 7.05 (s, 1H), 5.39 (brs, 1H), 5.03-4.93 (m, 1H), 4.22-3.92 (m, 5H), 3.64-3.52 (m, 1H), 3.50-3.45 (m, 1H), 2.59-2.51 (m, 1H), 2.45-2.30 (m, 2H), 2.19-2.06 (m, 4H), 2.03-2.00 (m, 1H), 1.97-1.92 (m, 1H), 1.86-1.67 (m, 2H), 0.85-0.79 (m, 3H).

Step 11: (3*S*,4*R*)-4-{[6-cyano-7-(2-ethyloxolan-2-yl)-5-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00526] To a stirred mixture of (3*S*,4*R*)-4-{[6-cyano-7-(2-ethyloxolan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (100 mg, 0.250 mmol) in DMF (1 mL) was added I_2 (254 mg, 1.000 mmol) at room temperature. The reaction mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (5 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (3 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford (3*S*,4*R*)-4-{[6-cyano-7-(2-ethyloxolan-2-yl)-5-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (116 mg, 88%) as a yellow solid; MS ESI calculated for $C_{20}H_{24}IN_5O_4$ $[M + H]^+$, 526.09, found 526.40.

Step 12: (3*S*,4*R*)-4-{[6-cyano-7-(2-ethyloxolan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00527] To a stirred mixture of (3*S*,4*R*)-4-{[6-cyano-7-(2-ethyloxolan-2-yl)-5-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (116 mg, 0.221 mmol), methyl 2,2-difluoro-2-sulfoacetate (212 mg, 1.105 mmol) and CuI (42 mg, 0.221 mmol) in DMF (2 mL) was added KF (38 mg, 0.663 mmol). The reaction mixture was stirred for 2 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (5 mL). The resulting mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (2 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*S*,4*R*)-4-{[6-cyano-7-(2-ethyloxolan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (67 mg, 64%) as an off-white solid; MS ESI calculated for $C_{21}H_{24}F_3N_5O_4$ $[M + H]^+$, 468.18, found 468.40;

Example 67:

(3*S*,4*R*)-4-{[6-cyano-7-(2-ethyloxolan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (single diastereoisomer, absolute chiral configuration of 2-ethyltetrahydrofuran-2-yl was not determined) (CHIRALPAK IG, CO_2/EtOH = 80/20, 1st peak)

Example 68:

(3*S*,4*R*)-4-{[6-cyano-7-(2-ethyloxolan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (single diastereoisomer, absolute chiral configuration of 2-

ethyltetrahydrofuran-2-yl was not determined) (CHIRALPAK IG, CO_2/EtOH = 80/20, 2nd peak)

[00528] To a stirred mixture of (3*S*,4*R*)-4-{[6-cyano-7-(2-ethyloxolan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (65 mg, 0.139 mmol) in MeOH (2 mg) was added K_2CO_3 (57.65 mg, 0.417 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 15% to 60%; detector, UV 254 nm. The crude product was purified by Prep-chrial-HPLC (Column: CHIRALPAK IG 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: EtOH; Flow rate: 85 mL/min; Gradient: A:B = 80:20; Wave Length: 220 nm;

[00529] RT_1: 5.92 min to afford (3*S*,4*R*)-4-{[6-cyano-7-(2-ethyloxolan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (single diastereoisomer, absolute chiral configuration of 2-ethyltetrahydrofuran-2-yl was not determined) (CHIRALPAK IG, CO_2/EtOH = 80/20, 1st peak) (13.7 mg, 23%) as an off-white solid; MS ESI calculated for $C_{19}H_{22}F_3N_5O_3$ $[M + H]^+$, 426.17, found 426.35. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.90 (s, 1H), 5.19 (s, 1H), 4.10-4.04 (m, 3H), 4.00-3.95 (m, 1H), 3.73-3.69 (m, 2H), 3.56-3.49 (m, 1H), 3.31-3.27 (m, 1H), 2.54-2.48 (m, 1H), 2.32-2.15 (m, 3H), 2.03-1.93 (m, 2H), 1.86-1.82 (m, 1H), 1.72-1.63 (m, 1H), 0.84-0.79 (m, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -54.93 (3F).

[00530] RT_2: 7.23 min to afford (3*S*,4*R*)-4-{[6-cyano-7-(2-ethyloxolan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (single diastereoisomer, absolute chiral configuration of 2-ethyltetrahydrofuran-2-yl was not determined) (CHIRALPAK IG, CO_2/EtOH = 80/20, 2nd peak) (11.9 mg, 20%) as an off-white solid; MS ESI calculated for $C_{19}H_{22}F_3N_5O_3$ $[M + H]^+$, 426.17, found 426.35. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.90 (s, 1H), 5.20 (s, 1H), 4.14-3.96 (m, 4H), 3.74-3.70 (m, 2H), 3.56-3.50 (m, 1H), 3.33-3.27 (m, 1H), 2.45-2.41 (m, 1H), 2.37-2.30 (m, 1H), 2.25-2.17 (m, 2H), 2.09-1.92 (m, 2H), 1.85-1.81 (m, 1H), 1.72-1.65 (m, 1H), 0.84-0.79 (m, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -54.94 (3F).

Example 69:

5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/MeOH/EtOH = 80/10/10, 1st peak)

Example 70:

5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer,

absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/MeOH/EtOH = 80/10/10, 2nd peak)

Step 1: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate

[00531] To a stirred mixture of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (80 mg, 0.18 mmol) in EtOAc (3 mL) was added methanesulfonic anhydride (57 mg, 0.32 mmol). The resulting mixture was stirred for 1 h at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (10 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (80 mg, 91%) as a yellow solid. MS ESI calculated for $C_{20}H_{27}ClN_6O_4S[M + H]^+$, 483.15, found 483.10.

Step 2: 5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00532] To a stirred mixture of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (80 mg, 0.16 mmol) in MeOH (3 mL) was added K_2CO_3 (45 mg, 0.33 mmol). The resulting mixture was stirred for 1 h at room temperature. The reaction was quenched by the addition of water/ice (20 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (70 mg, 93%) as a light yellow solid. MS ESI calculated for $C_{18}H_{25}ClN_6O_3S[M + H]^+$, 441.14, found 441.20.

Example 69:

5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/MeOH/EtOH = 80/10/10, 1st peak)

Example 70:

5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer,

absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/MeOH/EtOH = 80/10/10, 2nd peak)

[00533] 5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (70 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK AD-H, 2*25 cm, 5 μm; Mobile Phase A: hexane, Mobile Phase B: MeOH/EtOH (1/1); Flow rate: 20 mL/min; Gradient: A:B = 80:20; Wave Length: 254/220 nm;

[00534] RT_1: 15.84 min to afford 5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/MeOH/EtOH = 80/10/10, 1st peak) (26.4 mg, 34%) as a yellow solid. MS ESI calculated for $C_{18}H_{25}ClN_6O_3S$ $[M + H]^+$, 441.14, found 441.25 ^1H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 5.42 (brs, 1H), 3.97-3.93 (m, 1H), 3.84-3.76 (m, 3H), 3.27-3.22 (m, 1H), 2.98-2.91 (m, 1H), 2.87-2.80 (m, 4H), 2.36-2.17 (m, 2H), 1.77-1.70 (m, 1H), 1.45 (d, *J* = 7.2 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).

[00535] RT_2: 20.80 min to afford 5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/MeOH/EtOH = 80/10/10, 2nd peak) (22.8 mg, 30%) as a yellow solid. MS ESI calculated for $C_{18}H_{25}ClN_6O_3S$ $[M + H]^+$, 441.14, found 441.30 ^1H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 5.62 (brs, 1H), 3.95-3.90 (m, 1H), 3.86-3.74 (m, 3H), 3.27-3.22 (m, 1H), 2.98-2.91 (m, 1H), 2.87-2.80 (m, 4H), 2.31-2.16 (m, 2H), 1.80-1.72 (m, 1H), 1.45 (d, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H).

Example 71:

5-chloro-7-cyclopentyl-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[7-(cyclopent-1-en-1-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00536] To a solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({7-bromopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (2.20 g, 4.842 mmol) and 2-(cyclopent-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.41 g, 7.263 mmol) in 1,4-dioxane (80 mL) and water (20 mL) were added Pd(dppf)Cl_2.DCM (0.39 g, 0.484 mmol) and K_3PO_4 (2.06 g, 9.684 mmol). The reaction mixture was stirred for1 h at 100 °C under nitrogen atmosphere. The resulting mixture was diluted with water (300 mL) and extracted with EtOAc (2 x 300 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4. After filtration,

the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[7-(cyclopent-1-en-1-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (2.0 g, 93%) as a brown yellow solid. MS ESI calculated for $C_{23}H_{31}N_5O_4$ $[M + H]^+$, 442.24, found 442.25. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.57 (s, 1H), 6.99-6.98 (m, 1H), 6.71 (d, *J* = 4.8 Hz, 1H), 6.65 (d, *J* = 4.8 Hz, 1H), 5.32-4.98 (m, 2H), 4.01-3.89 (m, 2H), 3.85-3.78 (m, 1H), 3.31-3.29 (m, 2H), 2.87-2.83 (m, 2H), 2.67-2.63 (m, 2H), 2.46-2.38 (m, 1H), 2.07-2.05 (m, 3H), 2.04 -1.99 (m, 2H), 1.60-1.57 (m, 1H), 1.50 -1.48 (m, 9H).

Step 2: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({7-cyclopentylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00537] To a stirred solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[7-(cyclopent-1-en-1-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (2.1 g, 4.765 mmol) in EtOAc (100 mL) was added Pd/C (1.05 g, 9.845 mmol) at room temperature. The resulting mixture was stirred for 2 h at 50 °C under hydrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered, the filter cake was washed with EtOAc (3 x 50 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({7-cyclopentylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (660 mg, 31%) as a light yellow solid. MS ESI calculated for $C_{23}H_{33}N_5O_4$ $[M + H]^+$, 444.25, found 444.25. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.51 (s, 1H), 6.66 (d, *J* = 4.4 Hz, 1H), 6.51 (d, *J* = 4.8 Hz, 1H), 5.04-4.93 (m, 1H), 4.83-4.81 (m, 1H), 3.99-3.97 (m, 2H), 3.82-3.78 (m, 1H), 3.49-3.41 (m, 1H), 3.30-3.27 (m, 2H), 2.38-2.30 (m, 1H), 2.23-2.12 (m, 2H), 2.06 (s, 3H), 1.83-1.72 (m, 6H), 1.57-1.55 (m, 1H), 1.50-1.48 (m, 9H).

Step 3: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-cyclopentylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00538] To a stirred solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({7-cyclopentylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (600 mg, 4.353 mmol) in DMF (5 mL) was added NCS (216 mg, 1.624 mmol) at room temperature. The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, MeOH in water (10 mmol/L NH_4HCO_3), 40% to 90%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-cyclopentylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (600 mg, 92%) as a light yellow solid. MS ESI calculated for $C_{23}H_{32}ClN_5O_4$ $[M + H]^+$, 478.21, found 478.20. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.54 (s, 1H), 6.42 (s, 1H), 4.96-4.94 (m, 2H), 4.04-3.93 (m, 2H), 3.82-3.79 (m, 1H), 3.48-3.39 (m, 1H), 3.28-3.26 (m, 2H), 2.37-2.35 (m, 1H),

2.15-2.06 (m, 2H), 2.06-2.05 (m, 3H), 1.81-1.78 (m, 2H), 1.76-1.71 (m, 4H), 1.58-1.56 (m, 1H), 1.50-1.48 (m, 9H).

Step 4: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-cyclopentyl-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00539] To a stirred solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-cyclopentylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (80 mg, 0.167 mmol) in DMF (2 mL) was added I_2 (170 mg, 0.668 mmol) at room temperature. The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, MeOH in water (10 mmol/L NH_4HCO_3), 30% to 50%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-cyclopentyl-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (100 mg, 98%) as a light yellow solid. MS ESI calculated for $C_{23}H_{31}ClN_5O_4$ $[M + H]^+$, 604.11, found 604.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.54 (s, 1H), 5.14-5.10 (m, 1H), 4.91-4.89 (m, 1H), 3.97-3.95 (m, 1H), 3.91-3.78 (m, 2H), 3.57-3.51 (m, 1H), 3.25-3.23 (m, 2H), 2.33-2.29 (m, 1H), 2.25-2.18 (m, 2H), 2.08-2.06 (m, 3H), 1.96-1.84 (m, 4H), 1.76-1.74 (m, 2H), 1.62-1.52 (m, 1H), 1.50-1.48 (m, 9H).

Step 5: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-cyano-7-cyclopentylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00540] To a stirred solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-cyclopentyl-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (90 mg, 0.149 mmol) and $Zn(CN)_2$ (11 mg, 0.089 mmol) in DMF (2 mL) was added $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 50% to 70%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-cyano-7-cyclopentylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (60 mg, 80%) as a light yellow solid. MS ESI calculated for $C_{24}H_{31}ClN_6O_4$ $[M + H]^+$, 503.21, found 503.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.66 (s, 1H), 5.46 (s, 1H), 4.94-4.92 (m, 1H), 4.01-3.99 (m, 1H), 3.89-3.84 (m, 2H), 3.70-3.61 (m, 1H), 3.22-3.20 (m, 2H), 2.35-2.30 (m, 1H), 2.08-2.03 (m, 7H), 1.95-1.81 (m, 2H), 1.79-1.77 (m, 2H), 1.59-1.57 (m, 1H), 1.50-1.48 (m, 9H).

Step 6: (3*R*,4*R*)-4-({5-chloro-6-cyano-7-cyclopentylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-methanesulfonylpiperidin-3-yl acetate

[00541] A solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-cyano-7-cyclopentylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (60 mg, 0.119 mmol) and HCl (gas) in 1,4-

dioxane (2 mL) in DCM (2 mL) was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure. To this was added sat. $NaHCO_3$ (2 mL) and EtOAc (2 mL), followed by the addition of methanesulfonic anhydride (36 mg, 0.206 mmol) at 0 °C. The resulting mixture was stirred for 30 min at room temperature. The resulting mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*R*,4*R*)-4-({5-chloro-6-cyano-7-cyclopentylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-methanesulfonylpiperidin-3-yl acetate (45 mg, 68%) as a light yellow solid. MS ESI calculated for $C_{20}H_{25}ClN_6O_4S$ $[M + H]^+$, 481.13, found 481.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.67 (d, *J* = 1.2 Hz, 1H), 5.45-5.26 (m, 1H), 5.10-5.09 (m, 1H), 3.92-3.87 (m, 2H), 3.77-3.58 (m, 2H), 3.26-3.05 (m, 2H), 2.91-2.89 (m, 3H), 2.48-2.46 (m, 1H), 2.09-2.07 (m, 7H), 1.96-1.94 (m, 2H), 1.81-1.75 (m, 3H).

Example 71:

5-chloro-7-cyclopentyl-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00542] To a stirred solution of (3*R*,4*R*)-4-({5-chloro-6-cyano-7-cyclopentylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-methanesulfonylpiperidin-3-yl acetate (45 mg, 0.094 mmol) in MeOH (3 mL) was added K_2CO_3 (26 mg, 0.188 mmol) at room temperature. The resulting mixture was stirred for 30 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 20% to 50%; detector, UV 254 nm to afford 5-chloro-7-cyclopentyl-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (21 mg, 52%) as a light yellow solid. MS ESI calculated for $C_{18}H_{23}ClN_6O_3S$ $[M + H]^+$, 439.12, found 439.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 5.23 (brs, 1H), 3.97-3.93 (m, 1H), 3.85-3.80 (m, 3H), 3.66-3.60 (m, 1H), 2.96-2.90 (m, 1H), 2.90-2.88 (m, 3H), 2.82-2.77 (m, 1H), 2.31-2.27 (m, 1H), 2.16-1.92 (m, 6H), 1.84-1.69 (m, 3H).

Example 75:

5-chloro-2-[(1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: *N*-[5-chloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]-1-methanesulfonylpiperidin-4-amine

[00543] A solution of 2,5-dichloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine (190 mg, 0.513 mmol), 1-methanesulfonylpiperidin-4-amine (457 mg, 2.565 mmol) and DIEA (398 mg, 3.078 mmol) in NMP (2 mL) was stirred for 2 h at 100 °C under nitrogen atmosphere. The

mixture was allowed to cool down to room temperature and purified by reversed-phase chromatography with the following conditions: C18 column; CH_3CN in water (plus 10 mmol/L NH_4HCO_3); 45% to 70%;; Detector: 220/254 nm to afford *N*-[5-chloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]-1-methanesulfonylpiperidin-4-amine (200 mg, 76%) as a light yellow solid. MS ESI calculated for $C_{16}H_{23}ClIN_5O_2S$. $[M + H]^+$, 512.03, found 512.15.

Example 75:

5-chloro-2-[(1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00544] A solution of *N*-[5-chloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]-1-methanesulfonylpiperidin-4-amine (10 mg, 0.020 mmol), $Zn(CN)_2$ (1 mg, 0.010 mmol) and $Pd(PPh_3)_4$ (2 mg, 0.002 mmol) in DMF (0.5 mL) was stirred for 2 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature and diluted with water (5 mL). The resulting mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (3 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 5-chloro-2-[(1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (5.4 mg, 64%) as a light yellow solid. MS ESI calculated for $C_{17}H_{23}ClN_6O_2S$. $[M + H]^+$, 411.13, found 411.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 4.96 (brs, 1H), 3.86-3.75 (m, 3H), 3.02-2.95 (m, 2H), 2.90-2.85 (m, 5H), 2.26-2.15 (m, 3H), 1.77-1.69 (m, 2H), 1.01-0.98 (m, 6H).

Example 76:

7-isopropyl-2-[(1-methanesulfonylpiperidin-4-yl)amino]-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: 7-isopropyl-2-[(1-methanesulfonylpiperidin-4-yl)amino]pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00545] To a stirred mixture of 5-chloro-7-isopropyl-2-[(1-methanesulfonylpiperidin-4-yl)amino]pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (80 mg, 0.202 mmol), Et_3N (84 uL, 0.605 mmol), $Pd(dba)_2$ (12 mg, 0.020 mmol) and di-*tert*-butyl({2-[2,4,6-tris(propan-2-yl)phenyl]phenyl})phosphane (17 mg, 0.040 mmol) in dioxane (1 mL) was added triethylsilane (128 uL, 0.808 mmol) under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 100 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of water (20 mL) at room temperature. The resulting mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with

brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 7-isopropyl-2-[(1-methanesulfonylpiperidin-4-yl)amino]pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (50 mg, 61%) as an off-white solid. MS ESI calculated for $C_{16}H_{22}N_6O_2S$ $[M + H]^+$, 363.15, found 363.30. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.62 (s, 1H), 7.00 (s, 1H), 5.06 (brs, 1H), 3.90-3.86 (m, 1H), 3.78-3.64 (m, 3H), 3.06-3.03 (m, 2H), 2.85 (s, 3H), 2.28-2.23 (m, 2H), 1.76-1.70 (m, 2H), 1.50 (d, J = 7.2 Hz, 6H).

[00546] Step 2: 5-iodo-7-isopropyl-2-[(1-methanesulfonylpiperidin-4-yl)amino]pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00547] A mixture of 7-isopropyl-2-[(1-methanesulfonylpiperidin-4-yl)amino]pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (50 mg, 0.138 mmol) and I_2 (140 mg, 0.552 mmol) in DMF (1 mL) was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (20 mL). The resulting mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 5-iodo-7-isopropyl-2-[(1-methanesulfonylpiperidin-4-yl)amino]pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (60 mg, 84%) as an off-white solid. MS ESI calculated for $C_{16}H_{21}IN_6O_2S$ $[M + H]^+$, 489.05, found 489.15.

Example 76:

7-isopropyl-2-[(1-methanesulfonylpiperidin-4-yl)amino]-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00548] To a stirred mixture of 5-iodo-7-isopropyl-2-[(1-methanesulfonylpiperidin-4-yl)amino]pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (60 mg, 0.123 mmol) and KF (21 mg, 0.369 mmol) in DMF (1 mL) was added methyl 2,2-difluoro-2-sulfoacetate (118 mg, 0.614 mmol). The resulting mixture was stirred for 3 h at 80 °C under nitrogen atmosphere. The reaction was quenched by the addition of sat. $NH_4Cl/NH_3.H_2O$ (9/1) (50 mL). The resulting mixture was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 7-isopropyl-2-[(1-methanesulfonylpiperidin-4-yl)amino]-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (28.6 mg, 53%) as colorless oil. MS ESI calculated for $C_{17}H_{21}F_3N_6O_2S$ $[M + H]^+$, 431.14, found 431.30. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.86 (s, 1H), 5.03 (brs, 1H), 3.86-3.75 (m, 3H), 3.72-3.64 (m, 1H), 3.02-2.96

(m, 2H), 2.84 (s, 3H), 2.26-2.21 (m, 2H), 1.77-1.70 (m, 2H), 1.52-1.47 (m, 6H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -54.97 (3F).

Example 77:

5-chloro-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*S*,4*R*)-4-{[5-chloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate

[00549] To a stirred solution of 2,5-dichloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine (100 mg, 0.270 mmol) in NMP (2 mL) were added *tert*-butyl (3*S*,4*R*)-4-amino-3-hydroxypiperidine-1-carboxylate (292 mg, 1.350 mmol) and DIEA (209 mg, 1.620 mmol). The resulting mixture was stirred for 2 h at 100 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 50% to 70%; detector, UV 254 nm to afford *tert*-butyl (3*S*,4*R*)-4-{[5-chloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (105 mg, 70%) as a light yellow solid. MS ESI calculated for $C_{20}H_{29}ClIN_5O_3$ [M + H]$^+$, 550.10, found 550.10.

Step 2: *tert*-butyl(3*S*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00550] To a stirred solution of *tert*-butyl (3*S*,4*R*)-4-{[5-chloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (105 mg, 0.191 mmol) in DCM (2 mL) were added Ac_2O (29 mg, 0.286 mmol) and TEA (58 mg, 0.573 mmol). The resulting mixture was stirred for 16 h at 50 °C. The mixture was allowed to cool down to room temperature. The resulting mixture was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (100 mg, 88%) as light yellow oil. MS ESI calculated for $C_{22}H_{31}ClIN_5O_4$ [M + H]$^+$, 592.11, found 592.10.

Step 3: *tert*-butyl(3*S*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00551] To a stirred solution of *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (90 mg, 0.152 mmol) and $Zn(CN)_2$ (10 mg, 0.091 mmol) in DMF (2 mL) was added $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 130 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (5 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 5

mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 30% to 65%; detector, UV 254 nm to afford *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (42 mg, 56%) as a light yellow solid. MS ESI calculated for $C_{23}H_{31}ClN_6O_4$ $[M + H]^+$, 491.21, found 491.35. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 5.10 (brs, 1H), 5.06-5.01 (m, 1H), 4.49-4.45 (m, 1H), 4.35-4.31 (m, 1H), 4.07-4.02 (m, 1H), 3.02-2.87 (m, 4H), 2.25-2.20 (m, 1H), 2.11 (s, 3H), 1.91-1.88 (m, 1H), 1.80-1.75 (m, 1H), 1.50-1.45 (m, 9H), 1.01-0.97 (m, 6H).

Step 4: (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate

[00552] A solution of *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (42 mg, 0.086 mmol) in DCM (1 mL) was added HCl (gas) in 1,4-dioxane (1 mL, 4.000 mmol) at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure. To this was added sat. $NaHCO_3$ (1 mL) and methanesulfonic anhydride (44 mg, 0.258 mmol) in EtOAc (2 mL) at 0 °C. The reaction mixture was stirred for additional 40 min at room temperature. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (30 mg, 74%) as light yellow oil.. MS ESI calculated for $C_{19}H_{25}ClN_6O_4S$ $[M + H]^+$, 469.13, found 469.15.

Example 77:

5-chloro-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00553] A solution of (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (30 mg, 0.064 mmol) and K_2CO_3 (26.52 mg, 0.192 mmol) in MeOH (1 m) was stirred for 1 h at room temperature. The resulting mixture was diluted with water (5 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase,

CH_3CN in water (0.1% formic acid), 40% to 60%; detector, UV 254 nm to afford 5-chloro-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (9.4 mg, 34 %) as a white solid. MS ESI calculated for $C_{17}H_{23}ClN_6O_3S$ $[M + H]^+$, 427.12, found 427.30. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 5.47 (d, *J* = 8.0 Hz, 1H), 4.15-4.14 (m, 1H), 3.97-3.88 (m, 3H), 3.12 (d, *J* = 13.2 Hz, 1H), 2.98-2.82 (m, 6H), 2.24-2.20 (m, 1H), 2.09-2.05 (m, 1H), 1.99-1.92 (m, 1H), 1.01-0.97 (m, 6H).

Example 78:

5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*R*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IG, Hexane/EtOH/DCM = 70/15/15, 2nd peak)

Example 79:

5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*R*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IG, Hexane/EtOH/DCM = 70/15/15, 1st peak)

Step 1: (3*R*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol

[00554] To a stirred solution of 2,5-dichloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (90 mg, 0.326 mmol) and (3*R*,4*R*)-4-aminooxan-3-ol hydrochloride (75 mg, 0.489 mmol) in NMP (2 mL) was added DIEA (211 mg, 1.630 mmol) at room temperature. The resulting mixture was stirred for 16 h at 80 °C. The mixture was allowed to cool down to room temperature. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 20% to 50%; detector, UV 254 nm to afford (3*R*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (100 mg, 86%) as a light yellow solid. MS ESI calculated for $C_{16}H_{22}ClFN_4O_2$ $[M + H]^+$, 357.14, found 357.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.59 (s, 1H), 6.51 (s, 1H), 5.19-5.17 (m, 1H), 4.04-3.97 (m, 4H), 3.85-3.79 (m, 1H), 3.69-3.55 (m, 2H), 1.98-1.85 (m, 2H), 1.42-1.30 (m, 9H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -143.57 (1F).

Step 2: (3*R*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00555] To a stirred solution of (3*R*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (100 mg, 0.280 mmol) and Ac_2O (43 mg, 0.420 mmol) in DCM (2 mL) was added TEA (85 mg, 0.840 mmol) at room temperature. The resulting mixture

was stirred for 16 h at 50 °C. The mixture was allowed to cool down to room temperature. The resulting mixture was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*R*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (90 mg, 80%) as light yellow oil. MS ESI calculated for $C_{18}H_{24}ClFN_4O_3$ $[M + H]^+$, 399.15, found 399.20.

Step 3: (3*R*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00556] To a stirred solution of (3*R*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (90 mg, 0.226 mmol) in DMF (2 mL) was added I_2 (229 mg, 0.904 mmol) at room temperature. The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 50% to 80%; detector, UV 254 nm to afford (3*R*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (75 mg, 63%) as a light yellow solid. MS ESI calculated for $C_{18}H_{23}ClFIN_4O_3$ $[M + H]^+$, 525.05, found 525.20.

Step 4: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00557] To a stirred solution of (3*R*,4*R*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (70 mg, 0.133 mmol) and $Zn(CN)_2$ (9 mg, 0.080 mmol) in DMF (2 mL) was added $Pd(PPh_3)_4$ (15 mg, 0.013 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 100 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (50 mg, 88%) as light yellow oil. MS ESI calculated for $C_{19}H_{23}ClFN_5O_3$ $[M + H]^+$, 424.15, found 424.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 5.11-4.98 (m, 2H), 4.14-4.08 (m, 3H), 3.95-3.90 (m, 1H), 3.63-3.54 (m, 2H), 2.16-2.12 (m, 3H), 2.08-2.02 (m, 1H), 1.99-1.93 (m, 1H), 1.61-1.58 (m, 3H), 1.42-1.40 (m, 6H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -139.75 & -140.27 (1F).

Step 5: 5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-{[(3*R*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00558] To a stirred solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (55 mg, 0.130 mmol) in MeOH (2 mL) was added K_2CO_3 (36 mg, 0.260 mmol). The resulting mixture was stirred for 30 min at

room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 20% to 50%; detector, UV 254 nm to afford 5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-{[(3*R*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (35 mg, 70 %) as a light yellow solid. MS ESI calculated for $C_{17}H_{21}ClFN_5O_2$ $[M + H]^+$, 382.14, found 382.15.

Example 78:

5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*R*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IG, Hexane/EtOH/DCM = 70/15/15, 2nd peak)

Example 79:

5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*R*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IG, Hexane/EtOH/DCM = 70/15/15, 1st peak)

[00559] 5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-{[(3*R*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (37 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: hexane, Mobile Phase B: EtOH/DCM (1/1); Flow rate: 20 mL/min; Gradient: A:B = 70:30; Wave Length: 254/220 nm;

[00560] RT_1: 9.51 min to afford 5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*R*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IG, Hexane/EtOH/DCM = 70/15/15, 1st peak) (13 mg, 36%) as a light yellow solid. MS ESI calculated for $C_{17}H_{21}ClFN_5O_2$ $[M + H]^+$, 382.14, found 382.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 5.57 (brs, 1H), 4.03-3.87 (m, 5H), 3.66-3.62 (m, 1H), 3.54-3.47 (m, 1H), 2.01-1.96 (m, 1H), 1.90-1.79 (m, 1H), 1.58 (d, *J* = 7.2 Hz, 3H), 1.47-1.36 (m, 6H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -139.58 (1F).

[00561] RT_2: 11.63 min to afford 5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*R*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IG, Hexane/EtOH/DCM = 70/15/15, 2nd peak) (13 mg, 36%) as a light yellow solid. MS ESI calculated for $C_{17}H_{21}ClFN_5O_2$ $[M + H]^+$, 382.14, found 382.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 5.51 (brs, 1H), 4.03-3.86 (m, 5H), 3.65-3.61 (m, 1H), 3.57-3.49 (m, 1H), 2.01-1.83 (m, 2H), 1.58 (d, *J* = 7.2 Hz, 3H), 1.47-1.36 (m, 6H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -139.56 (1F).

Example 80:

5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*S*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IH, Hexane/EtOH = 85/15, 2nd peak)

Example 81:

5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*S*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IH, Hexane/EtOH = 85/15, 1st peak)

Step 1: (3*S*,4*S*)-4-((5-chloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol

[00562] A solution of 2,5-dichloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (110 mg, 0.398 mmol), (3*S*,4*S*)-4-aminooxan-3-ol (70 mg, 0.597 mmol) and DIEA (257 mg, 1.990 mmol) in NMP (2 mL) was stirred for 16h at 80 °C. The mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (4/1) to afford (3*S*,4*S*)-4-((5-chloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol (150 mg, 84%) as a yellow liquid. MS ESI calculated for $C_{16}H_{22}ClFN_4O_2$[M + H]$^+$, 357.14, found 357.20.

Step 2: (3*S*,4*S*)-4-((5-chloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino) tetrahydro-2*H*-pyran-3-yl acetate

[00563] A solution of (3*S*,4*S*)-4-((5-chloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino) tetrahydro-2*H*-pyran-3-ol(140 mg, 0.392 mmol), Ac_2O (60.mg, 0.588 mmol) and TEA (119 mg, 1.176 mmol) in DCM (1 mL) was stirred for 16 h at room temperature. The resulting mixture was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*S*,4*S*)-4-((5-chloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino) tetrahydro-2*H*-pyran-3-yl acetate (50 mg, 31%) as a yellow oil. MS ESI calculated for $C_{18}H_{24}ClFN_4O_3$ [M + H]$^+$, 399.10, found 399.10.

Step 3: (3*S*,4*S*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00564] To a stirred mixture of (3*S*,4*S*)-4-((5-chloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino) tetrahydro-2*H*-pyran-3-yl acetate (50 mg, 0.125 mmol) in DMF (0.5 mL) was added I_2 (127 mg, 0.500 mmol) at room temperature.The mixture was stirred for 1

h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase: CH_3CN in water (0.1% formic acid), 10% to 30%; detector, UV 254 nm to afford (3*S*,4*S*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (50 mg, 76%) as a yellow solid. MS ESI calculated for $C_{18}H_{23}ClFIN_4O_3$ $[M + H]^+$, 525.05, found 525.10.

Step 4: (3*S*,4*S*)-4-{[5-chloro-6-cyano-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00565] A solution of (3*S*,4*S*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (50 mg, 0.095 mmol), $Pd(PPh_3)_4$ (11 mg, 0.010 mmol) and $Zn(CN)_2$ (7 mg, 0.057 mmol) in DMF (1 mL) was stirred for 2 h at 120 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 30% to 60%; Detector: UV 254 nm to afford (3*S*,4*S*)-4-{[5-chloro-6-cyano-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (30 mg, 66%) as a yellow soild. MS ESI calculated for $C_{19}H_{23}ClFN_5O_3$ $[M + H]^+$, 424.15, found 424.30.

Step 5: 5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-{[(3*S*,4*S*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00566] A solution of (3*S*,4*S*)-4-{[5-chloro-6-cyano-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (40 mg, 0.094 mmol) and K_2CO_3 (26 mg, 0.188 mmol) in MeOH (1 mL) was stirred for 1 h at room temperature. The resulting mixture was purified by reversed-phase chromatography: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 40% to 60%; Detector: UV 254 nm to afford 5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-{[(3*S*,4*S*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (25 mg, 69%) as a yellow solid. MS ESI calculated for $C_{17}H_{21}ClFN_5O_2$ $[M + H]^+$, 382.14, found 382.20.

Example 80:

5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*S*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IH, Hexane/EtOH = 85/15, 2nd peak)

Example 81:

5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*S*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IH, Hexane/EtOH = 85/15, 1st peak)

[00567] 5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-{[(3*S*,4*S*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (25 mg) was purified by Prep-Chiral-HPLC (Column: CHIRALPAK IH, 2*25 cm, 5 μm; Mobile Phase A: Hexane, Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: A:B = 85:15; Wave Length: 254/220 nm;

[00568] RT_1: 16.99 min to afford 5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*S*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IH, Hexane/EtOH = 85/15, 2nd peak) (4.6 mg, 18%) as a light yellow solid. MS ESI calculated for $C_{17}H_{21}ClFN_5O_2$ $[M + H]^+$, 382.14, found 382.25; ^1H NMR (400 MHz, DMSO-d_6) δ 8.99 (s, 1H), 7.06 (d, J = 7.2 Hz, 1H), 4.86 (d, J = 4.8 Hz, 1H), 3.89-3.73 (m, 5H), 3.51-3.43 (m, 2H), 2.02-1.93 (m, 1H), 1.62-1.58 (m, 1H), 1.50-1.48 (m, 3H), 1.45-1.40 (m, 3H), 1.26-1.20 (m, 3H).

[00569] RT_2: 19.87 min to afford 5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*S*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IH, Hexane/EtOH = 85/15, 1st peak) (4.1 mg, 16%) as a light yellow solid. MS ESI calculated for $C_{17}H_{21}ClFN_5O_2$ $[M + H]^+$, 382.14, found 382.25; 1H NMR (400 MHz, DMSO-d_6) δ 8.99 (s, 1H), 6.90 (d, J = 6.8 Hz, 1H), 4.94 (d, J = 4.4 Hz, 1H), 3.92-3.74 (m, 5H), 3.52-3.40 (m, 2H), 1.95-1.86 (m, 1H), 1.69-1.60 (m, 1H), 1.51-1.48 (m, 3H), 1.46-1.39 (m, 3H), 1.26-1.21 (m, 3H).

Example 82:

5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*R*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IF, Hexane/EtOH/DCM = 80/10/10, 2nd peak)

Example 83:

5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*R*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IF, Hexane/EtOH/DCM = 80/10/10, 1st peak)

Step 1: (3*R*,4*S*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol

[00570] A solution of 2,5-dichloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (90 mg, 0.326 mmol), (3*R*,4*S*)-4-aminooxan-3-ol hydrochloride (75 mg, 0.489 mmol) and DIEA (211 mg, 1.630 mmol) in NMP (1 mL) was stirred for 16 h at 80 °C under nitrogen atmosphere. The

resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 30% to 50%; detector, UV 254 nm to afford (3*R*,4*S*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (88 mg, 75%) as a light yellow solid. MS ESI calculated for $C_{16}H_{22}ClFN_4O_2$ $[M + H]^+$, 357.14, found 357.10.

Step 2: (3*R*,4*S*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00571] A solution of (3*R*,4*S*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (80 mg, 0.224 mmol), Ac_2O (34 mg, 0.336 mmol) and TEA (68 mg, 0.672 mmol) in DCM (1 mL) was stirred for 16 h at 50 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*R*,4*S*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (80 mg, 89 %) as a light yellow solid. MS ESI calculated for $C_{18}H_{24}ClFN_4O_3$ $[M + H]^+$, 399.15, found 399.10.

Step 3: (3*R*,4*S*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00572] A solution of (3*R*,4*S*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (75 mg, 0.188 mmol) and I_2 (191 mg, 0.752 mmol) in DMF (2 mL) was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (50 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford (3*R*,4*S*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (65 mg, 65%) as a light yellow solid. MS ESI calculated for $C_{18}H_{23}ClFIN_4O_3$ $[M + H]^+$, 525.05, found 525.15.

Step 4: (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00573] A solution of (3*R*,4*S*)-4-{[5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (70 mg, 0.133 mmol), $Zn(CN)_2$ (9 mg, 0.080 mmol) and $Pd(PPh_3)_4$ (15 mg, 0.013 mmol) in DMF (2 mL) was stirred for 2 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18

column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (50 mg, 88%) as a light yellow solid. MS ESI calculated for $C_{19}H_{23}ClFN_5O_3$ $[M + H]^+$, 424.15, found 424.20.

Step 5: (3*S*,4*R*)-4-{[6-cyano-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-*yl*]amino}oxan-3-*yl* acetate

[00574] A solution of (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(3-fluoro-3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (50 mg, 0.118 mmol) and K_2CO_3 (48.91 mg, 0.354 mmol) in MeOH (1 mL) was stirred for 30 min at room temperature. The reaction was quenched by the addition of water (30 mL). The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-{[(3*R*,4*S*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (40 mg, 88%) as a light yellow solid. MS ESI calculated for $C_{17}H_{21}ClFN_5O_2$ $[M + H]^+$, 382.14, found 382.15.

Example 82:

5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*R*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IF, Hexane/EtOH/DCM = 80/10/10, 2nd peak)

Example 83:

5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*R*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IF, Hexane/EtOH/DCM = 80/10/10, 1st peak)

[00575] 5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-{[(3*R*,4*S*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (40 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: hexane, Mobile Phase B: EtOH/DCM (1/1); Flow rate: 20 mL/min; Gradient: A:B = 80:20; Wave Length: 254/220 nm;

[00576] RT_1: 14.65 min to afford 5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*R*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IF, Hexane/EtOH/DCM = 80/10/10, 1st peak) (12.7 mg, 31%) MS ESI calculated for $C_{17}H_{21}ClFN_5O_2$ $[M + H]^+$, 382.14; found 382.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 5.10 (brs, 1H), 4.10-4.06 (m, 1H), 4.03-3.82 (m, 3H), 3.70-3.64

(m, 1H), 3.55-3.48 (m, 1H), 3.29-3.23 (m, 1H), 2.18-2.12 (m, 1H), 1.73-1.68 (m, 1H), 1.60 (d, *J* = 7.2 Hz, 3H), 1.49-1.39 (m, 6H). ^{19}F NMR (376 MHz, Chloroform -*d*) δ -138.74 (1F).

[00577] RT_2: 17.21 min to afford 5-chloro-7-(3-fluoro-3-methylbutan-2-yl)-2-(((3*R*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-fluoro-3-methylbutan-2-yl was not determined) (CHIRALPAK IF, Hexane/EtOH/DCM = 80/10/10, 2nd peak) (12 mg, 29%) as a light yellow solid. MS ESI calculated for $C_{17}H_{21}ClFN_5O_2$ $[M + H]^+$, 382.14; found 382.25. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 5.13 (brs, 1H), 4.11-4.07 (m, 1H), 4.01-3.96 (m, 1H), 3.90-3.76 (m, 2H), 3.73-3.66 (m, 1H), 3.55-3.48 (m, 1H), 3.31-3.25 (m, 1H), 2.21-2.16 (m, 1H), 1.70-1.65 (m, 1H), 1.61 (d, *J* = 7.6 Hz, 3H), 1.49-1.36 (m, 6H). ^{19}F NMR (376 MHz, Chloroform -*d*) δ -140.17 (1F).

Example 84:

(3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-ol

Step 1: (3*R*,4*R*)-4-{[7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate

[00578] To a stirred mixture of 2-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (100 mg, 0.424 mmol) and *tert*-butyl (3*R*,4*R*)-4-amino-3-hydroxypiperidine-1-carboxylate (367 mg, 1.696 mmol) in NMP (1.5 mL) was added DIEA (274 mg, 2.120 mmol). The reaction mixture was stirred for 16 h at 80 °C. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (110 mg, 62%) as a light yellow solid; MS ESI calculated for $C_{22}H_{33}N_5O_3$ $[M + H]^+$, 415.26, found 416.40; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.50 (s, 1H), 6.77 (d, *J* = 4.8 Hz, 1H), 6.53 (d, *J* = 4.8 Hz, 1H), 5.07 (brs, 1H), 4.37-4.25 (m, 1H), 4.21-4.13 (m, 1H), 3.69-3.55 (m, 3H), 2.74 (m, 1H), 2.56-2.49 (m, 1H), 2.47-2.42 (m, 1H), 2.32-2.24 (m, 2H), 2.20-1.85 (m, 5H), 1.60-1.48 (m, 10H), 0.67-0.62 (m, 3H).

Step 2: (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate

[00579] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-4-{[7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (100 mg, 0.241 mmol) in DMF (1.5 mL) was added NCS (29 mg, 0.217 mmol). The reaction mixture was stirred for 16 h at room

temperature. The resulting mixture was diluted with sat. $NaHCO_3$ (20 mL). The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (100 mg, 92 %) as a light yellow solid; MS ESI calculated for $C_{22}H_{32}ClN_5O_3$ $[M + H]^+$, 449.22, found 450.45; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.51 (s, 1H), 6.50 (s, 1H), 5.60 (brs, 1H), 4.28-4.15 (m, 1H), 4.13-4.07 (m, 1H), 3.63-3.53 (m, 2H), 2.81-2.62 (m, 2H), 2.55-2.38 (m, 2H), 2.28-2.07 (m, 6H), 1.96-1.89 (m, 1H), 1.62-1.48 (m, 10H), 0.69-0.59 (m, 3H).

Step 3: (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-ol

[00580] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (100 mg, 0.222 mmol) in DCM (1 mL) was added HCl (gas) in 1,4-dioxane (1 mL, 32.913 mmol) at 0 °C. The reaction mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-ol hydrochloride (120 mg, crude) as a light yellow solid; MS ESI calculated for $C_{17}H_{25}Cl_2N_5O$ $[M - Cl]^+$, 350.17, found 350.30.

Example 84:

(3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-ol

[00581] To a stirred mixture of (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-ol hydrochloride (70 mg, 0.200 mmol) and sat. $NaHCO_3$ (2 mL) in EtOAc (2 mL) was added methanesulfonic anhydride (62 mg, 0.360 mmol). The reaction mixture was stirred for 1 h at room temperature. The resulting mixture was diluted with water (20 mL), extracted with EtOAc (3 x 15 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 25% to 60%; detector, UV 254 nm to afford (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-ol (31.3 mg, 36%) as a yellow solid; MS ESI calculated for $C_{18}H_{26}ClN_5O_3S$ $[M + H]^+$, 428.14, found 428.30; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.57 (s, 1H), 6.43 (s, 1H), 4.96-4.92 (m, 1H), 4.00-3.96 (m, 1H), 3.85-3.74 (m, 2H), 3.66-3.60 (m, 1H), 2.91-2.86 (m, 4H), 2.76-2.72 (m, 1H), 2.53-2.37 (m, 2H), 2.30-2.18 (m, 3H), 2.15-1.91 (m, 4H), 1.80-1.72 (m, 1H), 0.66-0.63 (m, 3H).

Example 85:

7-(*sec*-butyl)-5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (chiral resolution of 6-I intermediate, CHIRALPAK IG, CO_2/MeOH = 65/35, 1st peak)

Step 1: (3*R*,4*R*)-4-{[5-chloro-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate

[00582] To a stirred mixture of 2,5-dichloro-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazine (370 mg, 1.516 mmol) and *tert*-butyl (3*R*,4*R*)-4-amino-3-hydroxypiperidine-1-carboxylate (1.31 g, 6.064 mmol) in NMP (5 mL) was added DIEA (979 mg, 7.580 mmol). The reaction mixture was stirred for 16 h at 80 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 20% to 65%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (550 mg, 85%) as a yellow solid; MS ESI calculated for $C_{20}H_{30}ClN_5O_3$ $[M + H]^+$, 424.20, found 424.35.

Step 2: (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00583] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (550 mg, 1.297 mmol) and TEA (393.85 mg, 3.891 mmol) in DCM (5 mL) was added Ac_2O (264.89 mg, 2.594 mmol). The reaction mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (550 mg, 90%) as a yellow solid. MS ESI calculated for $C_{22}H_{32}ClN_5O_4$ $[M + H]^+$, 466.21, found 466.40; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.54 (s, 1H), 6.41 (s, 1H), 5.08 (d, *J* = 7.2 Hz, 1H), 4.97-4.89 (m, 1H), 3.97-3.89 (m, 2H), 3.83-3.79 (m, 1H), 3.33-3.27 (m, 2H), 2.36-2.30 (m, 1H), 2.08-2.04 (m, 3H), 1.87-1.72 (m, 1H), 1.67-1.54 (m, 2H), 1.51-1.47 (m, 9H), 1.34-1.24 (m, 4H), 0.92-0.88 (m, 3H).

Step 3: *tert*-butyl (3*R*,4*R*)-3-acetoxy-4-((7-(*sec*-butyl)-5-chloro-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)piperidine-1-carboxylate (single diastereoisomers, absolute chiral configuration of *sec*-butyl was not determined) (CHIRALPAK IG, CO_2/MeOH = 65/35) 1st peak & 2nd peak)

[00584] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-7-(*sec*-butyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (550 mg, 1.180 mmol) in DMF (6 mL) was added I_2 (1.19 g, 4.720 mmol). The reaction mixture was stirred for 16 h at room temperature.

The reaction was quenched by the addition of $Na_2S_2O_3$ (10 mL) at room temperature. The aqueous layer was extracted with EtOAc (3 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1). The crude product was separated with chiral-HPLC (Column: CHIRALPAK IG 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MeOH; Flow rate: 85 mL/min; Gradient: A:B = 65:35; Wave Length: 220 nm;

[00585] RT_1: 7.50 min to afford *tert*-butyl (3*R*,4*R*)-3-acetoxy-4-((7-(*sec*-butyl)-5-chloro-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)piperidine-1-carboxylate (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (CHIRALPAK IG, CO_2/MeOH = 65/35, 1st peak) (120 mg, 17%) as a yellow solid. ESI calculated for $C_{22}H_{31}ClIN_5O_4$ $[M + H]^+$, 592.11, found 592.45; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.51 (s, 1H), 4.97-4.92 (m, 1H), 3.92-3.89 (m, 2H), 3.80-3.75 (m, 1H), 3.41-3.83 (m, 3H), 2.34-2.28 (m, 1H), 2.20-2.04 (m, 4H), 1.81-1.77 (m, 1H), 1.67-1.63 (m, 1H), 1.52-1.42 (m, 12H), 0.86-0.82 (m, 3H).

[00586] RT_2: 10.22 min to afford *tert*-butyl (3*R*,4*R*)-3-acetoxy-4-((7-(*sec*-butyl)-5-chloro-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)piperidine-1-carboxylate (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (CHIRALPAK IG, CO_2/MeOH = 65/35, 2nd peak) (120 mg, 17%) as a yellow solid. MS ESI calculated for $C_{22}H_{31}ClIN_5O_4$ $[M + H]^+$, 592.11, found 592.45; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.51 (s, 1H), 4.95-4.92 (m, 1H), 3.91-3.87 (m, 2H), 3.82-3.73 (m, 1H), 3.41-3.39 (m, 3H), 2.17-2.13 (m, 1H), 2.11-2.07 (m, 4H), 1.86-1.71 (m, 1H), 1.65 (m, 1H), 1.52-1.44 (m, 12H), 0.85-0.80 (m, 3H).

Step 4: *tert*-butyl (3*R*,4*R*)-3-acetoxy-4-((7-(*sec*-butyl)-5-chloro-6-cyanopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)piperidine-1-carboxylate (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (chiral resolution of 6-I intermediate, CHIRALPAK IG, CO_2/MeOH = 65/35, 1st peak)

[00587] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-3-acetoxy-4-((7-(*sec*-butyl)-5-chloro-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)piperidine-1-carboxylate (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (CHIRALPAK IG, CO_2/MeOH = 65/35, 1st peak) (120 mg, 0.203 mmol) and $Pd(PPh_3)_4$ (23 mg, 0.020 mmol) in DMF (2 mL) was added $Zn(CN)_2$ (14 mg, 0.122 mmol). The reaction mixture was stirred for 2 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford *tert*-butyl (3*R*,4*R*)-3-acetoxy-4-((7-(*sec*-butyl)-5-chloro-6-cyanopyrrolo[2,1-*f*][1,2,4]triazin-2-

yl)amino)piperidine-1-carboxylate (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (chiral resolution of 6-I intermediate, CHIRALPAK IG, CO_2/MeOH = 65/35, 1st peak) (85 mg, 85%) as a light yellow solid; MS ESI calculated for $C_{23}H_{31}ClN_6O_4$ [M + H]$^+$, 491.21, found 491.45.

Step 5: (3*R*,4*R*)-4-((7-(*sec*-butyl)-5-chloro-6-cyanopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)piperidin-3-yl acetate (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (chiral resolution of 6-I intermediate, CHIRALPAK IG, CO_2/MeOH = 65/35, 1st peak)

[00588] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-3-acetoxy-4-((7-(*sec*-butyl)-5-chloro-6-cyanopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)piperidine-1-carboxylate (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (chiral resolution of 6-I intermediate, CHIRALPAK IG, CO_2/MeOH = 65/35, 1st peak) (65 mg, 0.132 mmol) in DCM (2 mL) was added HCl (gas) in 1,4-dioxane (2 mL) at 0 °C. The reaction mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford (3*R*,4*R*)-4-((7-(*sec*-butyl)-5-chloro-6-cyanopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)piperidin-3-yl acetate hydrochloride (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (chiral resolution of 6-I intermediate, CHIRALPAK IG, CO_2/MeOH = 65/35, 1st peak) (70 mg,crude) as a light yellow solid; MS ESI calculated for $C_{18}H_{24}Cl_2N_6O_2$ [M – Cl]$^+$, 391.16, found 391.10;

Step 6: (3*R*,4*R*)-4-((7-(*sec*-butyl)-5-chloro-6-cyanopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)-1-(methylsulfonyl)piperidin-3-yl acetate (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (chiral resolution of 6-I intermediate, CHIRALPAK IG, CO_2/MeOH = 65/35, 1st peak)

[00589] To a stirred mixture of (3*R*,4*R*)-4-((7-(*sec*-butyl)-5-chloro-6-cyanopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)piperidin-3-yl acetate hydrochloride (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (chiral resolution of 6-I intermediate, CHIRALPAK IG, CO_2/MeOH = 65/35, 1st peak) (60 mg, 0.140 mmol) in EtOAc (2 mL) and sat. $NaHCO_3$ (1 mL) was added methanesulfonic anhydride (44 mg, 0.252 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature. The aqueous layer was extracted with EtOAc (3 x 3 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*R*,4*R*)-4-((7-(*sec*-butyl)-5-chloro-6-cyanopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)-1-(methylsulfonyl)piperidin-3-yl acetate (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (chiral

resolution of 6-I intermediate, CHIRALPAK IG, CO_2/MeOH = 65/35, 1st peak) (65 mg, 98%) as a light yellow solid.; MS ESI calculated for $C_{19}H_{25}ClN_6O_4S$ $[M + H]^+$, 469.13, found 469.20.

Example 85:

7-(*sec*-butyl)-5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (chiral resolution of 6-I intermediate, CHIRALPAK IG, CO_2/MeOH = 65/35, 1st peak)

[00590] To a stirred mixture of (3*R*,4*R*)-4-((7-(*sec*-butyl)-5-chloro-6-cyanopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)-1-(methylsulfonyl)piperidin-3-yl acetate (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (chiral resolution of 6-I intermediate, CHIRALPAK IG, CO_2/MeOH = 65/35, 1st peak) (65 mg, 0.139 mmol) in MeOH (2 mL) was added K_2CO_3 (38 mg, 0.278 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 20% to 65%; detector, UV 254 nm to afford 7-(*sec*-butyl)-5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (chiral resolution of 6-I intermediate, CHIRALPAK IG, CO_2/MeOH = 65/35, 1st peak) (24.2 mg, 40 %) as a light yellow solid; MS ESI calculated for $C_{17}H_{23}ClN_6O_3S$ $[M + H]^+$, 427.12, found 427.20; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 5.17 (d, *J* = 6.8 Hz, 1H), 3.99-3.95 (m, 1H), 3.88-3.70 (m, 3H), 3.46-3.42 (m, 1H), 2.97-2.89 (m, 1H), 2.87 (s, 3H), 2.83-2.78 (m, 1H), 2.34-2.30 (m, 1H), 2.00-1.92 (m, 1H), 1.89-1.71 (m, 2H), 1.49-1.46 (m, 3H), 0.91-0.88 (m, 3H).

Example 86:

7-(*sec*-butyl)-5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (chiral resolution of 6-I intermediate, CHIRALPAK IG, CO_2/MeOH = 65/35, 2nd peak)

Step 1: *tert*-butyl (3*R*,4*R*)-3-acetoxy-4-((7-(*sec*-butyl)-5-chloro-6-cyanopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)piperidine-1-carboxylate (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (chiral resolution of 6-I intermediate, CHIRALPAK IG, CO_2/MeOH = 65/35, 2nd peak)

[00591] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-3-acetoxy-4-((7-(*sec*-butyl)-5-chloro-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)piperidine-1-carboxylate (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (CHIRALPAK IG, CO_2/MeOH = 65/35, 2nd peak) (120 mg, 0.20 mmol) and $Zn(CN)_2$ (8 mg, 0.12 mmol) in DMA (2 mL) was

added $Pd(PPh_3)_4$ (46 mg, 0.04 mmol). The resulting mixture was stirred for 2 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-3-acetoxy-4-((7-(*sec*-butyl)-5-chloro-6-cyanopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)piperidine-1-carboxylate (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (chiral resolution of 6-I intermediate, CHIRALPAK IG, CO_2/MeOH = 65/35, 2nd peak) (100 mg, 98%) as a yellow solid. MS ESI calculated for $C_{23}H_{31}ClN_6O_4$ $[M + H]^+$, 491.21 found 491.25.

Step 2: (3*R*,4*R*)-4-((7-(*sec*-butyl)-5-chloro-6-cyanopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)-1-(methylsulfonyl)piperidin-3-yl acetate (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (chiral resolution of 6-I intermediate, CHIRALPAK IG, CO_2/MeOH = 65/35, 2nd peak)

[00592] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-3-acetoxy-4-((7-(*sec*-butyl)-5-chloro-6-cyanopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)piperidine-1-carboxylate (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (chiral resolution of 6-I intermediate, CHIRALPAK IG, CO_2/MeOH = 65/35, 2nd peak) (100 mg, 0.20 mmol) in DCM (4 mL) was added HCl (gas) in 1,4-dioxane (4 mL) at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure and dissolved in EtOAc (2 mL) and sat. $NaHCO_3$ (2 mL). To this was added methanesulfonic anhydride (65 mg, 0.37 mmol) at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (20 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*R*,4*R*)-4-((7-(*sec*-butyl)-5-chloro-6-cyanopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)-1-(methylsulfonyl)piperidin-3-yl acetate (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (chiral resolution of 6-I intermediate, CHIRALPAK IG, CO_2/MeOH = 65/35, 2nd peak) (75 mg, 85%) as a yellow solid. MS ESI calculated for $C_{19}H_{25}ClN_6O_4S$ $[M + H]^+$, 469.13 found 469.20.

Example 86:

7-(*sec*-butyl)-5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (chiral resolution of 6-I intermediate, CHIRALPAK IG, CO_2/MeOH = 65/35, 2nd peak)

[00593] To a stirred mixture of (3*R*,4*R*)-4-((7-(*sec*-butyl)-5-chloro-6-cyanopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)-1-(methylsulfonyl)piperidin-3-yl acetate (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (chiral resolution of 6-I intermediate, CHIRALPAK IG, CO_2/MeOH = 65/35, 2nd peak) (75 mg, 0.16 mmol) in MeOH (2 mL) was added K_2CO_3 (44 mg, 0.32 mmol) at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford 7-(*sec*-butyl)-5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of *sec*-butyl was not determined) (chiral resolution of 6-I intermediate, CHIRALPAK IG, CO_2/MeOH = 65/35, 2nd peak) (39.7 mg, 58%) as a light yellow solid. MS ESI calculated for $C_{17}H_{23}ClN_6O_3S$ $[M + H]^+$, 427.12, found 427.30. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 5.02 (brs, 1H), 4.03-3.95 (m, 1H), 3.84-3.72 (m, 3H), 3.48-3.42 (m, 1H), 3.00-2.87 (m, 4H), 2.84-2.78 (m, 1H), 2.34-2.29 (m, 1H), 2.02-1.96 (m, 1H), 1.88-1.72 (m, 2H), 1.51-1.47 (m, 3H), 0.91-0.87 (m, 3H).

Example 87:

2-[(1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: 2-[(1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00594] To a stirred mixture of 5-chloro-2-[(1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (120 mg, 0.292 mmol), $Pd(dba)_2$ (33 mg, 0.058 mmol) and t-BuXPhos (49 mg, 0.117 mmol) in dioxane (2 mL) were added Et_3SiH (271 mg, 2.336 mmol) and TEA (177 mg, 1.752 mmol) at room temperature. The reaction mixture was stirred for 2 h at 100 °C under nitrogen atmosphere. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1). The fractions contained desired product were combined and concentrated to afford 2-[(1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (90 mg, 81%) as an off-white solid. MS ESI calculated for $C_{17}H_{24}N_6O_2S$ $[M + H]^+$, 377.17, found 377.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.61 (s, 1H), 6.95 (s, 1H), 4.90-4.86 (m, 1H), 3.90-3.70 (m, 3H), 2.98-2.94 (m, 2H), 2.90 (d, *J* = 7.2 Hz, 2H), 2.84 (s, 3H), 2.23-2.20 (m, 3H), 1.72-1.69 (m, 2H), 0.98-0.96 (m, 6H).

Step 2: 5-iodo-2-[(1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00595] A solution of 2-[(1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (80 mg, 0.212 mmol) and I_2 (215 mg, 0.848 mmol) in DMF (1 mL)was stirred for 2 h at room temperature. The reaction was quenched with sat. $Na_2S_2SO_3$(aq.) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (1/1) to afford 5-iodo-2-[(1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (86 mg, 80%) as a yellow solid. MS ESI calculated for $C_{17}H_{23}IN_6O_2S$. $[M + H]^+$, 503.06, found 503.15.

Example 87:

2-[(1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00596] To a stirred mixture of 5-iodo-2-[(1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (60 mg, 0.119 mmol) and methyl 2,2-difluoro-2-sulfoacetate (114 mg, 0.595 mmol) in DMF (1 mL) were added CuI (23 mg, 0.119 mmol) and KF (21 mg, 0.357 mmol) at room temperature. The reaction mixture was stirred for 2 h at 80 °C under nitrogen atmosphere. The resulting mixture was diluted with water (15 mL). The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (3 x 15 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1). The residue was purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30 x 150 mm, 5 μm; CH_3CN in water (10 mmol/L NH_4HCO_3); Flow rate: 60 mL/min; 45% to 75%; Wave Length: 254/220 nm to afford 2-[(1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (40 mg, 75%) as a white solid. MS ESI calculated for $C_{18}H_{23}F_3N_6O_2S$. $[M + H]^+$, 445.16, found 445.30. ^1H NMR (400 MHz, DMSO-d_6) δ 9.12 (s, 1H), 7.81 (d, J = 7.2 Hz, 1H), 3.74-3.69 (m, 1H), 3.58-3.52 (m, 2H), 2.95-2.86 (m, 7H), 2.19-2.12 (m, 1H), 2.10-2.04 (m, 2H), 1.66-1.58 (m, 2H), 0.94-0.91 (m, 6H). ^{19}F NMR (377 MHz, DMSO-d_6) δ -53.62 (3F).

Example 88:

5-chloro-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: *tert*-butyl (3*S*,4*R*)-3-hydroxy-4-({7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00597] A mixture of 2-chloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine (200 mg, 1.022 mmol), *tert*-butyl (3*S*,4*R*)-4-amino-3-hydroxypiperidine-1-carboxylate (663 mg, 3.067 mmol) and DIEA (0.7 mL, 4.076 mmol) in NMP (2 mL) was stirred for 16 h at 120 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 10% to 80%; detector, UV 254 nm to afford *tert*-butyl (3*S*,4*R*)-3-hydroxy-4-({7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (300 mg, 76%) as yellow oil. MS ESI calculated for $C_{19}H_{29}N_5O_3$ $[M + H]^+$, 376.23, found 376.35.

Step 2: *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-({7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00598] A mixture of *tert*-butyl (3*S*,4*R*)-3-hydroxy-4-({7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (300 mg, 0.799 mmol), Ac_2O (0.1 mL, 1.199 mmol) and TEA (0.6 mL, 3.995 mmol) in DCM (3 mL) was stirred for 16 h at 50 °C. The mixture was allowed to cool down to room temperature. The resulting mixture was purified by silica gel column chromatography, eluted with PE/EtOAc (0~60%) to afford *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-({7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (295 mg, 87%) as a light yellow solid. MS ESI calculated for $C_{21}H_{31}N_5O_4$ $[M + H]^+$, 418.24, found 418.30.

Step 3: *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00599] To a stirred mixture of *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-({7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (295 mg, 0.707 mmol) in DMF (3 mL) were added NCS (75 mg, 0.565 mmol) at 0 °C. The resulting mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (20 mL) at 0 °C. The resulting mixture was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (170 mg, 52%) as a yellow solid. MS ESI calculated for $C_{21}H_{30}ClN_5O_4$ $[M + H]^+$, 452.20, found 452.30. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.54 (s, 1H), 6.47 (s, 1H), 5.13-5.08 (m, 2H), 4.46-4.40 (m, 1H), 4.30-4.26 (m, 1H), 4.08-4.04 (m, 1H), 3.42-3.40 (m, 1H), 3.01-2.97 (m, 2H), 2.12 (s, 3H), 1.89-1.80 (m, 1H), 1.70-1.61 (m, 1H), 1.48-1.45 (m, 9H), 1.34-1.30 (m, 6H).

Step 4: *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-iodo-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00600] A mixture of *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (170 mg, 0.376 mmol) and I_2 (382 mg, 1.504 mmol) in DMF (2 mL) was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (20 mL) at room temperature. The resulting mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-iodo-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (200 mg, 87%) as an off-white solid. MS ESI calculated for $C_{21}H_{29}ClIN_5O_4$ $[M + H]^+$, 578.10, found 578.25.

Step 5: *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00601] A mixture of *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-iodo-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (200 mg, 0.346 mmol), $Zn(CN)_2$ (25 mg, 0.208 mmol) and $Pd(PPh_3)_4$ (40 mg, 0.035 mmol) in DMA (2 mL) was stirred for 2 h at 120 °C under nitrogen atmosphere. The reaction was quenched by the addition of water (40 mL) at room temperature. The resulting mixture was extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (50 mg, 27%) as a yellow solid. MS ESI calculated for $C_{22}H_{29}ClN_6O_4$ $[M + H]^+$, 477.19, found 477.10. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 5.42 (s, 1H), 5.14-5.08 (m, 1H), 4.47-4.35 (m, 1H), 4.35-4.31 (m, 1H), 4.05-4.01 (m, 1H), 3.67-3.63 (m, 1H), 2.97-2.80 (m, 2H), 2.25-2.13 (m, 4H), 1.52-1.44 (m, 10H), 1.31-1.27 (m, 6H).

Step 6: (3*S*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidin-3-yl acetate hydrochloride

[00602] To a stirred mixture of *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (50 mg, 0.105 mmol) in DCM (1 mL) was added HCl (gas) in 1,4-dioxane (1 mL) at 0°C. The reaction mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford (3*S*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-

yl}amino)piperidin-3-yl acetate hydrochloride (55 mg,crude) as a light yellow solid; MS ESI calculated for $C_{17}H_{22}Cl_2N_6O_2$ $[M - Cl]^+$, 377.14, found 377.30.

Step 7: (3*S*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-methanesulfonylpiperidin-3-yl acetate

[00603] To a stirred mixture of (3*S*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidin-3-yl acetate hydrochloride (40 mg, 0.097 mmol) in EtOAc (2 mL) and sat. $NaHCO_3$ (1 mL) was added methanesulfonic anhydride (30 mg, 0.175 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature. The aqueous layer was extracted with EtOAc (3 x 3 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*S*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-methanesulfonylpiperidin-3-yl acetate (45 mg, 95%) as a light yellow solid; MS ESI calculated for $C_{18}H_{23}ClN_6O_4S$ $[M + H]^+$, 455.12, found 455.15.

Example 88:

5-chloro-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00604] To a stirred mixture of (3*S*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-methanesulfonylpiperidin-3-yl acetate (52 mg, 0.114 mmol) in MeOH (1 mL) was added K_2CO_3 (31 mg, 0.228 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 10% to 60%; detector, UV 254 nm to afford 5-chloro-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (20 mg, 42%) as an off white solid; MS ESI calculated for $C_{16}H_{21}ClN_6O_3S$ $[M + H]^+$, 413.11, found 413.30. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 5.50 (brs, 1H), 4.14-4.13 (m, 1H), 3.96-3.86 (m, 3H), 3.66-3.58 (m, 1H), 3.13-3.09 (m, 1H), 2.99-2.91 (m, 4H), 2.08-2.03 (m, 1H), 2.01-1.89 (m, 1H), 1.48-1.46 (m, 6H).

Example 89:

(3*R*,4*R*)-*N*-[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]-3-fluoro-1-methanesulfonylpiperidin-4-amine

Step 1: *tert*-butyl (3*R*,4*R*)-4-{[7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00605] To a stirred mixture of 2-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (500 mg, 2.121 mmol) and *tert*-butyl (3*R*,4*R*)-4-amino-3-fluoropiperidine-1-carboxylate (1.38 g, 6.363

mmol) in NMP (6 mL) was added DIEA (1.37 g, 10.605 mmol) at room temperature. The reaction mixture was stirred for 16 h at 80 °C. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (630 mg, 71%) as a light yellow solid; MS ESI calculated for $C_{22}H_{32}FN_5O_2$ $[M + H]^+$, 418.25, found 418.45.

Step 2: (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00606] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-4-{[7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (100 mg, 0.240 mmol) in DMF (2 mL) was added NCS (32 mg, 0.240 mmol). The reaction mixture was stirred for 16 h at room temperature. The mixture was basified to pH 8 with sat. NaHCO3 (aq.). The resulting mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (3 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (65 mg, 60%) as a light yellow solid; MS ESI calculated for $C_{22}H_{31}ClFN_5O_2$ $[M + H]^+$, 452.22, found 452.30.

Step 3: (3*R*,4*R*)-*N*-[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]-3-fluoropiperidin-4-amine

[00607] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (50 mg, 0.111 mmol) in DCM (1 mL) was added HCl (gas) in 1,4-dioxane (1 mL) at 0 °C. The reaction mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford (3*R*,4*R*)-*N*-[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]-3-fluoropiperidin-4-amine hydrochloride (60 mg, crude) as a light yellow solid; MS ESI calculated for $C_{17}H_{24}Cl_2FN_5$ $[M - Cl]^+$, 352.16, found 352.20.

Example 89:

(3*R*,4*R*)-*N*-[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]-3-fluoro-1-methanesulfonylpiperidin-4-amine

[00608] To a stirred mixture of (3*R*,4*R*)-*N*-[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]-3-fluoropiperidin-4-amine hydrochloride (75 mg, 0.193 mmol) in EtOAc (3 mL) were added

sat. $MaHCO_3$ (2 mL) and methanesulfonic anhydride (60 mg, 0.347 mmol). The reaction mixture was stirred for 1h at room temperature. The aqueous layer was extracted with EtOAc (3 x 2 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 10% to 60%; detector, UV 254 nm to afford (3*R*,4*R*)-*N*-[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]-3-fluoro-1-methanesulfonylpiperidin-4-amine (36.4 mg, 43%) as an off-white solid.MS ESI calculated for $C_{18}H_{25}ClFN_5O_2S$ $[M + H]^+$, 430.14, found 430.30; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.58 (s, 1H), 6.42 (s, 1H), 5.04 (d, *J* = 5.6 Hz, 1H), 4.83-4.70 (m, 1H), 3.99-3.95 (m, 1H), 3.86-3.71 (m, 1H), 3.53-3.50 (m, 1H), 3.42-3.39 (m, 1H), 3.32-3.28 (m, 1H), 2.89 (s, 3H), 2.52-2.43 (m, 3H), 2.25-2.16 (m, 2H), 2.14-2.03 (m, 3H), 1.93-1.88 (m, 1H), 1.78-1.73 (m, 1H), 0.68-0.65 (m, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -188.75 (1F).

Example 90:

5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: 2,4-dichloro-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine

[00609] To a stirred mixture of 2,4-dichloropyrrolo[2,1-*f*][1,2,4]triazine (1 g, 5.319 mmol) and 1-methylcyclobutane-1-carboxylic acid (1.82 g, 15.95 mmol) in CH_3CN (30 mL) were added $(NH_4)_2S_2O_8$ (6.07 g, 26.59 mmol) and water (20 mL) at room temperature. The reaction mixture was stirred for 2 h at 50 °C. The resulting mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (50 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% TFA), 10% to 50%; detector, UV 254 nm. The fractions contained desired product were combined and concentrated to afford 2,4-dichloro-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (700 mg, 51%) as a yellow solid. MS ESI calculated for $C_{11}H_{11}Cl_2N_3$ $[M + H]^+$, 256.03, found 256.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.02 (d, *J* = 4.8 Hz, 1H), 6.78 (d, *J* = 4.8 Hz, 1H), 2.64-2.50 (m, 2H), 2.29-2.11 (m, 3H), 2.03-1.87 (m, 1H), 1.64 (s, 3H).

Step 2: 2-chloro-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine

[00610] To a stirred mixture of 2,4-dichloro-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (660 mg, 2.57 mmol) and *i*-PrOH (160 uL) in THF (8 mL) was added $NaBH_4$ (156 mg, 4.12 mmol) in portions at room temperature. The reaction mixture was stirred for 2 h at room temperature. The

resulting mixture was filtered, the filter cake was washed with DCM (3 x 50 mL). The filtrate was concentrated under reduced pressure. To this was added DDQ (877.41 mg, 3.86 mmol) and DCM (10 mL). The reaction mixture was stirred for additional 1 h at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (100 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford 2-chloro-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (560 mg, 98%) as yellow oil. MS ESI calculated for $C_{11}H_{12}ClN_3$ $[M + H]^+$, 222.07, found 222.05. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.72 (s, 1H), 6.92 (d, *J* = 4.8 Hz, 1H), 6.80 (d, *J* = 4.8 Hz, 1H), 2.67-2.53 (m, 2H), 2.30-2.12 (m, 3H), 2.04-1.88 (m, 1H), 1.65 (s, 3H).

Step 3: (3*S*,4*R*)-4-{[7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol

[00611] To a stirred mixture of 2-chloro-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (150 mg, 0.677 mmol) and (3*S*,4*R*)-4-aminooxan-3-ol (396.32 mg, 3.38 mmol) in NMP (2 mL) was added DIEA (707.15 μL, 4.06 mmol) at room temperature. The reaction mixture was stirred for 4 h at 120 °C. The mixture was allowed to cool down to room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% TFA), 10% to 50%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (160 mg, 78%) as yellow oil. MS ESI calculated for $C_{16}H_{22}N_4O_2$ $[M + H]^+$, 303.17, found 303.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.49 (s, 1H), 7.23 (d, *J* = 5.2 Hz, 1H), 6.85 (d, *J* = 5.2 Hz, 1H), 4.13-4.11 (m, 1H), 4.01-3.98 (m, 1H), 3.88-3.85 (m, 1H), 3.73-3.71 (m, 1H), 3.53-3.50 (m, 1H), 3.34-3.32 (m, 1H), 2.70-2.58 (m, 2H), 2.37-2.20 (m, 4H), 2.04-1.91 (m, 1H), 1.65-1.62 (m, 4H).

Step 4: (3*S*,4*R*)-4-{[7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00612] To a stirred mixture of (3*S*,4*R*)-4-{[7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (160 mg, 0.52 mmol) and TEA (147.10 μL, 1.05 mmol) in DCM (3 mL) was added Ac_2O (100 μL, 1.058 mmol) at room temperature. The resulting mixture was stirred for 16 h at 40 °C. The reaction was quenched by the addition of water (10 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1). The fractions contained desired product were combined and concentrated to afford (3*S*,4*R*)-4-{[7-(1-

methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (150 mg, 82%) as yellow oil. MS ESI calculated for $C_{18}H_{24}N_4O_3$ [M + H]$^+$, 345.18, found 345.30.

Step 5 : (3*S*,4*R*)-4-{[5-chloro-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00613] To a stirred mixture of (3*S*,4*R*)-4-{[7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (150 mg, 0.436 mmol) in DMF (1.5 mL) was added NCS (52.34 mg, 0.392 mmol) at room temperature. The reaction mixture was stirred for 16 h at room temperature. The resulting mixture was neutralized to pH 7 with sat. $NaHCO_3$ (aq.) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1). The fractions contained desired product were combined and concentrated to afford (3*S*,4*R*)-4-{[5-chloro-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (130 mg, 65%) as yellow oil. MS ESI calculated for $C_{18}H_{23}ClN_4O_3$ [M + H]$^+$, 379.15, found 379.10. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.57 (s, 1H), 6.37 (s, 1H), 4.96-4.92 (m, 2H), 4.04-3.98 (m, 1H), 4.00-3.85 (m, 2H), 3.65-3.55 (m, 1H), 3.49-3.39 (m, 1H), 2.70-2.56 (m, 2H), 2.45-2.42 (m, 1H), 2.25-2.13 (m, 1H), 2.17-2.00 (m, 6H), 1.99-1.86 (m, 1H), 1.68 (m, 4H).

Step 6: (3*S*,4*R*)-4-{[5-chloro-6-iodo-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00614] To a stirred mixture of (3*S*,4*R*)-4-{[5-chloro-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (130 mg, 0.343 mmol) in DMF (1.5 mL) was added I_2 (348 mg, 1.372 mmol) in portions at room temperature. The reaction mixture was stirred for 16 h at room temperature. The resulting was quenched with sat. $Na_2S_2O_3$ (aq.) (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% $NH_3.H_2O$), 55% to 95%; detector, UV 254 nm. The fractions contained desired product were combined and concentrated to afford (3*S*,4*R*)-4-{[5-chloro-6-iodo-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (60 mg, 33%) as a yellow solid. MS ESI calculated for $C_{18}H_{22}ClIN_4O_3$ [M + H]$^+$, 505.04, found 505.20.

Step 7: (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00615] To a stirred mixture of (3*S*,4*R*)-4-{[5-chloro-6-iodo-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (60 mg, 0.119 mmol) and $Zn(CN)_2$ (17 mg, 0.143

mmol) in DMF (1 mL) was added $Pd(PPh_3)_4$ (14 mg, 0.012 mmol). The reaction mixture was stirred for 2 h at 130 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 40% to 85%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (30 mg, 62%) as a yellow solid. MS ESI calculated for $C_{19}H_{22}ClN_5O_3$ $[M + H]^+$, 404.14, found 404.20.

Example 90:

5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00616] To a stirred mixture of (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (30 mg, 0.074 mmol) in MeOH (0.5 mL) was added K_2CO_3 (20 mg, 0.148 mmol) at room temperature. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% $NH_3.H_2O$), 15% to 50%; detector, UV 254 nm to afford 5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (15.2 mg, 56%) as a light yellow solid. MS ESI calculated for $C_{17}H_{20}ClN_5O_2$ $[M + H]^+$, 362.13, found 362.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 5.21 (brs, 1H), 4.11-4.06 (m, 1H), 4.01-3.97 (m, 1H), 3.72-3.67 (m, 2H), 3.51-3.48 (m, 1H), 3.30-3.25 (m, 1H), 2.79-2.70 (m, 2H), 2.50-2.26 (m, 3H), 2.25-2.17 (m, 1H), 2.01-1.96 (m, 1H), 1.71-1.60 (m, 4H).

Example 91:

5-chloro-2-{[(3*R*,4*R*)-3-fluoro-1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: 5-chloro-2-{[(3*R*,4*R*)-3-fluoropiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride

[00617] To a stirred solution of *tert*-butyl (3*R*,4*R*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate (55 mg, 0.126 mmol) in DCM (1.5 mL) was added HCl (gas) in 1,4-dioxane (1.5 mL, 4 M). The reaction mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford 5-chloro-2-{[(3*R*,4*R*)-3-fluoropiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (45 mg, crude) as a light yellow solid. MS ESI calculated for $C_{15}H_{19}Cl_2FN_6$ $[M - Cl]^+$, 337.13, found 337.15.

Example 91:

5-chloro-2-{[(3*R*,4*R*)-3-fluoro-1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00618] To a stirred solution of 5-chloro-2-{[(3*R*,4*R*)-3-fluoropiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (50 mg, 0.134 mmol) and DIEA (86 mg, 0.670 mmol) in DCM (2 mL) was added TFAA (141 mg, 0.670 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature. The resulting mixture was diluted with water (20 mL) and extracted with DCM (2 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 20% to 50%; detector, UV 254 nm to afford 5-chloro-2-{[(3*R*,4*R*)-3-fluoro-1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (30 mg, 52%) as a white solid. MS ESI calculated for $C_{17}H_{17}ClF_4N_6O$ $[M + H]^+$, 433.11, found 433.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 5.22 (brs, 1H), 4.77-4.62 (m, 1H), 4.28-3.96 (m, 2H), 3.88-3.81 (m, 1H), 3.76-3.54 (m, 3H), 2.46-2.36 (m, 1H), 1.83-1.75 (m, 1H), 1.49-1.44 (m, 6H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -68.57 (3F), -189.13 (1F).

Example 92:

5-ethyl-2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: *tert*-butyl(3*R*,4*R*)-3-fluoro-4-{[7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00619] To a stirred mixture of 2-chloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine (185 mg, 0.882 mmol), *tert*-butyl (3*R*,4*R*)-4-amino-3-fluoropiperidine-1-carboxylate (963 mg, 4.410 mmol) in NMP (2 mL) was added DIEA (684 mg, 5.292 mmol). The reaction mixture was stirred for 24 h at 120 °C. The mixture was allowed to cool down to room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column: CH_3CN in water (10 mmol/L NH_4HCO_3); 40% to 55%; detector: 220/254 nm to afford *tert*-butyl (3*R*,4*R*)-3-fluoro-4-{[7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (210 mg, 60%) as a light yellow solid. MS ESI calculated for $C_{20}H_{30}FN_5O_2$ $[M + H]^+$, 392.24, found 392.40. ^1H NMR (400 MHz, DMSO-d_6) δ 8.70 (s, 1H), 6.69 (d, J = 4.4 Hz, 1H), 6.50 (d, J = 4.4 Hz, 1H), 4.69-4.51 (m, 1H), 4.11-3.94 (m, 2H), 3.85-3.78 (m, 1H), 3.64-3.56 (m, 1H), 3.21-3.18 (m, 1H), 2.72 (d, J = 7.2 Hz, 2H), 2.07-1.96 (m, 2H), 1.55-1.51 (m, 1H), 1.41 (s, 9H), 0.90 (d, J = 6.8 Hz, 6H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -187.12 (1F).

Step 2: *tert*-butyl(3*R*,4*R*)-4-{[5-bromo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00620] To a stirred solution of *tert*-butyl (3*R*,4*R*)-3-fluoro-4-{[7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (180 mg, 0.460 mmol) in DMF (2 mL) was added NBS (65.47 mg, 0.368 mmol). The reaction mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The mixture was quenched with sat. $NaHCO_3$ (20 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (4/1). The fractions contained desired product were combined and concentrated to afford *tert*-butyl (3*R*,4*R*)-4-{[5-bromo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (200 mg, 73%) as a yellow solid. MS ESI calculated for $C_{20}H_{29}BrFN_5O_2$ $[M + H]^+$, 470.15, 472.15, found 470.20, 472.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.48 (s, 1H), 6.51 (s, 1H), 4.98 (brs, 1H), 4.66-4.50 (m, 1H), 4.03-3.96 (m, 2H), 3.72-3.64 (m, 1H), 3.34-3.27 (m, 2H), 2.75 (d, *J* = 7.2 Hz, 2H), 2.42-2.27 (m, 2H), 1.58-1.47 (m, 10H), 0.95-0.91 (m, 6H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -189.56 (1F).

Step 3: *tert*-butyl(3*R*,4*R*)-4-{[5-ethyl-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00621] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-4-{[5-bromo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (140 mg, 0.298 mmol) and potassium ethyltrifluoroboranuide (81 mg, 0.595 mmol) in toluene (2 mL) were added Cs_2CO_3 (291 mg, 0.894 mmol) and 2nd Generation RuPhos precatalyst (23 mg, 0.030 mmo). The reaction mixture was stirred for 2 h at 100 °C under nitrogen atmosphere. The resulting mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (4/1). The fractions contained desired product were combined and concentrated to afford *tert*-butyl (3*R*,4*R*)-4-{[5-ethyl-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (80 mg, 64%) as yellow oil. MS ESI calculated for $C_{22}H_{34}FN_5O_2$ $[M + H]^+$, 420.27, found 420.30.

Step 4: *tert*-butyl(3*R*,4*R*)-4-{[5-ethyl-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00622] To a stirred solution of *tert*-butyl (3*R*,4*R*)-4-{[5-ethyl-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (100 mg, 0.238 mmol) in DMF (2

mL) was added I_2 (242 mg, 0.952 mmol). The reaction mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction was quenched with sat. $Na_2S_2SO_3$(20 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[5-ethyl-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (90 mg, 69%) as a light yellow solid. MS ESI calculated for $C_{22}H_{33}FIN_5O_2$ $[M + H]^+$, 546.17, found 546.30.

Step 5: *tert*-butyl(3*R*,4*R*)-4-{[6-cyano-5-ethyl-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00623] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-4-{[5-ethyl-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (70 mg, 0.128 mmol), $Pd(PPh_3)_4$ (15 mg, 0.013 mmol) in DMF (1 mL) was added $Zn(CN)_2$ (9 mg, 0.077 mmol). The reaction mixture was stirred for 2 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; CH_3CN in water (10 mmol/L NH_4HCO_3); 45% to 70%; detector: 220/254 nm to afford *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-5-ethyl-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (45 mg, 78%) as a light yellow solid. MS ESI calculated for $C_{23}H_{33}FN_6O_2$ $[M + H]^+$, 445.26, found 445.30. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.62 (s, 1H), 5.16 (d, *J* = 6.4 Hz, 1H), 4.60-4.48 (m, 1H), 4.23-3.93 (m, 2H), 3.82-3.72 (m, 1H), 3.40-3.15 (m, 2H), 2.94-2.84 (m, 4H), 2.33-2.27 (m, 1H), 2.22-2.14 (m, 1H), 1.58-1.47 (m, 10H), 1.36-1.32 (m, 3H), 0.99-0.95 (m, 6H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -189.49 (1F).

Step 6: 5-ethyl-2-(((3R,4*R*)-3-fluoropiperidin-4-yl)amino)-7-isobutylpyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile hydrochloride

[00624] To a stirred solution of *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-5-ethyl-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (40 mg, 0.090 mmol) in DCM (1 mL) was added HCl (gas) in 1,4-dioxane (1 mL, 4 M). The reaction mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford 5-ethyl-2-(((3*R*,4*R*)-3-fluoropiperidin-4-yl)amino)-7-isobutylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (40 mg, crude) as a yellow solid. MS ESI calculated for $C_{18}H_{26}ClFN_6$. $[M - Cl]^+$, 345.21, found 345.25.

Example 92:

5-ethyl-2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00625] To a stirred mixture of 5-ethyl-2-(((3*R*,4*R*)-3-fluoropiperidin-4-yl)amino)-7-isobutylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (35 mg, 0.102 mmol) and sat. $NaHCO_3$ (aq.) (2 mL) in EtOAc (2 mL) was added methanesulfonic anhydride (26 mg, 0.153 mmol) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (4/1). The crude product was purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30 x 150 mm, 5 μm; Mobile Phase: CH_3CN in water (10 mmol/L NH_4HCO_3), Flow rate: 60 mL/min; 42% to 72 %; Wave Length: 254/220 nm to afford 5-ethyl-2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (22.0 mg, 51%) as a light yellow solid. MS ESI calculated for $C_{19}H_{27}FN_6O_2S$ $[M + H]^+$, 423.19, found 423.30. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.65 (s, 1H), 5.06 (brs, 1H), 4.83-4.69 (m, 1H), 4.08-4.04 (m, 1H), 3.93-3.84 (m, 1H), 3.64-3.60 (m, 1H), 3.34-3.20 (m, 2H), 2.94-2.88 (m, 7H), 2.49-2.43 (m, 1H), 2.26-2.18 (m, 1H), 1.81-1.76 (m, 1H), 1.39-1.34 (m, 3H), 1.01-0.99 (m, 6H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -188.67 (1F).

Example 93:

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-(2-hydroxyacetyl)piperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-(2-hydroxyacetyl)piperidin-3-yl acetate

[00626] A mixture of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (50 mg, 0.110 mmol), glycolic acid (13 mg, 0.171 mmol) and EDCI (25 mg, 0.132 mmol) in DCM (1 mL) was stirred for 20 min at room temperature. To this was added DIEA (42 mg, 0.331 mmol). The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was purified by Prep-TLC with PE/EtOAc (1/1) to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-(2-hydroxyacetyl)piperidin-3-yl acetate (35 mg, 66%) as a yellow solid. MS ESI calculated for $C_{22}H_{27}ClN_6O_4$ $[M + H]^+$, 475.18; found 475.25.

Example 93:

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-(2-hydroxyacetyl)piperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00627] A mixture of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-(2-hydroxyacetyl)piperidin-3-yl acetate (35 mg, 0.074 mmol) and K_2CO_3 (30 mg, 0.221 mmol) in MeOH (1 mL) was stirred for 30 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions:C18 column; CH_3CN in water (10 mmol/L NH_4HCO_3); 30% to 55%; detector: 220/254 nm to afford 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-(2-hydroxyacetyl)piperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (14.4 mg, 44%) as a light yellow solid. MS ESI calculated for $C_{20}H_{25}ClN_6O_3$ $[M + H]^+$, 433.17; found 433.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 5.14-5.09 (m, 1H), 4.72-4.58 (m, 1H), 4.24 (d, *J* = 6.0 Hz, 2H), 3.82-3.42 (m, 4H), 3.13-2.87 (m, 2H), 2.77-2.63 (m, 2H), 2.39-2.33 (m, 2H), 2.27-1.91 (m, 5H), 1.62-1.53 (m, 1H), 0.84-0.80 (m, 3H).

Example 94:

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-(oxetane-3-carbonyl)piperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-(oxetane-3-carbonyl)piperidin-3-yl acetate

[00628] To a stirred solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (40 mg, 0.088 mmol) and oxetane-3-carboxylic acid (18 mg, 0.176 mmol) in DCM (2 mL) were added EDCI (20 mg, 0.106 mmol) and DIEA (34 mg, 0.264 mmol) at room temperature. The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (1/2) to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-(oxetane-3-carbonyl)piperidin-3-yl acetate (30 mg, 67%) as a light yellow solid. MS ESI calculated for $C_{24}H_{29}ClN_6O_4$ $[M + H]^+$, 501.19, found 501.20.

Example 94:

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-(oxetane-3-carbonyl)piperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00629] To a stirred solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-(oxetane-3-carbonyl)piperidin-3-yl acetate (25 mg, 0.050 mmol) in MeOH (2 mL) was added K_2CO_3 (21 mg, 0.150 mmol) at room temperature. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 20% to 50%; detector, UV 254 nm to afford 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-(oxetane-3-carbonyl)piperidin-4-

yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (6 mg, 26%) as a light yellow solid. MS ESI calculated for $C_{22}H_{27}ClN_6O_3$ [M + H]$^+$, 459.18, found 459.10. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 5.21-5.02 (m, 1H), 4.96-4.83 (m, 4H), 4.66-4.54 (m, 1H), 4.07-4.03 (m, 1H), 3.69-3.65 (m, 1H), 3.56-3.51 (m, 1H), 3.38-3.02 (m, 1H), 2.96-2.86 (m, 2H), 2.74-2.63 (m, 2H), 2.39-2.29 (m, 2H), 2.25-1.93 (m, 5H), 1.62-1.16 (m, 1H), 0.83-0.79 (m, 3H).

Example 95:

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-[(2*S*)-2-hydroxypropanoyl]piperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-[(2*S*)-2-hydroxypropanoyl]piperidin-3-yl acetate

[00630] To a stirred solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (100 mg, 0.221 mmol), EDCI (101 mg, 0.530 mmol) and (α)-lactate (79 mg, 0.884 mmol) in DCM (5 mL) was added DIEA (171 mg, 1.326 mmol) at 0 °C. The resulting mixture was stirred for 16 h at room temperature. The reaction was quenched with water (5 mL). The resulting mixture was extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (2 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE:EA:EtOH (6:5:1) to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-[(2*S*)-2-hydroxypropanoyl]piperidin-3-yl acetate (40 mg, 37%) as light yellow oil. MS ESI calculated for $C_{23}H_{29}ClN_6O_4$ [M + H]$^+$, 489.19, found 489.20.

Example 95:

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-[(2*S*)-2-hydroxypropanoyl]piperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00631] A solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-[(2*S*)-2-hydroxypropanoyl]piperidin-3-yl acetate (40 mg, 0.082 mmol) and K_2CO_3 (34 mg, 0.246 mmol) in MeOH (1.5 mL) was stirred for 1 h at room temperature. The resulting mixture was diluted with water (5 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 30% to 50%; detector, UV 254 nm to afford 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-[(2*S*)-2-hydroxypropanoyl]piperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (18.1 mg, 49%) as an off-white solid. MS ESI calculated for $C_{21}H_{27}ClN_6O_3$ [M + H]$^+$ 447.18, found 447.20. ^{1}H NMR (400 MHz, DMSO-

*d*6) δ 8.94 (s, 1H), 7.43-7.31 (m, 1H), 5.13-5.09 (m, 1H), 4.93-4.87 (m, 1H), 4.44-4.31 (m, 2H), 4.04-3.94 (m, 2H), 3.63-3.51 (m, 2H), 3.15-2.87 (m, 1H), 2.63-2.54 (m, 3H), 2.27-2.22 (m, 2H), 2.15-1.99 (m, 4H), 1.92-1.87 (m, 1H), 1.21-1.16 (m, 3H), 0.74-0.68 (m, 3H).

Example 96:

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-[(2*R*)-2-hydroxypropanoyl]piperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-[(2*R*)-2-hydroxypropanoyl]piperidin-3-yl acetate

[00632] To a mixture of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (60 mg, 0.132 mmol), D-lactic acid (24 mg, 0.266 mmol) and DCM (0.5 mL) was added DIEA (51 mg, 0.397 mmol) at 0 °C. The resulting mixture was stirred for 16 h at room temperature. The residue was purified by Prep-TLC with PE/EtOAc (1/1) to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-[(2*R*)-2-hydroxypropanoyl]piperidin-3-yl acetate (35 mg, 54%) as a yellow solid. MS ESI calculated for $C_{23}H_{29}ClN_6O_4$ $[M + H]^+$, 489.19; found 489.20.

Example 96:

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-[(2*R*)-2-hydroxypropanoyl]piperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00633] A mixture of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-[(2*R*)-2-hydroxypropanoyl]piperidin-3-yl acetate (50 mg, 0.102 mmol) and K_2CO_3 (42 mg, 0.306 mmol) in MeOH (2 mL) was stirred for 30 min at room temperature. The reaction mixture purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 30% to 55%; detector, UV 254 nm to afford 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-[(2*R*)-2-hydroxypropanoyl]piperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (26.1 mg, 57%) as a yellow solid. MS ESI calculated for $C_{23}H_{29}ClN_8$ $[M + H]^+$, 447.18; found 447.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 5.19-5.10 (m, 1H), 4.71-4.50 (m, 2H), 3.95-3.64 (m, 3H), 3.23-2.82 (m, 2H), 2.77-2.64 (m, 2H), 2.38-2.36 (m, 3H), 2.31-2.19 (m, 2H), 2.18-1.88 (m, 4H), 1.60-1.56 (m, 1H), 1.38 (d, *J* = 6.8 Hz, 3H), 0.82 (t, *J* = 7.2 Hz, 3H).

Example 97:

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-1-(3-fluoroazetidine-3-carbonyl)-3-hydroxypiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: *tert*-butyl 3-[(3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carbonyl]-3-fluoroazetidine-1-carboxylate

[00634] To a stirred solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (90 mg, 0.199 mmol) and 1-(*tert*-butoxycarbonyl)-3-fluoroazetidine-3-carboxylic acid (87 mg, 0.398 mmol) in DCM (2 mL) were added EDCI (46 mg, 0.239 mmol) and DIEA (77 mg, 0.597 mmol). The resulting mixture was stirred for 3 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl 3-[(3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carbonyl]-3-fluoroazetidine-1-carboxylate (120 mg, 97%) as a light yellow solid. MS ESI calculated for $C_{29}H_{37}ClFN_7O_5$ $[M + H]^+$, 618.25, found 618.30.

Step 2: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-(3-fluoroazetidine-3-carbonyl)piperidin-3-yl acetate hydrochloride

[00635] A solution of *tert*-butyl 3-[(3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carbonyl]-3-fluoroazetidine-1-carboxylate (120 mg, 0.194 mmol) and HCl (gas) in 1,4-dioxane (1 mL) in DCM (1 mL) was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-(3-fluoroazetidine-3-carbonyl)piperidin-3-yl acetate hydrochloride (80 mg, 74%) as a light yellow solid. MS ESI calculated for $C_{24}H_{30}Cl_2FN_7O_3$ $[M - Cl]^+$, 518.20, found 518.25.

Example 97:

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-1-(3-fluoroazetidine-3-carbonyl)-3-hydroxypiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00636] To a stirred solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-(3-fluoroazetidine-3-carbonyl)piperidin-3-yl acetate hydrochloride (70 mg, 0.126 mmol) in MeOH (2 mL) was added K_2CO_3 (35 mg, 0.252 mmol) at room temperature. The resulting mixture was stirred for 30 min at room temperature. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 20% to 50%; detector, UV 254 nm to afford 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-1-(3-fluoroazetidine-3-carbonyl)-3-hydroxypiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (23 mg, 38%) as a white solid. MS ESI calculated for $C_{22}H_{27}ClFN_7O_2$ $[M + H]^+$, 476.19, found 476.25. ^1H NMR (400 MHz, DMSO-d_6) δ 8.94 (s, 1H), 7.38 (d, J = 6.0 Hz, 1H), 5.23-5.19 (m, 1H), 4.23-3.84 (m, 3H), 3.75-3.47 (m, 5H), 3.10-2.94 (m, 2H), 2.80-2.74 (m, 1H), 2.62-2.59 (m, 2H), 2.25-2.23 (m,

2H), 2.09-2.01 (m, 4H), 1.99-1.86 (m, 1H), 1.40-1.37 (m, 1H), 0.72-0.68 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -146.76 (1F).

Example 98:

2-[(3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidin-1-yl]-*N*-methylacetamide

Step 1: *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-[(methylcarbamoyl)methyl]piperidin-3-yl acetate

[00637] To a stirred solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (100 mg, 0.22 mmol) and acetamide, 2-chloro-*N*-methyl- (119 mg, 1.10 mmol) in NMP (10 mL) was added DIEA (231 uL, 1.32 mmol) at room temperature. The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol / L NH_4HCO_3), 20% to 50%; detector, UV 254 nm to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-[(methylcarbamoyl)methyl]piperidin-3-yl acetate (90 mg, 83%) as a yellow oil. MS ESI calculated for $C_{23}H_{30}ClN_7O_3$ $[M + H]^+$, 488.21, found 488.25.

Example 98:

2-[(3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidin-1-yl]-*N*-methylacetamide

[00638] A solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-[(methylcarbamoyl)methyl]piperidin-3-yl acetate (90 mg, 0.184 mmol) and K_2CO_3 (51 mg, 0.368 mmol) in MeOH (1 mL) was stirred for 1 h at 0 °C. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 20% to 50%; detector, UV 254 nm to afford 2-[(3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidin-1-yl]-*N*-methylacetamide (51.2 mg, 62%) as a light yellow solid. MS ESI calculated for $C_{21}H_{28}ClN_7O_2$ $[M + H]^+$, 446.20, found 446.20. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (s, 1H), 7.68 (d, J = 5.2 Hz, 1H), 7.29 (d, J = 6.8 Hz, 1H), 4.85-4.80 (m, 1H), 3.67-3.62 (m, 1H), 3.27-3.23 (m, 1H), 2.98-2.85 (m, 3H), 2.75-2.70 (m, 1H), 2.65-2.56 (m, 5H), 2.25-2.20 (m, 2H), 2.15-1.94 (m, 6H), 1.89-1.84 (m, 1H), 1.44-1.39 (m, 1H), 0.71-0.66 (m, 3H).

Example 99:

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate

[00639] A mixture of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (80 mg, 0.155 mmol) and K_2CO_3 (64 mg, 0.463 mmol) in MeOH (1 mL) was stirred for 1 h at room temperature. The residue was purified by Prep-TLC with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (58 mg, 78%) as a yellow solid. MS ESI calculated for $C_{23}H_{31}ClN_6O_3$ $[M + H]^+$, 475.21; found 475.30.

Step 2: 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxypiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride

[00640] A mixture of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (58 mg, 0.122 mmol) and HCl (gas) in 1,4-dioxane (1 mL, 1.000 mmol) in DCM (1 mL) was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxypiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (45 mg, 89%) as a yellow solid. MS ESI calculated for $C_{18}H_{24}Cl_2N_6O$ $[M - Cl]^+$, 375.16; found 375.20.

Example 99:

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00641] A mixture of 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxypiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (60 mg, 0.146 mmol), TFAA (153 mg, 0.730 mmol) and DIEA (94 mg, 0.730 mmol) in DCM (1 mL) was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 40% to 65%; detector, UV 254 nm to afford 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (44.8 mg, 64%) as a yellow solid. MS ESI calculated for $C_{20}H_{22}ClF_3N_6O_2$ $[M + H]^+$, 471.14; found 471.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 5.23-5.16 (m, 1H), 4.65-4.46 (m, 1H), 4.22-4.17 (m, 1H), 4.03-3.98 (m, 1H), 3.77-3.72 (m, 2H), 3.37-3.11 (m, 1H), 3.03-2.96 (m, 1H), 2.77-2.68 (m, 2H), 2.39-2.34 (m, 2H), 2.32-2.16 (m, 2H), 2.09-2.04 (m, 2H), 1.99-1.94 (m, 1H), 1.69-1.63 (m, 1H), 0.84-0.80 (m, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -68.92 (3F).

Example 100:

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-fluoro-1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00642] A solution of *tert*-butyl (3*R*,4*R*)-4-{[7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (80 mg, 0.192 mmol) and NCS (36 mg, 0.269 mmol) in DMF (1.5 mL) was stirred for 16 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 60 % to 80%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (43 mg, 49%) as a light yellow solid. MS ESI calculated for $C_{22}H_{31}ClFN_5O_2$ $[M + H]^+$, 452.22, found 452.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.52 (s, 1H), 6.49 (s, 1H), 5.58 (brs, 1H), 4.68-4.52 (m, 1H), 3.97-3.93 (m, 2H), 3.71-4.68 (m, 1H), 3.43-3.39 (m, 2H), 2.50-2.44 (m, 2H), 2.33-2.28 (m, 1H), 2.26-2.16 (m, 2H), 2.16-2.01 (m, 3H), 1.97-1.88 (m, 1H), 1.68-1.63 (m, 1H), 1.51-1.45 (m, 9H), 0.72-0.67 (m, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -189.53 (1F).

Step 2: *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00643] A solution of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (43 mg, 0.095 mmol) and I_2 (96 mg, 0.380 mmol) in DMF (1.5 mL) was stirred for 16 h at room temperature. The reaction was quenched with sat. $Na_2S_2O_3$ (aq.) (3 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (3 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (45 mg, 81%) as a light yellow solid. MS ESI calculated for $C_{22}H_{30}ClFIN_5O_2$ $[M + H]^+$, 578.11, found 578.20.

Step 3: *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00644] To a stirred solution of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (40 mg, 0.069 mmol) in DMF (2.5 mL) were added $Zn(CN)_2$ (8 mg, 0.069 mmol) and $Pd(PPh_3)_4$ (8 mg, 0.007 mmol) under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 140 °C under nitrogen atmosphere. The resulting mixture was diluted with water (5 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 5

mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 30% to 60%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (20 mg, 60%) as yellow oil. MS ESI calculated for $C_{23}H_{30}ClFN_6O_2$ $[M + H]^+$, 477.21 found 477.25.

Example 100:

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-fluoro-1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00645] A solution of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (15 mg, 0.031 mmol) in DCM (1.5 mL) was added HCl (gas) in 1,4-dioxane (1.5 mL) at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure. To this was added trifluoroacetic anhydride (10 mg, 0.046 mmol) and TEA (9.55 mg, 0.093 mmol) in DCM (1.5 mL) at 0 °C. The resulting mixture was stirred for additional 2 h at room temperature. The resulting mixture was diluted with water (5 mL). The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (2 x 5 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc/EtOH (6/5/1) to afford 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-fluoro-1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (3.6 mg, 23%) as a white solid. MS ESI calculated for $C_{20}H_{21}ClF_4N_6O$ $[M + H]^+$, 473.14, found 473.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 5.00 (brs, 1H), 4.81-4.68 (m, 1H), 4.25-3.98 (m, 2H), 3.79-3.54 (m, 3H), 2.71-2.65 (m, 2H), 2.43-2.31 (m, 3H), 2.27-2.16 (m, 1H), 2.11-1.92 (m, 3H), 1.80-1.74 (m, 1H), 0.83-0.79 (m, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -68.98 (3F), -189.35 (1F).

Example 101:

5-ethyl-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo [2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: *tert*-butyl (3*R*,4*R*)-4-{[5-bromo-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00646] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-4-{[7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (300 mg, 0.719 mmol) in DMF (2.5 mL) was added NBS (115 mg, 0.647 mmol). The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was diluted with sat. $NaHCO_3$ (50 mL). The resulting

mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 50% to 95%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-4-{[5-bromo-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (330 mg, 92%) as yellow oil. MS ESI calculated for $C_{22}H_{31}BrFN_5O_2$ $[M + H]^+$, 496.16, 498.16, found 496.40, 498.40.

Step 2: *tert*-butyl (3*R*,4*R*)-4-{[5-ethyl-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00647] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-4-{[5-bromo-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (80 mg, 0.161 mmol) and potassium ethyltrifluoroboranuide (44 mg, 0.322 mmol) in toluene (2 mL) and water (0.5 mL) were added Cs_2CO_3 (158 mg, 0.483 mmol) and 2nd Generation RuPhos precatalyst (13 mg, 0.016 mmol) at room temperature. The reaction mixture was stirred for 2 h at 100 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[5-ethyl-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (60 mg, 75%) as a light yellow solid. MS ESI calculated for $C_{24}H_{36}FN_5O_2$ $[M + H]^+$, 446.29, found 446.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.42 (s, 1H), 6.34 (s, 1H), 5.24 (brs, 1H), 4.70-4.55 (m, 1H), 3.98-3.75 (m, 2H), 3.63-3.61 (m, 1H), 3.47-3.39 (m, 2H), 2.76 (q, J = 7.6 Hz, 2H), 2.51-2.46 (m, 2H), 2.35-2.28 (m, 1H). 2.19-2.15 (m, 2H), 2.14-2.00 (m, 3H), 1.95-1.87 (m, 1H), 1.57-1.51 (m, 1H), 1.47 (s, 9H), 1.30-1.27 (m, 3H), 0.65-0.62 (m, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -189.70 (1F).

Step 3: *tert*-butyl (3*R*,4*R*)-4-{[5-ethyl-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00648] A solution of *tert*-butyl (3*R*,4*R*)-4-{[5-ethyl-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (50 mg, 0.112 mmol) and I_2 (114 mg, 0.448 mmol) in DMF (1 mL) was stirred for 2 h at room temperature. The reaction was quenched with $Na_2S_2O_3$ (20 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (4/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[5-ethyl-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-

fluoropiperidine-1-carboxylate (50 mg, 77%) as a light yellow solid. MS ESI calculated for $C_{24}H_{35}FIN_5O_2$ $[M + H]^+$, 572.18, found 572.25.

Step 4: *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-5-ethyl-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00649] A mixture of *tert*-butyl (3*R*,4*R*)-4-{[5-ethyl-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (45 mg, 0.079 mmol), $Zn(CN)_2$ (5 mg, 0.047 mmol) and $Pd(PPh_3)_4$ (9 mg, 0.008 mmol) in DMF (1 mL) was stirred for 2 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (15 mL). The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (4/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-5-ethyl-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (40 mg, 86%) as a light yellow solid. MS ESI calculated for $C_{25}H_{35}FN_6O_2$ $[M + H]^+$, 471.28, found 471.45.

Step 5: 5-ethyl-7-(1-ethylcyclobutyl)-2-(((3*R*,4*R*)-3-fluoropiperidin-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride

[00650] A mixture of *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-5-ethyl-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (35 mg, 0.074 mmol) and HCl (gas) in 1,4-dioxane (1 mL) in DCM (1 mL) as stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford 5-ethyl-7-(1-ethylcyclobutyl)-2-(((3*R*,4*R*)-3-fluoropiperidin-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (30 mg, 87%) as a light yellow solid. MS ESI calculated for $C_{20}H_{28}ClFN_6$ $[M - Cl]^+$, 371.23, found 371.35.

Example 101:

5-ethyl-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo [2,1-*f*][1,2,4]triazine-6-carbonitrile

[00651] To a stirred mixture of 5-ethyl-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-fluoropiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (30 mg, 0.081 mmol) and sat. $NaHCO_3$ (2 mL) in EtOAc (2 mL) was added methanesulfonic anhydride (21 mg, 0.121 mmol) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (1/1). The crude product was purified by

Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30 x 150 mm, 5 μm; Mobile Phase: CH_3CN in water (10 mM NH_4HCO_3); Flow rate: 60 mL/min; Gradient: 48% to 73%; Wave Length: 254 nm/220 nm to afford 5-ethyl-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (18.1 mg, 49%) as a light yellow solid. MS ESI calculated for $C_{21}H_{29}FN_6O_2S$ [M + H]$^+$, 449.21, found 449.35. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (s, 1H), 7.43 (d, J = 8.0 Hz, 1H), 4.81-4.67 (m, 1H), 3.89-3.85 (m, 1H), 3.65-3.61 (m, 1H), 3.45-3.41 (m, 1H), 3.24-3.20 (m, 1H), 3.12-3.09 (m, 1H), 2.95 (s, 3H), 2.87-2.81 (m, 2H), 2.63-2.58 (m, 2H), 2.29-2.24 (m, 2H), 2.17-2.11 (m, 2H), 2.06-2.01 (m, 2H), 1.92-1.86 (m, 1H), 1.66-1.63 (m, 1H), 1.25 (t, J = 7.6 Hz, 3H), 0.69 (t, J = 7.6 Hz, 3H). ^{19}F NMR (377 MHz, DMSO-d_6) δ -186.62 (1F).

Example 102:

2-{[(3*R*,4*R*)-1-(1-amino-3,3-difluorocyclobutanecarbonyl)-3-hydroxypiperidin-4-yl]amino}-5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*R*,4*R*)-1-{1-[(*tert*-butoxycarbonyl)amino]-3,3-difluorocyclobutanecarbonyl}-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate

[00652] To a stirred solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (100 mg, 0.22 mmol) and 1-[(*tert*-butoxycarbonyl)amino]-3,3-difluorocyclobutane-1-carboxylic acid (111 mg, 0.44 mmol) in DCM (5 mL) was added EDCI (51 mg, 0.26 mmol) and DIEA (115 uL, 0.66 mmol). The resulting mixture was stirred for 16 h at room temperature. The reaction was quenched with water (50 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*R*,4*R*)-1-{1-[(*tert*-butoxycarbonyl)amino]-3,3-difluorocyclobutanecarbonyl}-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate (90 mg, 63%) as a yellow solid. The crude product was used in the next step (EB2305000-097) directly without further purification. MS ESI calculated for $C_{30}H_{38}ClF_2N_7O_5$ [M + H]$^+$, 650.26 found 652.45.

Step 2: *tert*-butyl *N*-{1-[(3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carbonyl]-3,3-difluorocyclobutyl}carbamate

[00653] A solution of (3*R*,4*R*)-1-{1-[(*tert*-butoxycarbonyl)amino]-3,3-difluorocyclobutanecarbonyl}-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate (120 mg, 0.18 mmol) and K_2CO_3 (51 mg, 0.37 mmol) in MeOH (0.2 mL) was stirred for 1 h at 0 °C. The resulting mixture was purified by reversed-phase chromatography with the

following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 20% to 50%; detector, UV 254 nm to afford *tert*-butyl *N*-{1-[(3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carbonyl]-3,3-difluorocyclobutyl}carbamate (100 mg, 89%) as a yellow solid. MS ESI calculated for $C_{28}H_{36}ClF_2N_7O_4$ $[M + H]^+$, 608.25, found 608.50.

Example 102:

2-{[(3*R*,4*R*)-1-(1-amino-3,3-difluorocyclobutanecarbonyl)-3-hydroxypiperidin-4-yl]amino}-5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00654] A solution of *tert*-butyl *N*-{1-[(3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carbonyl]-3,3-difluorocyclobutyl}carbamate (100 mg, 0.16 mmol) and HCl (gas) in 1,4-dioxane (0.2 mL) in DCM (0.1 mL) was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 30% to 60%; detector, UV 254 nm to afford 2-{[(3*R*,4*R*)-1-(1-amino-3,3-difluorocyclobutanecarbonyl)-3-hydroxypiperidin-4-yl]amino}-5-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (61.6 mg, 73%) as a light yellow solid. MS ESI calculated for $C_{23}H_{28}ClF_2N_7O_2$ $[M + H]^+$, 508.20, found 508.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.65 (s, 1H), 5.06 (brs, 1H), 3.99-3.72 (m, 4H), 3.65-3.20 (m, 4H), 2.80-2.62 (m, 4H), 2.41-2.28 (m, 4H), 2.25-1.93 (m, 6H), 1.72-1.64 (m, 1H), 0.90 (t, *J* = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -89.12--91.63 (2F).

Example 103:

1-(5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-6-yl)ethanone

Step 1: 6-bromo-2,5-dichloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine

[00655] To a stirred solution of 2,5-dichloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine (113 mg, 0.463 mmol) in DMF (2 mL) was added NBS (247 mg, 1.389 mmol). The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (20/1) to afford 6-bromo-2,5-dichloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine (100 mg, 66%) as light yellow oil. MS ESI calculated for $C_{10}H_{10}BrCl_2N_3$ $[M + H]^+$, 321.94, 323.94, found 322.00, 324.00. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.76 (s, 1H), 2.97 (d, *J* = 7.6 Hz, 2H), 2.32-2.22 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 6H).

Step 2: (3*S*,4*R*)-4-{[6-bromo-5-chloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol

[00656] To a stirred solution of 6-bromo-2,5-dichloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine (100 mg, 0.310 mmol) and (3*S*,4*R*)-4-aminooxan-3-ol hydrochloride (143 mg, 0.930 mmol) in NMP (2 mL) was added DIEA (200 mg, 1.550 mmol). The resulting mixture was stirred for 16 h at 80 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 30% to 50%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[6-bromo-5-chloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (80 mg, 64%) as a light yellow solid. MS ESI calculated for $C_{15}H_{20}BrClN_4O_2$ $[M + H]^+$, 403.05, 405.05, found 403.10, 405.10.

Step 3: (3*S*,4*R*)-4-{[6-bromo-5-chloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00657] To a stirred solution of (3*S*,4*R*)-4-{[6-bromo-5-chloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (80 mg, 0.198 mmol) and Ac_2O (30 mg, 0.297 mmol) in DCM (2 mL) was added TEA (80 mg, 0.792 mmol). The resulting mixture was stirred for 16 h at 50 °C. The resulting mixture was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford (3*S*,4*R*)-4-{[6-bromo-5-chloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (66 mg, 74%) as a light yellow solid. MS ESI calculated for $C_{17}H_{22}BrClN_4O_3$ $[M + H]^+$, 445.06, 447.06, found 445.05, 447.05.

Step 4: (3*S*,4*R*)-4-{[6-acetyl-5-chloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00658] To a stirred solution of (3*S*,4*R*)-4-{[6-bromo-5-chloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (15 mg, 0.034 mmol) and tributyl(1-ethoxyethenyl)stannane (15 mg, 0.041 mmol) in 1,4-dioxane (1 mL) was added $Pd(PPh_3)_2Cl_2$ (3 mg, 0.003 mmol) under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 100 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. To this was added HCl (1 M, 0.2 mL). The resulting mixture was stirred for additional 30 min at room temperature. The resulting mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 20% to 50%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[6-acetyl-5-chloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (5 mg, 36%) as a yellow solid. MS ESI calculated for $C_{19}H_{25}ClN_4O_4$ $[M + H]^+$, 409.16, found 409.20.

Example 103:

1-(5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-6-yl)ethenone

[00659] A solution of (3*S*,4*R*)-4-{[6-acetyl-5-chloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (5 mg, 0.012 mmol) and K_2CO_3 (3 mg, 0.024 mmol) in MeOH (0.5 mL) was stirred for 30 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 20% to 50%; detector, UV 254 nm to afford 1-(5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-6-yl)ethanone (2 mg, 55%) as a light yellow solid. MS ESI calculated for $C_{17}H_{23}ClN_4O_3$ $[M + H]^+$, 367.15, found 367.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 4.96 (d, *J* = 5.6 Hz, 1H), 4.12-4.09 (m, 1H), 4.03-4.00 (m, 1H), 3.85-3.76 (m, 2H), 3.70-3.68 (m, 1H), 3.54-3.40 (m, 1H), 3.28-3.23 (m, 1H), 3.17-3.04 (m, 2H), 2.87 (s, 3H), 2.17-2.07 (m, 2H), 1.77-1.67 (m, 1H), 0.96-0.91 (m, 6H).

Example 104:

7-(1-ethylcyclobutyl)-2-{[(3S,4R)-3-hydroxyoxan-4-yl]amino}-5-propylpyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile

Step 1: (3*S*,4*R*)-4-{[6-Cyano-7-(1-ethylcyclobutyl)-5-propylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00660] To a stirred mixture of (3*S*,4*R*)-4-{[5-bromo-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (40 mg, 0.087 mmol) and potassium trifluoro(propyl)boranuide (26 mg, 0.174 mmol) in toluene (1 mL) and water (0.25 mL) were added Cs_2CO_3 (85 mg, 0.261 mmol) and 2nd Generation RuPhos precatalyst (7 mg, 0.009 mmol) at room temperature. The reaction mixture was stirred for 2 h at 100 °C under nitrogen atmosphere. The mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (2/1) to afford (3*S*,4*R*)-4-{[6-cyano-7-(1-ethylcyclobutyl)-5-propylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (30 mg, 65%) as light yellow oil. MS ESI calculated for $C_{23}H_{31}N_5O_3$ $[M + H]^+$, 426.24, found 426.25.

Step 2: 7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-5-propylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00661] A mixture of (3*S*,4*R*)-4-{[6-cyano-7-(1-ethylcyclobutyl)-5-propylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (20 mg, 0.047 mmol) and K_2CO_3 (13 mg, 0.094 mmol) in MeOH (0.5 mL) was stirred for 1 h at room temperature. The resulting mixture was purified by reverse phase Flash chromatography with the following conditions: Column: WelFlash TM C18-I, 20-40 μm, 40 g; mobile phase: CH_3CN in water (10 mM NH_4HCO_3); Gradient: 30% to 50%; Flow

rate: 40 mL/min; Detector: 220/254 nm to afford 7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-5-propylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (2.4 mg, 13%) as an off-white solid. MS ESI calculated for $C_{21}H_{29}N_5O_2$ $[M + H]^+$, 384.23, found 384.30. ^1H NMR (400 MHz, DMSO-d_6) δ 8.95 (s, 1H), 7.02 (d, J = 6.4 Hz, 1H), 4.92 (d, J = 4.8 Hz, 1H), 3.84-3.81 (m, 2H), 3.60-3.42 (m, 2H), 3.30-3.26 (m, 1H), 3.06-3.03 (m, 1H), 2.82-2.79 (m, 2H), 2.62-2.54 (m, 2H), 2.30-1.95 (m, 6H), 1.90-1.86 (m, 1H), 1.66-1.62 (m, 2H), 1.46-1.39 (m, 1H), 0.91-0.88 (m, 3H), 0.69-0.66 (m, 3H).

Example 106:

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: *tert*-butyl (3*S*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate

[00662] To a stirred solution of 2,5-dichloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazine (90 mg, 0.227 mmol) and *tert*-butyl (3*S*,4*R*)-4-amino-3-hydroxypiperidine-1-carboxylate (246 mg, 1.136 mmol) in NMP (2 mL) was added DIEA (177 mg, 1.363 mmol). The resulting mixture was stirred for 16 h at 80 °C. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (3x10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (2/1) to afford *tert*-butyl (3*S*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (38 mg, 29%) as a yellow solid. MS ESI calculated for $C_{22}H_{31}ClIN_5O_3$ $[M + H]^+$, 576.12, found 576.15.

Step 2: *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00663] To a stirred solution of *tert*-butyl (3*S*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (30 mg, 0.052 mmol) and TEA (16 mg, 0.156 mmol) in DCM (3 mL) was added Ac_2O (22 mg, 0.208 mmol). The resulting mixture was stirred for 16 h at 50 °C. The residue was purified by Prep-TLC with PE/EtOAc (3/1) to afford *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (26 mg, 81%) as a yellow solid. MS ESI calculated for $C_{24}H_{33}ClIN_5O_4$ $[M + H]^+$, 618.13, found 618.25.

Step 3: *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00664] To a stirred solution of *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (25 mg, 0.040 mmol) and

$Zn(CN)_2$ (3 mg, 0.024 mmol) in DMF (2 mL) was added $Pd(PPh_3)_4$ (5 mg, 0.004 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 130 °C under nitrogen atmosphere. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (3/1) to afford *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (16 mg, 76%) as a yellow solid. MS ESI calculated for $C_{25}H_{33}ClN_6O_4$ $[M + H]^+$, 517.23, found 517.20.

Step 4: *tert*-butyl (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate

[00665] A stirred solution of *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (16 mg, 0.031 mmol) and K_2CO_3 (13 mg, 0.093 mmol) in MeOH (2 mL) was stirred for 1 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: Column: WelFlash TM C18-I, 20-40 μm, 25 g; CH_3CN in water (10 mM NH_4HCO_3); Gradient: 5% to 95%; Flow rate: 25 mL/min; Detector: 220/254 nm to afford *tert*-butyl (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (7.5 mg, 51%) as a white solid. MS ESI calculated for $C_{23}H_{31}ClN_6O_3$ $[M + H]^+$, 475.21, found 475.30.

Step 5: 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-hydroxypiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride

[00666] To a stirred solution of *tert*-butyl (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (7 mg, 0.016 mmol) and HCl (gas) in 1,4-dioxane (0.5 mL) in DCM (0.5 mL) at room temperature. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-hydroxypiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride as a white soild. MS ESI calculated for $C_{18}H_{24}Cl_2N_6O$ $[M - Cl]^+$, 375.16, found 375.25.

Example 106:

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00667] A solution of 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-hydroxypiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (7 mg, 0.019 mmol) and methanesulfonic anhydride (5 mg, 0.028 mmol) in sat. $NaHCO_3$ (0.5 mL) and EtOAc (1 mL)

was stirred for 1 h at room temperature. The resulting mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by was purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30 x 150 mm, 5 μm; Mobile Phase: CH_3CN in water (10 mM NH_4HCO_3); Flow rate: 60 mL/min; Gradient: 35% to 65%; Wave Length: 254/220 nm to afford 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (2.2 mg, 26%) as a light yellow solid. MS ESI calculated for $C_{19}H_{25}ClN_6O_3S$ $[M + H]^+$, 453.14, found 453.20. ^1H NMR (400 MHz, DMSO-d_6) δ 8.96 (d, J = 1.2 Hz, 1H), 7.02 (d, J = 7.6 Hz, 1H), 5.16 (brs, 1H), 4.02-4.00 (m, 1H), 3.69-3.44 (m, 3H), 3.06-3.03 (m, 1H), 2.99-2.92 (m, 4H), 2.68-2.57 (m, 2H), 2.26-2.09 (m, 3H), 2.06-1.88 (m, 4H), 1.76-1.71 (m, 1H), 0.72-0.69 (m, 3H).

Example 107:

5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl was not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 70/15/15, 2nd peak)

Example 108:

5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl was not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 70/15/15, 1st peak)

Step 1: *tert*-butyl 4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3,3-difluoropiperidine-1-carboxylate

[00668] A mixture of 2,5-dichloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazine (60 mg, 0.151 mmol), *tert*-butyl 4-amino-3,3-difluoropiperidine-1-carboxylate (54 mg, 0.226 mmol) and DIEA (78 mg, 0.604 mmol) in NMP (0.5 mL) was stirred for 16 h at 100 °C. The resulting mixture was purified by reversed-phase chromatography the following conditions: Column: WelFlash TM C18-I, 20-40 μm, 25 g; mobile phase: CH_3CN in water (5 mmol/L NH_4HCO_3); Gradient: 45% to 70%; Flow rate: 25 mL/min; Detector: 220/254 nm to afford *tert*-butyl 4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3,3-difluoropiperidine-1-carboxylate (50 mg, 55%) as a yellow solid. MS ESI calculated for $C_{22}H_{29}ClF_2IN_5O_2$ $[M + H]^+$, 596.10; found 596.20.

Step 2: *tert*-butyl 4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3,3-difluoropiperidine-1-carboxylate

[00669] To a stirred solution of *tert*-butyl 4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3,3-difluoropiperidine-1-carboxylate (50 mg, 0.084 mmol) and $Zn(CN)_2$ (6 mg, 0.050 mmol) in DMF (1 mL, 12.922 mmol) was added $Pd(PPh_3)_4$ (10 mg, 0.008 mmol). The resulting mixture was stirred for 2 h at 120 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 50% to 70%; detector, UV 254 nm to afford *tert*-butyl 4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3,3-difluoropiperidine-1-carboxylate (30 mg, 72%) as a light yellow solid. MS ESI calculated for $C_{23}H_{29}ClF_2N_6O_2$ $[M + H]^+$, 495.20, found 495.40.

Step 3: 5-chloro-2-[(3,3-difluoropiperidin-4-yl)amino]-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride

[00670] A solution of *tert*-butyl 4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3,3-difluoropiperidine-1-carboxylate (30 mg, 0.061 mmol) and HCl (gas) in 1,4-dioxane (1 mL) in DCM (1 mL) was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford 5-chloro-2-[(3,3-difluoropiperidin-4-yl)amino]-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (20 mg, 76%) as a light yellow solid. MS ESI calculated for $C_{18}H_{22}Cl_2F_2N_6$ $[M - Cl]^+$, 395.15, found 395.25.

Step 4: 5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00671] To a stirred solution of 5-chloro-2-[(3,3-difluoropiperidin-4-yl)amino]-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (20 mg, 0.046 mmol) in EtOAc (2 mL) and sat. $NaHCO_3$ (2 mL) was added methanesulfonyl methanesulfonate (12 mg, 0.069 mmol). The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (1/1) to afford 5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (18 mg, 82%) as a yellow solid. MS ESI calculated for $C_{19}H_{23}ClF_2N_6O_2S$ $[M + H]^+$, 473.13, found 473.20.

Example 107:

5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl was not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 70/15/15, 2nd peak)

Example 108:

5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl was not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 70/15/15, 1st peak)

[00672] 5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (18 mg) was purified by Prep-Chiral-HPLC with the following conditions: Column: CHIRAL ART Cellulose-SC, 2 x 25 cm, 5 μm; Mobile Phase A: Hexane, Mobile Phase B: EtOH/ DCM (1/1); Flow rate: 20 mL/min; Gradient: A:B = 70:30; Wave Length: 254/220 nm.

[00673] RT_1: 10.97 min to afford 5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl was not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 70/15/15, 1st peak) (7.1 mg, 34%) as a light yellow solid. MS ESI calculated for $C_{19}H_{23}ClF_2N_6O_2S$ $[M + H]^+$, 473.13, found 473.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 5.39 (d, *J* = 6.4 Hz, 1H), 4.28-4.09 (m, 2H), 3.96-3.92 (m, 1H), 3.31-3.10 (m, 2H), 2.97 (s, 3H), 2.76-2.66 (m, 2H), 2.36-1.87 (m, 8H), 0.83-0.79 (m, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -110.22&-110.87 (1F), -118.83&-119.48 (1F).

[00674] RT_2: 13.98 min to afford 5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl was not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 70/15/15, 2nd peak) (7.6 mg, 37%) as a light yellow solid. MS ESI calculated for $C_{19}H_{23}ClF_2N_6O_2S$ $[M + H]^+$, 473.13, found 473.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 5.28 (d, *J* = 7.6 Hz, 1H), 4.28-4.10 (m, 2H), 3.96-3.92 (m, 1H), 3.30-3.09 (m, 2H), 2.97 (s, 3H), 2.76-2.65 (m, 2H), 2.35-2.19 (m, 4H), 2.17-1.86 (m, 4H), 0.83-0.79 (m, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -110.29&-110.93 (1F), -118.98&-119.63 (1F).

Example 109:

5-chloro-2-{[(3*R*,4*R*)-1-(dimethylphosphoryl)-3-hydroxypiperidin-4-yl]amino}-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-(dimethylphosphoryl)piperidin-3-yl acetate

[00675] To a stirred solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (70 mg, 0.154 mmol) and dimethylphosphinoyl chloride (35 mg, 0.308 mmol) in DCM (1.8 mL) was added DIEA (80 mg,

0.616 mmol) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was diluted with water (3 mL). The resulting mixture was extracted with DCM (2 x 5 mL). The combined organic layers were washed with brine (3 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with EtOAc/EtOH (5/1) to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-(dimethylphosphoryl)piperidin-3-yl acetate (46 mg, 60%) as a yellow solid. MS ESI calculated for $C_{22}H_{30}ClN_6O_3P$ $[M + H]^+$, 493.18; found 493.20.

Example 109:

5-chloro-2-{[(3*R*,4*R*)-1-(dimethylphosphoryl)-3-hydroxypiperidin-4-yl]amino}-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00676] A solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-(dimethylphosphoryl)piperidin-3-yl acetate (40 mg, 0.081 mmol) and K_2CO_3 (33 mg, 0.243 mmol) in MeOH (2 mL) was stirred for 1 h at room temperature. The resulting mixture was diluted with water (5 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 30% to 50%; detector, UV 254 nm to afford 5-chloro-2-{[(3*R*,4*R*)-1-(dimethylphosphoryl)-3-hydroxypiperidin-4-yl]amino}-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (8 mg, 23%) as a white solid. MS ESI calculated for $C_{20}H_{28}ClN_6O_2P$ $[M + H]^+$, 451.17; found 451.30. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.66 (s, 1H), 5.31 (d, *J* = 5.6 Hz, 1H), 3.72-3.58 (m, 3H), 3.47-3.42 (m, 1H), 2.89-2.65 (m, 4H), 2.37-2.28 (m, 3H), 2.23-2.15 (m, 1H), 2.10-2.04 (m, 2H), 2.00-1.94 (m, 2H), 1.74-1.54 (m, 6H), 0.82-0.78 (m, 3H). ^{31}P NMR (162 MHz, Chloroform-*d*) δ -43.98.

Example 110:

5-chloro-2-[(4,4-difluorocyclohexyl)amino]-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: 5-chloro-*N*-(4,4-difluorocyclohexyl)-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-amine

[00677] To a stirred solution of 2,5-dichloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazine (50 mg, 0.126 mmol) and 4,4-difluorocyclohexan-1-amine hydrochloride (87 mg, 0.504 mmol) in NMP (2 mL) was added DIEA (81 mg, 0.630 mmol). The resulting mixture was stirred for 16 h at 100 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 50% to

80%; detector, UV 254 nm to afford 5-chloro-*N*-(4,4-difluorocyclohexyl)-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-amine (35 mg, 56%) as brown oil. MS ESI calculated for $C_{18}H_{22}ClF_2IN_4$ $[M + H]^+$, 495.05, found 495.15.

Example 110:

5-chloro-2-[(4,4-difluorocyclohexyl)amino]-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00678] To a stirred solution of 5-chloro-*N*-(4,4-difluorocyclohexyl)-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-amine (30 mg, 0.061 mmol) and $Zn(CN)_2$ (4 mg, 0.037 mmol) in DMA (2 mL) was added $Pd(PPh_3)_4$ (7 mg, 0.006 mmol) under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 120 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford 5-chloro-2-[(4,4-difluorocyclohexyl)amino]-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (11 mg, 47%) as a light yellow solid. MS ESI calculated for $C_{19}H_{22}ClF_2N_5$ $[M + H]^+$, 394.15, found 394.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.65 (s, 1H), 5.01 (d, *J* = 6.0 Hz, 1H), 3.70-3.68 (m, 1H), 2.75-2.67 (m, 2H), 2.36-2.21 (m, 2H), 2.18-2.06 (m, 7H), 2.04-1.87 (m, 3H), 1.74-1.68 (m, 2H), 0.82 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -95.45--100.10 (2F).

Example 111:

5-chloro-7-(1-ethylcyclobutyl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: 5-chloro-7-(1-ethylcyclobutyl)-6-iodo-*N*-(oxan-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-amine

[00679] A solution of 2,5-dichloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazine (25 mg, 0.063 mmol), oxan-4-amine (26 mg, 0.252 mmol) and DIEA (49 mg, 0.378 mmol) in NMP (0.2 mL) was stirred for 2 h at 80 °C under nitrogen atmosphere. The resulting mxiture was purified by reverse flash chromatography: C18 column; mobile phase: CH_3CN in water (10 mM NH_4HCO_3), 30% to 80%; detector: UV 254 nm to afford 5-chloro-7-(1-ethylcyclobutyl)-6-iodo-*N*-(oxan-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-amine (25 mg) as a yellow solid. MS ESI calculated for $C_{17}H_{22}ClIN_4O$ $[M + H]^+$, 461.05, found 461.30; ^1H NMR (400 MHz, DMSO-d_6) δ 8.70 (s, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 3.93-3.85 (m, 2H), 3.67-3.59 (m, 1H), 3.40-3.36 (m, 2H), 2.70-2.58 (m, 2H), 2.32-2.27 (m, 2H), 2.15-2.08 (m, 1H), 2.04-2.00 (m, 2H), 1.92-1.89 (m, 2H), 1.82-1.80 (m, 1H), 1.54-1.45 (m, 2H), 0.73 (t, *J* = 7.2 Hz, 3H).

Example 111:

5-chloro-7-(1-ethylcyclobutyl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00680] A solution of 5-chloro-7-(1-ethylcyclobutyl)-6-iodo-*N*-(oxan-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-amine (25 mg, 0.054 mmol), $Pd(PPh_3)_4$ (6 mg, 0.005 mmol) and $Zn(CN)_2$ (4 mg, 0.032 mmol) in DMF (1 mL) was stirred for 3 h at 120 °C under nitrogen atmosphere. The resulting mxiture was purified by reverse flash chromatography: C18 column; mobile phase: CH_3CN in water (10 mM NH_4HCO_3), 30% to 60%; Detector: UV 254 nm to afford 5-chloro-7-(1-ethylcyclobutyl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (3.5 mg, 18%) as a light yellow solid. MS ESI calculated for $C_{18}H_{22}ClN_5O$ $[M + H]^+$, 360.15, found 360.20; ^1H NMR (400 MHz, DMSO-d_6) δ 8.93 (s, 1H), 7.48 (d, J = 6.8 Hz, 1H), 3.90-3.87 (m, 2H), 3.62-3.57 (m, 3H), 2.26-2.57 (m, 2H), 2.24-2.19 (m, 3H), 2.05-2.00 (m, 2H), 1.92-1.84 (m, 3H), 1.57-1.47 (m, 2H), 0.70 (t, J = 7.2 Hz, 3H).

Example 112:

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate

[00681] A solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (50 mg, 0.120 mmol), $NaHCO_3$ (71 mg, 0.840 mmol) and methanesulfonic anhydride (42 mg, 0.240 mmol) in EtOAc (2 mL) and water (2 mL) was stirred for 40 min at room temperature. The reaction was diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (52 mg, 87%) as a light yellow solid. MS ESI calculated for $C_{21}H_{27}ClN_6O_4S$ $[M + H]^+$, 495.15, found 495.20.

Example 112:

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00682] A solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (50 mg, 0.101 mmol) and K_2CO_3 (42 mg, 0.303 mmol) in MeOH (1 mL) was stirred for 30 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 45% to 70%; detector, UV 254 nm to afford 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-

yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (28.0 mg, 61%) as a light yellow solid. MS ESI calculated for $C_{19}H_{25}ClN_6O_3S$ $[M + H]^+$, 453.14; found 453.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 5.07 (d, *J* = 6.8 Hz, 1H), 4.01-3.92 (m, 1H), 3.85-3.75 (m, 2H), 3.68-3.63 (m, 1H), 3.01-2.89 (m, 4H), 2.81-2.65 (m, 3H), 2.41-2.28 (m, 3H), 2.25-2.15 (m, 1H), 2.10-1.92 (m, 4H), 1.77-1.66 (m, 1H), 0.82 (t, *J* = 7.6 Hz, 3H).

Example 113:

5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbaldehyde

Step 1: (3*S*,4*R*)-4-{[5-chloro-6-ethenyl-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00683] To a stirred solution of (3*S*,4*R*)-4-{[6-bromo-5-chloro-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (200 mg, 0.449 mmol) and 2-ethenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (76 mg, 0.494 mmol) in 1,4-dioxane (2.5 mL) and water (0.5 mL) were added $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (36 mg, 0.045 mmol) and K_3PO_4 (190 mg, 0.898 mmol) under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 100 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*S*,4*R*)-4-{[5-chloro-6-ethenyl-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (100 mg, 56%) as a light yellow solid. MS ESI calculated for $C_{19}H_{25}ClN_4O_3$ $[M + H]^+$, 393.16, found 393.25.

Step 2: (3*S*,4*R*)-4-{[5-chloro-6-formyl-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00684] To a stirred solution of (3*S*,4*R*)-4-{[5-chloro-6-ethenyl-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (100 mg, 0.255 mmol) and $K_2OsO_4.2H_2O$ (1 mg, 0.003 mmol) in THF (1.5 mL) and water (1.5 mL) was added $NaIO_4$ (163 mg, 0.765 mmol) at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (2/1) to afford (3*S*,4*R*)-4-{[5-chloro-6-formyl-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (25 mg, 24%) as light yellow oil. MS ESI calculated for $C_{18}H_{23}ClN_4O_4$ $[M + H]^+$, 395.14, found 395.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 10.21 (s, 1H), 8.70 (s, 1H), 6.05 (brs, 1H), 5.02-5.00 (m, 1H), 4.07-3.97 (m, 3H), 3.62-3.61 (m, 1H), 3.50-3.49 (m, 1H), 3.14 (d, *J* = 7.2 Hz, 2H), 2.44-2.40 (m, 1H), 2.19-2.16 (m, 1H), 2.10 (s, 3H), 1.78-1.7 (m, 1H), 0.97 (t, *J* = 6.4 Hz, 6H).

Example 113:

5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbaldehyde

[00685] To a stirred solution of (3*S*,4*R*)-4-{[5-chloro-6-formyl-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (15 mg, 0.038 mmol) in MeOH (1 mL) was added K_2CO_3 (10 mg, 0.076 mmol). The resulting mixture was stirred for 30 min at room temperature. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 15% to 40%; detector, UV 254 nm to afford 5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbaldehyde (6 mg, 47%) as a light yellow solid. MS ESI calculated for $C_{16}H_{21}ClN_4O_3$ $[M + H]^+$, 353.13, found 353.05. ^1H NMR (400 MHz, Chloroform-*d*) δ 10.20 (s, 1H), 8.71 (s, 1H), 5.48 (brs, 1H), 4.10-4.06 (m, 1H), 4.00-3.97 (m, 1H), 2.82-3.79 (m, 1H), 3.72-3.67 (m, 1H), 3.53-3.50 (m, 1H), 3.28-3.23 (m, 1H), 3.14-3.02 (m, 2H), 2.18-2.11 (m, 3H), 1.75-1.65 (m, 1H), 0.97-0.94 (m, 6H).

Example 114:

5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl was not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 65/17.5/17.5, 2nd peak)

Example 115:

5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl was not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 65/17.5/17.5, 1st peak)

Step 1: *tert*-butyl 4-{[5-chloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3,3-difluoropiperidine-1-carboxylate

[00686] A solution of 2,5-dichloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine (80 mg, 0.216 mmol), *tert*-butyl 4-amino-3,3-difluoropiperidine-1-carboxylate (153 mg, 0.648 mmol) and DIEA (140 mg, 1.080 mmol) in NMP (1 mL) was stirred for 48 h at 100 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford *tert*-butyl 4-{[5-chloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3,3-difluoropiperidine-1-carboxylate (75 mg, 60%) as a light yellow solid. MS ESI calculated for $C_{20}H_{27}ClF_2IN_5O_2$ $[M + H]^+$, 570.09, found 570.10.

Step 2: *tert*-butyl 4-{[5-chloro-6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3,3-difluoropiperidine-1-carboxylate

[00687] A solution of *tert*-butyl 4-{[5-chloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3,3-difluoropiperidine-1-carboxylate (56 mg, 0.098 mmol), $Zn(CN)_2$ (7 mg, 0.059 mmol) and $Pd(PPh_3)_4$ (11 mg, 0.010 mmol) in DMA (1 mL) was stirred for 2 h at 130 °C under nitrogen atmosphere. The resulting mixure was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 70%; detector, UV 254 nm to afford *tert*-butyl 4-{[5-chloro-6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3,3-difluoropiperidine-1-carboxylate (37 mg, 80%) as a light yellow solid. MS ESI calculated for $C_{21}H_{27}ClF_2N_6O_2$ $[M + H]^+$, 469.19, found 469.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 5.20 (d, *J* = 9.0 Hz, 1H), 2.97 (s, 2H), 2.92-2.88 (m, 2H), 2.23-2.18 (m, 1H), 1.79-1.73 (m, 1H), 1.69-1.65 (m, 4H), 1.51 (s, 9H), 1.02-0.98 (m, 6H).

Step 3: (5-chloro-2-[(3,3-difluoropiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride

[00688] A solution of *tert*-butyl 4-{[5-chloro-6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3,3-difluoropiperidine-1-carboxylate (40 mg, 0.085 mmol) in HCl (gas) in 1,4-dioxane (2 mL) and DCM (2 mL) was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford (5-chloro-2-[(3,3-difluoropiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (33 mg, 95%). MS ESI calculated for $C_{16}H_{20}Cl_2F_2N_6$ $[M - Cl]^+$, 369.13, found 369.20.

Step 4: 5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00689] A solution of 5-chloro-2-[(3,3-difluoropiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (45 mg, 0.111 mmol), methanesulfonic anhydride (39 mg, 0.222 mmol) and $NaHCO_3$ (93 mg, 1.110 mmol) in EtOAc (1 mL) and water (2 mL) was stirred for 40 min at room temperature. The resulting mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (40 mg, 80%) as a light yellow solid. MS ESI calculated for $C_{17}H_{21}ClF_2N_6O_2S$ $[M + H]^+$, 447.11, found 447.35.

Example 114:

5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl was not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 65/17.5/17.5, 2nd peak)

Example 115:

5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl was not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 65/17.5/17.5, 1st peak)

[00690] 5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (40 mg) was purified by Prep-Chiral-HPLC with the following conditions: Column: CHIRAL ART Cellulose-SC, 2*25 cm, 5 μm; Mobile Phase A: Hexane, Mobile Phase B: EtOH/DCM (1/1); Flow rate: 20 mL/min; Gradient: A:B = 65:35; Wave Length: 254/220 nm.

[00691] RT_1: 8.31 min to afford 5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl was not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 65/17.5/17.5, 1st peak) (7.9 mg, 19%) as an off-white solid MS ESI calculated for $C_{17}H_{21}ClF_2N_6O_2S$ $[M + H]^+$, 447.11; found 447.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.72 (s, 1H), 5.15 (d, *J* = 8.8 Hz, 1H), 4.39-4.35 (m, 1H), 4.23-4.16 (m, 1H), 3.99-3.95 (m, 1H), 3.30-3.10 (m, 2H), 2.97 (s, 3H), 2.90 (d, *J* = 6.8 Hz, 2H), 2.31-2.16 (m, 2H), 1.94-1.86 (m, 1H), 1.02-0.98 (m, 6H). ^{19}F NMR (376 MHz, Chloroform -*d*) δ -110.49&-111.13 (1F), -119.19&-119.84 (1F).

[00692] RT_2: 10.62 min to afford 5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl was not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 65/17.5/17.5, 2nd peak) (5.3 mg, 12%) as an off-white solid MS ESI calculated for $C_{17}H_{21}ClF_2N_6O_2S$ $[M + H]^+$, 447.11; found 447.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.72 (s, 1H), 5.13 (d, *J* = 8.4 Hz, 1H), 4.39-4.36 (m, 1H), 4.24-4.16 (m, 1H), 3.99-3.95 (m, 1H), 3.30-3.10 (m, 2H), 2.97 (s, 3H), 2.93-2.89 (m, 2H), 2.30-2.16 (m, 2H), 1.94-1.85 (m, 1H), 1.02-0.98 (m, 6H). ^{19}F NMR (376 MHz, Chloroform -*d*) δ -110.50&-111.15 (1F), -119.22&-119.87 (1F).\

Example 116:

5-chloro-2-{[(3*R*,4*R*)-4-fluoro-1-methanesulfonylpyrrolidin-3-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: *tert*-butyl (3*R*,4*R*)-3-{[5-chloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-4-fluoropyrrolidine-1-carboxylate

[00693] To a stirred solution of 5-chloro-6-iodo-2-methyl-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine (60 mg, 0.172 mmol) and *tert*-butyl (3*R*,4*R*)-3-amino-4-fluoropyrrolidine-1-carboxylate (175 mg, 0.860 mmol) in NMP (1.50 mL) was added DIEA (133 mg, 1.032 mmol) at room temperature. The resulting mixture was stirred for 16 h at 100 °C. The reaction was quenched with water (10 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (2/1) to afford *tert*-butyl (3*R*,4*R*)-3-{[5-chloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-4-fluoropyrrolidine-1-carboxylate (55 mg, 59%) as an orange solid. MS ESI calculated for $C_{19}H_{26}ClFIN_5O_2$ $[M + H]^+$, 538.08; found 538.0. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.57 (s, 1H), 5.30-5.14 (m, 1H), 4.88 (s, 1H), 4.45-4.35 (m, 1H), 3.89-3.81 (m, 1H), 3.79-3.49 (m, 3H), 2.95-2.80 (m, 2H), 2.29-2.20 (m, 1H), 1.51 (s, 9H), 1.02-0.97 (m, 6H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -180.31 (1F).

Step 2: *tert*-butyl (3*R*,4*R*)-3-{[5-chloro-6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-4-fluoropyrrolidine-1-carboxylate

[00694] To a stirred solution of *tert*-butyl (3*R*,4*R*)-3-{[5-chloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-4-fluoropyrrolidine-1-carboxylate (55 mg, 0.102 mmol) in DMA (2 mL) were added $Zn(CN)_2$ (2 mg, 0.010 mmo) and $Pd(PPh_3)_4$ (71 mg, 0.061 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 130°C under nitrogen atmosphere. The reaction was quenched with water (15 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford *tert*-butyl (3*R*,4*R*)-3-{[5-chloro-6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-4-fluoropyrrolidine-1-carboxylate (30 mg, 67%) as yellow oil. MS ESI calculated for $C_{20}H_{26}ClFN_6O_2$ $[M + H]^+$, 437.18; found 437.20.

Example 116:

5-chloro-2-{[(3*R*,4*R*)-4-fluoro-1-methanesulfonylpyrrolidin-3-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00695] A solution of *tert*-butyl (3*R*,4*R*)-3-{[5-chloro-6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-4-fluoropyrrolidine-1-carboxylate (30 mg, 0.069 mmol) in DCM (1 mL) was added HCl (gas) in 1,4-dioxane (1 mL) dropwise at 0 °C. The resulting mixture was

stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure. To this were added sat. $NaHCO_3$ (1 mL) and methanesulfonic anhydride (36 mg, 0.207 mmol) in EtOAc (1 mL) at 0 °C. The reaction mixture was stirred for additional 40 min at room temperature. The resulting mixture was diluted with water (5 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 70% to 85%; detector, UV 254 nm to afford 5-chloro-2-{[(3*R*,4*R*)-4-fluoro-1-methanesulfonylpyrrolidin-3-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (10 mg, 38%) as an off-white solid. MS ESI calculated for $C_{16}H_{20}ClFN_6O_2S$ $[M + H]^+$, 415.10; found 415.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.73 (s, 1H), 5.33-5.20 (m, 2H), 4.55-4.50 (m, 1H), 3.93-3.75 (m, 2H), 3.67-3.57 (m, 2H), 2.98-2.87 (m, 5H), 2.28-2.19 (m, 1H), 1.03-0.98 (m, 6H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -178.31 (1F).

Example 117:

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: 5-chloro-7-(1-ethylcyclobutyl)-*N*-[(3*S*,4*R*)-3-fluorooxan-4-yl]-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-amine

[00696] To a stirred solution of 2,5-dichloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazine (50 mg, 0.126 mmol) and (3*S*,4*R*)-3-fluorooxan-4-amine hydrochloride (58 mg, 0.378 mmol) in NMP (1.5 mL) was added DIEA (97 mg, 0.756 mmol) at room temperature. The resulting mixture was stirred for 16 h at 100 °C. The reaction was quenched with water (15 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (2/1) to afford 5-chloro-7-(1-ethylcyclobutyl)-*N*-[(3*S*,4*R*)-3-fluorooxan-4-yl]-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-amine (27 mg, 44%) as yellow oil. MS ESI calculated for $C_{17}H_{21}ClFIN_4O$ $[M + H]^+$, 479.04; found 479.00.

Example 117:

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00697] To a stirred solution of 5-chloro-7-(1-ethylcyclobutyl)-*N*-[(3*S*,4*R*)-3-fluorooxan-4-yl]-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-amine (27 mg, 0.056 mmol) and $Zn(CN)_2$ (4 mg, 0.034 mmol) in DMA (1 mL) was added $Pd(PPh_3)_4$ (7 mg, 0.006 mmol) at room temperature under nitrogen

atmosphere. The resulting mixture was stirred for 2 h at 130 °C under nitrogen atmosphere. The resulting mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1). The crude product was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (7.1 mg, 33%) as a white solid. MS ESI calculated for $C_{18}H_{21}ClFN_5O$ $[M + H]^+$, 378.14; found 378.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 5.05-5.02 (m, 1H), 4.63-4.47 (m, 1H), 4.12-4.04 (m, 1H), 3.97-3.88 (m, 2H), 3.64-3.55 (m, 2H), 2.76-2.64 (m, 2H), 2.42-2.32 (m, 3H), 2.23-2.16 (m, 1H), 2.11-2.07 (m, 2H), 2.00-1.92 (m, 1H), 1.70-1.61 (m, 1H), 0.82-0.78 (m, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -193.48 (1F).

Example 118:

5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-difluoromethanesulfonylpiperidin-3-yl acetate

[00698] To a stirred solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (50 mg, 0.110 mmol) in EtOAc (2 mL) and sat. $NaHCO_3$ (2 mL) was added difluoromethanesulfonyl chloride (33 mg, 0.220 mmol). The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-difluoromethanesulfonylpiperidin-3-yl acetate (30 mg, 51%) as a light yellow solid. MS ESI calculated for $C_{21}H_{25}ClF_2N_6O_4S$ $[M + H]^+$, 531.13, found 531.35.

Example 118:

5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00699] To a stirred solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-difluoromethanesulfonylpiperidin-3-yl acetate (30 mg, 0.056

mmol) in MeOH (2 mL) was added K_2CO_3 (16 mg, 0.112 mmol). The resulting mixture was stirred for 30 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford 5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (13 mg, 49%) as a light yellow solid. MS ESI calculated for $C_{19}H_{23}ClF_2N_6O_3S$ $[M + H]^+$, 489.12, found 489.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 6.24 (t, *J* = 53.6 Hz, 1H), 4.98 (t, *J* = 6.8 Hz, 1H), 4.12-4.07 (m, 1H), 3.96-3.92 (m, 1H), 3.77-3.67 (m, 2H), 3.26-3.23 (m, 1H), 3.15-3.04 (m, 2H), 2.70-2.68 (m, 2H), 2.36-2.27 (m, 3H), 2.20-2.17 (m, 1H), 2.08-2.02 (m, 2H), 1.96-1.94 (m, 1H), 1.71- 1.68 (m, 1H), 0.79 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -121.40 (2F).

Example 119:

(3*S*,4*R*)-4-((5-chloro-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol

Step 1: 2,5-dichloro-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine

[00700] To a stirred mixture of 2-chloro-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (300 mg, 1.353 mmol) in DMF (3 mL) was added NCS (145mg, 1.082 mmol) in portions at 0 °C. The resulting mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (50 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (20/1) to afford 2,5-dichloro-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (230 mg, 66%) as a yellow solid. MS ESI calculated for $C_{11}H_{11}Cl_2N_3$ $[M + H]^+$, 256.03, found 256.00. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.76 (s, 1H), 6.71 (s, 1H), 2.63-2.50 (m, 2H), 2.29-2.13 (m, 3H), 1.99-1.87 (m, 1H), 1.63 (s, 3H).

Example 119:

(3*S*,4*R*)-4-((5-chloro-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-ol

[00701] A mixture of 2,5-dichloro-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (30 mg, 0.117 mmol), DIEA (91 mg, 0.702 mmol) and (3*S*,4*R*)-4-aminooxan-3-ol hydrochloride (90 mg, 0.585 mmol) in NMP (0.5 mL) was stirred for 16 h at 80 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 50% to 70%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (23.3 mg,

59%) as a yellow solid. MS ESI calculated for $C_{16}H_{21}ClN_4O_2$ [M + H]$^+$, 337.14, found 337.15. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.56 (s, 1H), 6.41 (s, 1H), 4.99 (d, *J* = 5.6 Hz, 1H), 4.12-4.08 (m, 1H), 4.02-3.96 (m, 1H), 3.75-3.66 (m, 2H), 3.53-3.46 (m, 1H), 3.27-3.22 (m, 1H), 2.63-2.49 (m, 2H), 2.22-2.11 (m, 4H), 1.97-1.90 (m, 1H), 1.75-1.65 (m, 1H), 1.59 (s, 3H).

Example 120:

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-trifluoromethanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-trifluoromethanesulfonylpiperidin-3-yl acetate

[00702] To a stirred solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (50 mg, 0.110 mmol) in EtOAc (2 mL) and sat. $NaHCO_3$ (2 mL) was added trifluoromethanesulfonyl chloride (37 mg, 0.220 mmol). The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-trifluoromethanesulfonylpiperidin-3-yl acetate (50 mg, 37%) as a light yellow solid. MS ESI calculated for $C_{21}H_{24}ClF_3N_6O_4S$ [M + H]$^+$, 549.12, found 549.30.

Example 120:

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-trifluoromethanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00703] To a stirred solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-trifluoromethanesulfonylpiperidin-3-yl acetate (40 mg, 0.073 mmol) in MeOH (2 mL) was added K_2CO_3 (30 mg, 0.219 mmol). The resulting mixture was stirred for 30 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 30% to 60%; detector, UV 254 nm to afford 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-trifluoromethanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (6 mg, 17%) as a light yellow solid. MS ESI calculated for $C_{19}H_{22}ClF_3N_6O_3S$ [M + H]$^+$, 507.11, found 507.15. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 5.04-5.03 (m, 1H), 4.11-4.08 (m, 1H), 3.96-3.93 (m, 1H), 3.81-3.75 (m, 1H), 3.71-3.67 (m, 1H), 3.23-3.19 (m, 1H), 3.05-3.00 (m, 1H), 2.73-2.68 (m, 2H), 2.36-2.30 (m, 3H), 2.28-1.95

(m, 5H), 1.76-1.71 (m, 1H), 0.79 (t, J = 7.2 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-d) δ -75.80 (3F).

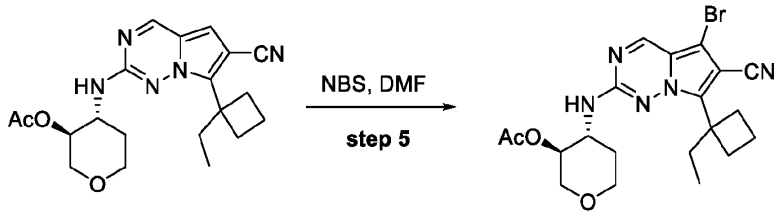
Example 121: (3*R*,4*R*)-4-((5-chloro-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)-1-(methylsulfonyl)piperidin-3-ol

Example 121: (3*R*,4*R*)-4-((5-chloro-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)-1-(methylsulfonyl)piperidin-3-ol

[00704] A mixture of 2,5-dichloro-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (30 mg, 0.117 mmol) DIEA (91 mg, 0.702 mmol) and (3*R*,4*R*)-4-amino-1-methanesulfonylpiperidin-3-ol (114 mg, 0.585 mmol) in NMP (0.5 mL) was stirred for 16 h at 100 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 50% to 70%; detector, UV 254 nm to afford (3*R*,4*R*)-4-{[5-chloro-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-ol (31.4 mg, 65%) as a yellow solid. MS ESI calculated for $C_{17}H_{24}ClN_5O_3S$ $[M + H]^+$, 414.13, found 414.25. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.56 (s, 1H), 6.41 (s, 1H), 4.91 (d, J = 6.0 Hz, 1H), 4.01-3.97 (m, 1H), 3.83-3.77 (m, 2H), 3.70-3.62 (m, 1H), 2.92-2.86 (m, 4H), 2.76-2.70 (m, 1H), 2.60-2.50 (m, 2H), 2.30-2.25 (m, 1H), 2.22-2.12 (m, 3H), 1.97-1.88 (m, 1H), 1.80-1.74 (m, 1H), 1.58 (s, 3H).

Example 122: 7-(1-Ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-5-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00705] Step 1: (3*S*,4*R*)-4-{[5-bromo-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate



[00706] To a stirred mixture of (3*S*,4*R*)-4-{[6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (95 mg, 0.24 mmol) in DMF (1 mL) was added NBS (66 mg, 0.37 mmol). The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was diluted with water (30 mL) and extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column

chromatography, eluted with PE/EtOAc (2/1) to afford (3*S*,4*R*)-4-{[5-bromo-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (100 mg, 87%) as yellow oil. MS ESI calculated for $C_{20}H_{24}BrN_5O_3$ $[M+H]^+$, 462.11, 464.11, found 462.20, 464.20.

Step 2: (3*S*,4*R*)-4-{[6-cyano-7-(1-ethylcyclobutyl)-5-(prop-1-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00707] To a stirred mixture of (3*S*,4*R*)-4-{[5-bromo-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (40 mg, 0.08 mmol), $Pd(dppf)Cl_2.CH_2Cl_2$ (7 mg, 0.01 mmol) and Cs_2CO_3 (56 mg, 0.17 mmol) in dioxane (0.4 mL) and water (0.1 mL) was added 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (29 mg, 0.17 mmol) under a nitrogen atmosphere. The resulting mixture was stirred for 2 h at 80 °C under a nitrogen atmosphere. The resulting mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (5/1) to afford (3*S*,4*R*)-4-{[6-cyano-7-(1-ethylcyclobutyl)-5-(prop-1-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (20 mg, 55%) as a yellow solid. MS ESI calculated for $C_{23}H_{29}N_5O_3$ $[M+H]^+$, 424.23, found 424.25.

Step 3: (3*S*,4*R*)-4-{[6-cyano-7-(1-ethylcyclobutyl)-5-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00708] To a stirred mixture of (3*S*,4*R*)-4-{[6-cyano-7-(1-ethylcyclobutyl)-5-(prop-1-en-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (14 mg, 0.03 mmol) and K_3PO_4 (14 mg, 0.06 mmol) in CH_3CN (1 mL) was added 2-nitrobenzenesulfonohydrazide (29 mg, 0.13 mmol). The reaction mixture was stirred for 30 min at 60 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (2/1) to afford (3*S*,4*R*)-4-{[6-cyano-7-(1-ethylcyclobutyl)-5-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (15 mg, 95%) as a yellow solid. MS ESI calculated for $C_{23}H_{31}N_5O_3$ $[M+H]^+$, 426.24, found 426.35.

Example 122:

7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-5-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00709] To a stirred mixture of (3*S*,4*R*)-4-{[6-cyano-7-(1-ethylcyclobutyl)-5-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (15 mg, 0.03 mmol) in MeOH (0.5 mL) was added K_2CO_3 (10 mg, 0.07 mmol). The resulting mixture was stirred for 1 h at room temperature under a nitrogen atmosphere. The resulting mixture was purified by reverse phase Flash

chromatography with the following conditions: C18 column; CH_3CN in water (10 mM NH_4HCO_3); Gradient: 20% to 70%; Detector: 220/254 nm to afford 7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-5-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (2.1 mg, 14%) as an off-white solid. MS ESI calculated for $C_{21}H_{29}N_5O_2$ $[M + H]^+$, 384.23, found 384.20; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 4.95 (brs, 1H), 4.11-4.06 (m, 1H), 4.01-3.97 (m, 1H), 3.69-3.65 (m, 2H), 3.53-3.46 (m, 1H), 3.37-3.33 (m, 1H), 3.27-3.21 (m, 1H), 2.75-2.67 (m, 2H), 2.41-2.36 (m, 2H), 2.23-1.92 (m, 6H), 1.46 (d, J = 6.8 Hz, 6H), 0.81 (t, J = 7.2 Hz, 3H).

Example 123:

2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/^{i}PrOH = 90/10, 1st peak)

Example 124:

2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/^{i}PrOH = 90/10, 2nd peak)

Step 1: *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00710] To a stirred solution of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (166 mg, 0.357 mmol) in dioxane (4.5 mL) were added Et_3SiH (166 mg, 1.428 mmol), $Pd(dba)_2$ (20 mg, 0.036 mmol), *t*-BuXPhos (30 mg, 0.071 mmol) and TEA (108 mg, 1.071 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 100 °C under nitrogen atmosphere. The reaction was quenched with water (30 mL. The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (110 mg, 71%) as a yellow solid. MS ESI calculated for $C_{22}H_{31}FN_6O_2$ $[M + H]^+$, 431.25; found 431.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.63 (s, 1H), 7.03 (s, 1H), 5.22 (brs, 1H), 4.66-4.47 (m, 1H), 4.08-3.98 (m, 2H), 3.85-3.74 (m, 1H), 3.47-3.18 (m, 3H), 2.40-2.25 (m, 2H), 1.60-1.53 (m, 1H), 1.50 (s, 9H), 1.35-1.32 (m, 3H), 1.06 (d, J = 6.8 Hz, 3H), 0.80 (d, J = 6.8 Hz, 3H).

Step 2: *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-5-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00711] A solution of *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (100 mg, 0.232 mmol) and I_2 (235 mg, 0.928 mmol) in DMF (2 mL) was stirred for 2 h at room temperature. The reaction was quenched with sat. $Na_2S_2O_3$ (10 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (4 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (2/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-5-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (100 mg, 77%) as a yellow solid. MS ESI calculated for $C_{22}H_{30}FIN_6O_2$ $[M + H]^+$, 557.15; found 557.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.49 (s, 1H), 5.24 (brs, 1H), 4.63-4.46 (m, 1H), 4.15-4.12 (m, 1H), 4.05-3.98 (m, 1H), 3.87-3.76 (m, 1H), 3.38-3.20 (m, 3H), 2.36-2.19 (m, 2H), 1.57-1.47 (m, 13H), 1.06 (d, J = 6.8 Hz, 3H), 0.80 (d, J = 6.8 Hz, 3H).

Step 3: *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-7-(3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00712] To a stirred solution of *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-5-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (90 mg, 0.162 mmol) and methyl 2,2-difluoro-2-sulfoacetate (155 mg, 0.810 mmol) in DMF (2 mL) were added CuI (62 mg, 0.324 mmol) and KF (28 mg, 0.486 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 80 °C under nitrogen atmosphere. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-7-(3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (60 mg, 74%) as colorless oil. MS ESI calculated for $C_{23}H_{30}F_4N_6O_2$ $[M + H]^+$, 499.24; found 499.35.

Step 4: 2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00713] To a stirred solution of *tert*-butyl (3*R*,4*R*)-4-{[6-cyano-7-(3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (60 mg, 0.120 mmol) in DCM (1 mL) was added HCl (gas) in 1,4-dioxane (1 mL). The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure. To this was added sat. $NaHCO_3$ (1 mL) and methanesulfonic anhydride (60

mg, 0.345 mmol) in EtOAc (1 mL) at 0 °C. The resulting mixture was stirred for additional 1 h at room temperature. The resulting mixture diluted with water (10 mL) and was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by Prep-TLC with PE/EtOAc (2/1) to afford 2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (40 mg, 73%) as colorless oil. MS ESI calculated for $C_{19}H_{24}F_4N_6O_2S$ $[M + H]^+$, 477.16; found 477.20.

Example 123:

2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/^{i}PrOH = 90/10, 1st peak)

Example 124:

2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/^{i}PrOH = 90/10, 2nd peak)

[00714] 2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (40 mg) was purified by Prep-Chiral-HPLC with the following conditions: Column: CHIRALPAK AD-H, 2 x 25 cm, 5 μm; Mobile Phase A: Hexane, Mobile Phase B: *i*-PrOH; Flow rate: 20 mL/min; Gradient: A:B = 90:10; Wave Length: 254/220 nm.

[00715] RT_1: 21.28 min to afford 2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/^{i}PrOH = 90/10, 1st peak) (10 mg, 26%) as a white solid. MS ESI calculated for $C_{19}H_{24}F_4N_6O_2S$ $[M + H]^+$, 477.16; found 477.25. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 1H), 7.98 (d, J = 7.6 Hz, 1H), 4.80-4.66 (m, 1H), 4.04-3.97 (m, 1H), 3.74-3.66 (m, 1H), 3.53-3.46 (m, 1H), 3.30-3.20 (m, 2H), 3.14-3.09 (m, 1H), 2.97 (s, 3H), 2.22-2.11 (m, 2H), 1.75-1.70 (m, 1H), 1.45-1.41 (m, 3H), 1.03-0.99 (m, 3H), 0.78-0.74 (m, 3H). ^{19}F NMR (377 MHz, DMSO-d_6) δ -53.65 (3F), -186.75 (1F).

[00716] RT_2: 26.21 min to afford 2-{[(3*R*,4*R*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined)

(CHIRALPAK AD-H, Hexane/^{i}PrOH = 90/10, 2nd peak) (10 mg, 26%) as a white solid. MS ESI calculated for $C_{19}H_{24}F_4N_6O_2S$ [M + H]$^+$, 477.16; found 477.35. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.14 (s, 1H), 7.99 (brs, 1H), 4.83-4.70 (m, 1H), 4.04-3.98 (m, 1H), 3.77-3.70 (m, 1H), 3.52-3.46 (m, 1H), 3.32-3.20 (m, 2H), 3.13-3.07 (m, 1H), 2.97 (s, 3H), 2.22-2.12 (m, 2H), 1.70-1.65 (m, 1H), 1.45-1.41 (m, 3H), 1.02-0.99 (m, 3H), 0.79-0.76 (m, 3H). ^{19}F NMR (377 MHz, DMSO-d_6) δ -53.65 (3F), -186.54 (1F).

Example 125:

5-chloro-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IE, Hexane/MeOH/EtOH = 50/25/25, 2nd peak)

Example 126:

5-chloro-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IE, Hexane/MeOH/EtOH = 50/25/25, 1st peak)

Step 1: *tert*-butyl (3*S*,4*R*)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate

[00717] To a stirred solution of 2,5-dichloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (100 mg, 0.26 mmol) and *tert*-butyl (3*S*,4*R*)-4-amino-3-hydroxypiperidine-1-carboxylate (281 mg, 1.30 mmol) in NMP (1.00 mL, 10.35 mmol) was added DIEA (202 mg, 1.56 mmol). The reaction mixture was stirred for 16 h at 100 °C.

[00718] The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 50% to 80%; detector, UV 254 nm to afford *tert*-butyl (3*S*,4*R*)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (120 mg, 82%) as a light yellow solid. MS ESI calculated for $C_{21}H_{31}ClIN_5O_3$ [M + H]$^+$, 564.12, found 564.20.

Step 2: *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00719] To a stirred solution of *tert*-butyl (3*S*,4*R*)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (120 mg, 0.21 mmol) and acetic anhydride (65 mg, 0.64 mmol) in DCM (2 mL) was added TEA (65 mg, 0.64 mmol). The resulting mixture was stirred for 16 h at 50 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-{[5-

chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (110 mg, 85%) as a light yellow solid. MS ESI calculated for $C_{23}H_{33}ClIN_5O_4$ [M + H]$^+$, 606.13, found 606.25.

Step 3: *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00720] To a stirred solution of *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (100 mg, 0.17 mmol) and $Pd(PPh_3)_4$ (19 mg, 0.02 mmol) in DMA (1 mL) was added $Zn(CN)_2$ (12 mg, 0.10 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for additional 2 h at 120 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 60% to 70%; detector, UV 254 nm to afford *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (60 mg, 72%) as a light yellow solid. MS ESI calculated for $C_{24}H_{33}ClN_6O_4$ [M + H]$^+$, 505.23, found 505.25. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.66 (s, 1H), 5.15-5.06 (m, 2H), 4.50-4.43 (m, 1H), 4.37-4.29 (m, 1H), 4.05-3.97 (m, 1H), 3.30-3.22 (m, 1H), 3.07-2.84 (m, 2H), 2.27-2.20 (m, 1H), 2.11 (s, 3H), 1.93-1.88 (m, 2H), 1.49-1.45 (m, 12H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H).

Step 4: (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate

[00721] To a stirred solution of *tert*-butyl (3*S*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (60 mg, 0.12 mmol) in DCM (6 mL) was added HCl (gas) in 1,4-dioxane (6 mL, 197.48 mmol) dropwise at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure. To this were added methanesulfonic anhydride (58 mg, 0.33 mmol), EtOAc (0.5 mL) and sat. $NaHCO_3$ (0.5 mL). The resulting mixture was stirred for additional 2 h at room temperature. The resulting mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (50 mg, 46%) as a light yellow solid. MS ESI calculated for $C_{20}H_{27}ClN_6O_4S$ [M + H]$^+$, 483.15, found 483.15.

Step 5: 5-chloro-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00722] To a stirred solution of (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (50 mg, 0.10 mmol) in MeOH (0.5 mL) was added K_2CO_3 (29 mg, 0.21 mmol) at room temperature. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford to afford 5-chloro-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (40 mg, 88%) as a light yellow solid. MS ESI calculated for $C_{18}H_{25}ClN_6O_3S[M + H]^+$, 441.14, found 441.10.

Example 125:

5-chloro-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IE, Hexane/MeOH/EtOH = 50/25/25, 2nd peak)

Example 126:

5-chloro-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IE, Hexane/MeOH/EtOH = 50/25/25, 1st peak)

[00723] 5-chloro-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (40 mg,) was purified by Prep-Chiral-HPLC with the following conditions: Column: CHIRALPAK IE, 2 x 25 cm, 5 μm; Mobile Phase A: Hexane, Mobile Phase B: MeOH/EtOH (1/1); Flow rate: 20 mL/min; Gradient: A:B = 50:50; Wave Length: 254/220 nm.

[00724] RT_1: 9.26 min to afford 5-chloro-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IE, Hexane/MeOH/EtOH = 50/25/25, 1st peak) (10 mg, 25%) as a light yellow solid. MS ESI calculated for $C_{18}H_{25}ClN_6O_3S$ $[M + H]^+$, 441.14, found 441.35. ^1H NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H), 7.12 (d, J = 7.2 Hz, 1H), 5.16 (, J = 4.4 Hz, 1H) 4.05-4.02 (m, 1H), 3.79-3.75 (m, 1H), 3.57-3.51 (m, 2H), 3.33-3.23 (m, 1H), 3.10-2.93 (m, 5H), 2.15-2.10 (m, 1H), 2.00-1.96 (m, 1H), 1.74-1.70 (m, 1H), 1.42-1.39 (m, 3H), 1.02-0.98 (m, 3H), 0.80-0.76 (m, 3H).

[00725] RT_2: 11.03 min to afford 5-chloro-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IE, Hexane/MeOH/EtOH = 50/25/25, 2nd peak) (13.3 mg, 33%) as a light yellow solid. MS ESI calculated for $C_{18}H_{25}ClN_6O_3S$ $[M + H]^+$, 441.14, found 441.30. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 5.52 (brs, 1H), 4.16-4.14 (m, 1H), 3.98-3.88 (m, 3H), 3.27-3.23 (m, 1H), 3.15-3.11 (m, 1H), 2.99-2.93 (m, 4H), 2.25-2.20 (m, 1H), 2.10-1.91 (m, 2H), 1.48-1.45 (m, 3H), 1.08-1.05 (m, 3H), 0.83-0.81 (m, 3H).

Example 127:

5-chloro-2-{[(3*R*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IF, Hexane/MeOH/DCM = 60/20/20, 1st peak)

Example 128:

5-chloro-2-{[(3*R*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IF, Hexane/MeOH/DCM = 60/20/20, 2nd peak)

Step 1: *tert*-butyl (3*R*,4*S*)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate

[00726] To a stirred solution of 2,5-dichloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (100 mg, 0.260 mmol) and *tert*-butyl (3*R*,4*S*)-4-amino-3-hydroxypiperidine-1-carboxylate (113 mg, 0.520 mmol) in NMP (1 mL) was added DIEA (135 mg, 1.040 mmol). The resulting mixture was stirred for 16 h at 80 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 40% to 50%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*S*)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (128 mg, 87%) as a yellow solid. MS ESI calculated for $C_{21}H_{31}ClIN_5O_3$ $[M + H]^+$, 564.12, found 564.25.

[00727] Step 2: *tert*-butyl (3*R*,4*S*)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00728] To a stirred solution of *tert*-butyl (3*R*,4*S*)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (125 mg, 0.222 mmol) and TEA (90 mg, 0.888 mmol) in DCM (1 mL) was added Ac_2O (34 mg, 0.333 mmol). The resulting mixture was stirred for 16 h at 50 °C. The resulting mixture was concentrated

under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*S*)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (110 mg, 82%) as a yellow solid. MS ESI calculated for $C_{23}H_{33}ClIN_5O_4$ $[M + H]^+$, 606.13, found 606.20.

Step 3: *tert*-butyl (3*R*,4*S*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00729] To a stirred solution of *tert*-butyl (3*R*,4*S*)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (95 mg, 0.157 mmol) and $Zn(CN)_2$ (18 mg, 0.157 mmol) in DMF (1 mL) was added $Pd(PPh_3)_4$ (18 mg, 0.016 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 120 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% $NH_3.H_2O$), 10% to 50%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*S*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (75 mg, 95%) as a yellow solid. MS ESI calculated for $C_{24}H_{33}ClN_6O_4$ $[M + H]^+$, 505.23, found 505.30.

Step 4: (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride

[00730] A solution of *tert*-butyl (3*R*,4*S*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (80 mg, 0.204 mmol) and HCl (gas) in 1,4-dioxane (2 mL) in DCM (2 mL) was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (70 mg, 85%) as a yellow solid. MS ESI calculated for $C_{19}H_{26}Cl_2N_6O_2$ $[M - Cl]^+$, 405.17, found 405.20.

Step 5: (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate

[00731] A solution of (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetateydrochloride (70 mg, 0.173 mmol) and methanesulfonic anhydride (60 mg, 0.346 mmol) in EtOAc (1 mL) was added sat. $NaHCO_3$ (1 mL). The reaction mixture was stirred for 1 h at room temperature. The resulting mixture was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (75 mg, 90%) as a yellow solid. MS ESI calculated for $C_{20}H_{27}ClN_6O_4S$ $[M + H]^+$, 482.15, found 483.25.

Step 6: 5-chloro-2-{[(3*R*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00732] A solution of (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (85 mg, 0.176 mmol) and K_2CO_3 (73 mg, 0.528 mmol) in MeOH (2 mL) was stirred for 30 min at room temperature. The resulting mixture was filtered, the filtrate was concentrated under reduced pressure to afford 5-chloro-2-{[(3*R*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (75 mg, crude) as a yellow solid. MS ESI calculated for $C_{18}H_{25}ClN_6O_3S$ $[M + H]^+$, 441.05, found 441.15.

Example 127:

5-chloro-2-{[(3*R*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IF, Hexane/MeOH/DCM = 60/20/20, 1st peak)

Example 128:

5-chloro-2-{[(3*R*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IF, Hexane/MeOH/DCM = 60/20/20, 2nd peak)

[00733] 5-chloro-2-{[(3*R*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (35 mg) was purified by Prep-Chiral-HPLC with the following conditions: Column: CHIRALPAK IF, 2 x 25 cm, 5 μm; Mobile Phase A: Hexane, Mobile Phase B: MeOH/DCM (1/1); Flow rate: 20 mL/min; Gradient: A:B = 60:40; Wave Length: 254/220 nm.

[00734] RT_1: 9.35 min to afford 5-chloro-2-{[(3*R*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IF, Hexane/MeOH/DCM = 60/20/20, 1st peak) (9.7 mg, 27.63%) as a white solid. MS ESI calculated for $C_{18}H_{25}ClN_6O_3S$ $[M + H]^+$, 441.05, found 441.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 5.51 (brs, 1H), 4.16-4.14 (m, 1H), 3.97-3.88 (m, 3H), 3.28-3.20 (m, 1H), 3.15-3.11 (m, 1H), 3.00-2.94 (m, 4H), 2.26-2.19 (m, 1H), 2.08-1.91 (m, 2H), 1.46 (d, J = 7.2 Hz, 3H), 1.07 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 7.2 Hz, 3H).

[00735] RT_2: 12.41 min to afford 5-chloro-2-{[(3*R*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined)

(CHIRALPAK IF, Hexane/MeOH/DCM = 60/20/20, 2nd peak) (9.8 mg, 27.94%) as a white solid. MS ESI calculated for C18H25ClN6O3S [M + H]+, 441.14, found 441.10. 1H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 5.67 (brs, 1H), 4.16-4.14 (m, 1H), 3.97-3.87 (m, 3H), 3.30-3.22 (m, 1H), 3.16-3.12 (m, 1H), 3.00-2.93 (m, 4H), 2.30-2.05 (m, 2H), 1.99-1.90 (m, 1H), 1.46 (d, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 7.2 Hz, 3H).

Example 129:

5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IE, Hexane/EtOH/DCM = 85/7.5/7.5, 1st peak)

Example 130:

5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IE, Hexane/EtOH/DCM = 85/7.5/7.5, 2nd peak)

Step 1: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-difluoromethanesulfonylpiperidin-3-yl acetate

[00736] To a stirred mixture of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (40 mg, 0.091 mmol) and sat. $NaHCO_3$ (0.25 mL) in EtOAc (1 mL) was added difluoromethanesulfonyl chloride (27 mg, 0.182 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature. The resulting mixture was diluted with water (5 mL). The resulting mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (3 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-difluoromethanesulfonylpiperidin-3-yl acetate (20 mg, 42%) as a light yellow solid. MS ESI calculated for $C_{20}H_{25}ClF_2N_6O_4S$ [M + H]+, 519.13, found 519.45.

Example 129:

5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IE, Hexane/EtOH/DCM = 85/7.5/7.5, 1st peak)

Example 130:

5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IE, Hexane/EtOH/DCM = 85/7.5/7.5, 2nd peak)

[00737] To a stirred mixture of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-difluoromethanesulfonylpiperidin-3-yl acetate (20 mg, 0.039 mmol) in MeOH (1 mL) was added K_2CO_3 (10 mg, 0.078 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 20% to 60%; detector, UV 254 nm. The crude product was purified by Prep-Chiral-HPLC with the following conditions: Column: CHIRALPAK IE, 2 x 25 cm, 5 μm; Mobile Phase A: Hexane, Mobile Phase B: EtOH/DCM (1/1); Flow rate: 20 mL/min; Gradient: A:B = 85:15; Wave Length: 254/220 nm.

[00738] RT_1: 23.72 min to afford 5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IE, Hexane/EtOH/DCM = 85/7.5/7.5, 1st peak) (2.9 mg, 15%) as a light yellow solid. MS ESI calculated for $C_{18}H_{23}ClF_2N_6O_3S$ $[M + H]^+$, 477.12, found 477.35. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 6.26 (t, *J* = 53.6 Hz, 1H), 5.24 (brs, 1H), 4.15-4.11 (m, 1H), 4.00-3.95 (m, 1H), 3.82-3.79 (m, 2H), 3.32-3.22 (m, 2H), 3.17-3.10 (m, 1H), 2.33-2.19 (m, 2H), 1.81-1.72 (m, 1H), 1.47 (d, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-d) δ -121.40 (1F).

[00739] RT_2: 27.39 min to afford 5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK IE, Hexane/EtOH/DCM = 85/7.5/7.5, 2nd peak) (2.6 mg, 14%) as a light yellow solid. MS ESI calculated for $C_{18}H_{23}ClF_2N_6O_3S$ $[M + H]^+$, 477.12, found 477.35. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 6.26 (t, *J* = 53.6 Hz, 1H), 5.35 (brs, 1H), 4.16-4.12 (m, 1H), 4.00-3.96 (m, 1H), 3.81-3.78 (m, 2H), 3.31-3.22 (m, 2H), 3.15-3.09 (m, 1H), 2.35-2.19 (m, 1H), 1.77-1.73 (m, 1H), 1.47 (d, *J* = 7.2 Hz, 3H), 1.07 (d, *J* = 6.4 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-d) δ -121.40 (1F).

Example 131:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer,

absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 95/5, 1st peak)

Example 132:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 95/5, 2nd peak)

Step 1: 5-chloro-2-{[(3*R*,4*R*)-3-hydroxypiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00740] To a stirred mixture of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (40 mg, 0.091 mmol) in MeOH (1 mL) was added K_2CO_3 (25 mg, 0.182 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 20% to 60%; detector, UV 254 nm to afford 5-chloro-2-{[(3*R*,4*R*)-3-hydroxypiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (25 mg, 76%) as a light yellow solid. MS ESI calculated for $C_{17}H_{23}ClN_6O$ $[M + H]^+$, 363.16, found 363.25.

Example 131:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 95/5, 1st peak)

Example 132:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 95/5, 2nd peak)

[00741] To a stirred mixture of 5-chloro-2-{[(3*R*,4*R*)-3-hydroxypiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (30 mg, 0.083 mmol) and DIEA (53 mg, 0.415 mmol) in DCM (1 mL) was added TFAA (86 mg, 0.415 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 20% to 60%; detector, UV 254 nm. The crude product was purified with Prep-Chiral-HPLC (Column: CHIRALPAK AD-H, 2 x 25 cm,

5 μm; Mobile Phase A: Hexane, Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: A:B = 95:5; Wave Length: 254/220 nm.

[00742] RT_1: 26.18 min to afford 5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 95/5, 1st peak) (1.6 mg, 4%) as a light yellow solid. MS ESI calculated for $C_{19}H_{22}ClF_3N_6O_2$ $[M + H]^+$, 459.14, found 459.35; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 5.20-5.16 (m, 1H), 4.60-4.54 (m, 1H), 4.20-3.96 (m, 1H), 3.88-3.68 (m, 2H), 3.35-3.12 (m, 2H), 2.99-2.92 (m, 1H), 2.33-2.13 (m, 2H), 1.72-1.67 (m, 1H), 1.47-1.44 (m, 3H), 1.08-1.05 (m, 3H), 0.87-0.84 (m, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -68.92 (3F).

[00743] RT_2: 32.32 min to afford 5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 95/5, 2nd peak) (1.2 mg, 3%) as a light yellow solid. MS ESI calculated for $C_{19}H_{22}ClF_3N_6O_2$ $[M + H]^+$, 459.14, found 459.30. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 5.07-5.02 (m, 1H), 4.63-4.54 (m, 1H), 4.20-3.99 (m, 1H), 3.87-3.67 (m, 2H), 3.35-3.11 (m, 2H), 3.00-2.93 (m, 1H), 2.34-2.17 (m, 2H), 1.48-1.44 (m, 4H), 1.07-1.03 (m, 3H), 0.81-0.78 (m, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -68.94 (3F).

Example 133:

5-chloro-2-(((3R,4R)-3-hydroxy-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(1-methylcyclobutyl)pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile

Step 1: 2,5-dichloro-6-iodo-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine

[00744] A mixture of 2,5-dichloro-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (750 mg, 2.928 mmol) and I_2 (2.97 g, 11.712 mmol) in DMF (8 mL) was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. NaS_2O_3 (aq.) (50 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (10/1) to afford 2,5-dichloro-6-iodo-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (1.08 g, 96%) as a yellow solid. MS ESI calculated for $C_{11}H_{10}Cl_2IN_3$ $[M + H]^+$, 381.93, found 381.90. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.72 (s, 1H), 2.76-2.68 (m, 2H), 2.47-2.40 (m, 2H), 2.29-2.19 (m, 1H), 1.90-1.82 (m, 1H), 1.60 (s, 3H).

Step 2: *tert*-butyl (3*R*,4*R*)-4-((5-chloro-6-iodo-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)-3-hydroxypiperidine-1-carboxylate

[00745] A mixture of 2,5-dichloro-6-iodo-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (500 mg, 1.309 mmol) DIEA (507 mg, 3.927 mmol) and *tert*-butyl (3*R*,4*R*)-4-amino-3-hydroxypiperidine-1-carboxylate (566 mg, 2.618 mmol) in NMP (8 mL) was stirred for 16 h at 120 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 50% to 70%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-iodo-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (530 mg, 72%) as a yellow solid. MS ESI calculated for $C_{21}H_{29}ClIN_5O_3$ $[M + H]^+$, 562.10, found 562.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.53 (s, 1H), 4.90 (d, *J* = 6.4 Hz, 1H), 4.35-4.24 (m, 1H), 4.14-4.11 (m, 1H), 3.71-3.54 (m, 3H), 2.91-2.85 (m, 1H), 2.78-2.67 (m, 2H), 2.41-2.33 (m, 2H), 2.27-2.09 (m, 2H), 1.91-1.81 (m, 1H), 1.56 (s, 3H), 1.55-1.48 (m, 10H).

Step 3: *tert*-butyl (3*R*,4*R*)-3-acetoxy-4-((5-chloro-6-iodo-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)piperidine-1-carboxylate

[00746] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-iodo-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (530 mg, 0.943 mmol) and TEA (286 mg, 2.829 mmol) in DCM (5 mL) was added Ac_2O (178 uL, 1.886 mmol). The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (500 mg, 88%) as a yellow solid. MS ESI calculated for $C_{23}H_{31}ClIN_5O_4$ $[M + H]^+$, 604.11, found 604.15.

Step 4: *tert*-butyl (3*R*,4*R*)-3-acetoxy-4-((5-chloro-6-cyano-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)piperidine-1-carboxylate

[00747] A mixture of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (440 mg, 0.729 mmol), $Pd(PPh_3)_4$ (95 mg, 0.083 mmol) and $Zn(CN)_2$ (58 mg, 0.497 mmol) in DMF (5 mL) was stirred for 3 h at 120 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 60% to 80%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate as a yellow solid. MS ESI calculated for $C_{24}H_{31}ClN_6O_4$ $[M + H]^+$, 503.21, found 503.40.

Step 5: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride

[00748] A mixture of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (450 mg, 0.895 mmol) and HCl (gas) in 1,4-dioxane (4.5 mL) in DCM (4.5 mL) was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (380 mg, 97%) as a yellow green solid. MS ESI calculated for $C_{19}H_{24}Cl_2N_6O_2$ $[M - Cl]^+$, 403.16, found 403.20.

Example 133:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00749] To a solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (60 mg, 0.137 mmol) in water (1.5 mL) and EtOAc (1.5 mL) was added $NaHCO_3$ (46 mg, 0.548 mmol) and methanesulfonic anhydride (28 mg, 0.164 mmol). The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was dissolved in MeOH (1 mL). To this was added K_2CO_3 (57 mg, 0.411 mmol). The resulting mixture was stirred for additional 1 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 50%; detector, UV 254 nm to afford 5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (15.9 mg, 26%) as a yellow solid. MS ESI calculated for $C_{18}H_{23}ClN_6O_3S$ $[M + H]^+$, 439.12, found 439.25. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 5.07 (d, *J* = 6.4 Hz, 1H), 3.98-3.94 (m, 1H), 3.86-3.77 (m, 2H), 3.70-3.62 (m, 1H), 2.94-2.88 (m, 4H), 2.80-2.72 (m, 3H), 2.33-2.19 (m, 4H), 1.99-1.92 (m, 1H), 1.78-1.70 (m, 1H), 1.62 (s, 3H).

Example 134:

5-chloro-2-(((3*R*,4*R*)-1-((difluoromethyl)sulfonyl)-3-hydroxypiperidin-4-yl)amino)-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*R*,4*R*)-4-((5-chloro-6-cyano-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)-1-((difluoromethyl)sulfonyl)piperidin-3-yl acetate

[00750] To a stirred solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (60 mg, 0.137 mmol) in EtOAc (2 mL) were added sat. $NaHCO_3$ (1 mL) and difluoromethanesulfonyl chloride (36 mg, 0.239

mmol). The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was diluted with water (10 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-difluoromethanesulfonylpiperidin-3-yl acetate (36 mg, 51%) as light yellow oil. MS ESI calculated for $C_{20}H_{23}ClF_2N_6O_4S$ [M + H]$^+$, 517.12, found 517.15.

Example 134:

5-chloro-2-(((3*R*,4*R*)-1-((difluoromethyl)sulfonyl)-3-hydroxypiperidin-4-yl)amino)-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00751] A mixture of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-difluoromethanesulfonylpiperidin-3-yl acetate (30 mg, 0.058 mmol) and K_2CO_3 (24 mg, 0.174 mmol) in MeOH (1 mL) was stirred for 1 h at room temperature. The resulting mixture was filtered, the filter cake was washed with MeOH (3 x 6 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford 5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (11.9 mg, 43%) as a yellow green solid. MS ESI calculated for $C_{18}H_{21}ClF_2N_6O_3S$ [M + H]$^+$, 475.11, found 475.30. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 6.26 (t, *J* = 53.6 Hz, 1H), 5.09 (d, *J* = 6.4 Hz, 1H), 4.14-4.09 (m, 1H), 3.98-3.94 (m, 1H), 3.82-3.71 (m, 2H), 3.29-3.22 (m, 1H), 3.11-3.05 (m, 1H), 2.78-2.71 (m, 2H), 2.34-2.24 (m, 4H), 2.01-1.93 (m, 1H), 1.75-1.69 (m, 1H), 1.62 (s, 3H).

Example 135:

5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-((trifluoromethyl)sulfonyl)piperidin-4-yl)amino)-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-trifluoromethanesulfonylpiperidin-3-yl acetate

[00752] To a mixture of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (50 mg, 0.114 mmol) and EtOAc (2.5 mL) were added sat. $NaHCO_3$ (1 mL) and trifluoromethanesulfonyl chloride (23 mg, 0.137 mmol). The resulting mixture was stirred for 40 min at room temperature. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous

Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-trifluoromethanesulfonylpiperidin-3-yl acetate (34 mg, 56%) as an off-white solid. MS ESI calculated for $C_{20}H_{22}ClF_3N_6O_4S$ [M + H]$^+$, 535.11, found 535.15.

Example 135:

5-chloro-2-(((3*R*,4*R*)-3-hydroxy-1-((trifluoromethyl)sulfonyl)piperidin-4-yl)amino)-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00753] A mixture of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-difluoromethanesulfonylpiperidin-3-yl acetate (30 mg, 0.058 mmol) and K_2CO_3 (24 mg, 0.174 mmol) in MeOH (1 mL) was stirred for 1 h at room temperature. The resulting mixture was filtered, the filter cake was washed with MeOH (3 x 6 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford 5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (11.9 mg, 43.13%) as a yellow green solid. MS ESI calculated for $C_{18}H_{20}ClF_3N_6O_3S$ [M + H]$^+$, 493.10, found 493.30. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 5.12 (brs, 1H), 4.13-4.10 (m, 1H), 3.99-3.95 (m, 1H), 3.84-3.71 (m, 2H), 3.25-3.21 (m, 1H), 3.07-3.03 (m, 1H), 2.77-3.71 (m, 2H), 2.36-2.28 (m, 4H), 2.06-1.95 (m, 1H), 1.78-1.72 (m, 1H), 1.68 (s, 3H).

Example 136:

(3*S*,4*R*)-4-[(7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol

Step 1: 5-(3,3,3-trifluoroprop-1-en-2-yl)pyridin-2-amine

[00754] To a solution of 5-bromopyridin-2-amine (50 g, 288.996 mmol) and 4,4,6-trimethyl-2-(3,3,3-trifluoroprop-1-en-2-yl)-1,3,2-dioxaborinane (64.16 g, 288.996 mmol) in dioxane (500 mL) and water (100 mL) were added Cs_2CO_3 (188.32 g, 577.992 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (23.54 g, 28.900 mmol). The reaction mixture was stirred for 5 h at 85°C under a nitrogen atmosphere. The resulting mixture was allowed to cool down to room temperature, then filtered. The filter cake was washed with EtOAc (3 x 500 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 5-(3,3,3-trifluoroprop-1-en-2-yl)pyridin-2-amine (48 g, 88%) as yellow oil. MS ESI calculated for $C_8H_7F_3N_2$ [M + H]$^+$, 189.06 found 189.10. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 (d, *J* = 2.4 Hz, 1H), 7.56 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.53 (d, *J* = 8.8 Hz, 1H), 5.88 (q, *J*

= 1.6 Hz, 1H), 5.70 (q, *J* = 1.6 Hz, 1H), 4.68 (br, 2H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -65.20.

Step 2: 5-(1,1,1-trifluoropropan-2-yl)pyridin-2-amine

[00755] To a solution of 5-(3,3,3-trifluoroprop-1-en-2-yl)pyridin-2-amine (48 g, 255.112 mmol) in MeOH (500 mL) was added Pd/C (10%, 9.23g). The mixture was hydrogenated for 4 h at room temperature under 2 atm hydrogen atmosphere. The resulting mixture was filtered, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 5-(1,1,1-trifluoropropan-2-yl)pyridin-2-amine (40 g, 82%) as brown oil. MS ESI calculated for $C_8H_9F_3N_2$ $[M + H]^+$, 191.07 found 190.95. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (d, *J* = 2.4 Hz, 1H), 7.44 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.54 (dd, *J* = 8.4 Hz, 1H), 4.48 (br, 2H), 3.36-3.28 (m, 1H), 1.49 (d, *J* = 7.2 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -72.12.

Step 3: 2-bromo-5-(1,1,1-trifluoropropan-2-yl)pyridine

[00756] To a stirred solution of 5-(1,1,1-trifluoropropan-2-yl)pyridin-2-amine (45 g, 236.632 mmolv) in HBr (300 mL, 40% in water) was added Br_2 (58.56 mL, 1142.933 mmol) dropwise at -20 °C. The resulting mixture was stirred for 1.5 h at -20°C. To this was added $NaNO_2$ (76.57 g, 1109.804 mmol) in water (450 mL) dropwise at -20 °C. The resulting mixture was stirred for additional 1 h at 10~20 °C. The mixture was allowed to cool down to -20°C. The reaction was quenched with NaOH (300.12 g, 7503.601 mmol) in water (450 mL) at -20 °C. The resulting mixture was extracted with EtOAc (3 x 500 L). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (8/1) to afford 2-bromo-5-(1,1,1-trifluoropropan-2-yl)pyridine (42 g, 70%) as brown oil. MS ESI calculated for $C_8H_7BrF_3N$ $[M + H]^+$, 253.97, 255.97 found 253.90, 255.90. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.34 (d, *J* = 2.4 Hz, 1H), 7.57-7.51 (m, 2H), 3.54-3.41 (m, 1H), 1.55 (d, *J* = 7.2 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -71.65.

Step 4: 2-bromo-5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridine & 2-bromo-5-[(2*R*)-1,1,1-trifluoropropan-2-yl]pyridine

[00757] 2-bromo-5-(1,1,1-trifluoropropan-2-yl)pyridine (60 g) was resolved by Prep-Chiral-HPLC with the following conditions: Column: CHIRAL ART Cellulose-SB, 7*25 cm, 10 μm; Mobile Phase A: hexane, Mobile Phase B: EtOH; Flow rate: 200 mL/min; Gradient: A:B = 90:10; Wave Length: 220 nm.

[00758] RT_1: 6.0 min to afford 2-bromo-5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridine (29.4 g, 49%) as a yellow oil.

[00759] RT_2: 8.4 min to afford 2-bromo-5-[(2*R*)-1,1,1-trifluoropropan-2-yl]pyridine (27.4 g, 45.67%) as a yellow oil.

Step 5: (3*S*,4*R*)-4-[(7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate

[00760] To a solution of (3*S*,4*R*)-4-({7-bromopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (150 mg, 0.422 mmol) in 1,4-dioxane (4 mL) were added bis(pinacolato)diboron (214 mg, 0.844 mmol), PPh_3 (22 mg, 0.084 mmol), $Pd(PPh_3)_2Cl_2$ (30 mg, 0.042 mmol) and KOAc (124 mg, 1.266 mmol). The reaction mixture was stirred for 16 h at 100 °C under nitrogen atmosphere. To this were added 2-bromo-5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridine (193 mg, 0.760 mmol), $Pd(dppf)Cl_2CH_2Cl_2$ (34 mg, 0.042 mmol) and Cs_2CO_3 (413 mg, 1.266 mmol) in water (0.8 mL) at room temperature. The resulting mixture was stirred for additional 2 h at 100 °C under nitrogen atmosphere. The reaction was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with (2 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-[(7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate (110 mg, 57%) as yellow oil. MS ESI calculated for $C_{21}H_{22}F_3N_5O_3$ $[M + H]^+$, 450.17, found 450.20.

Example 136:

(3*S*,4*R*)-4-[(7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol

[00761] A solution of (3*S*,4*R*)-4-[(7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate (103 mg, 0.229 mmol) and K_2CO_3 (95 mg, 0.687 mmol) in MeOH (2 mL) was stirred for 30 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford (3*S*,4*R*)-4-[(7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol (72.6 mg, 77%) as a light yellow solid. MS ESI calculated for $C_{19}H_{20}F_3N_5O_2$ $[M + H]^+$, 408.16; found 408.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.76-8.73 (m, 2H), 8.57-8.53 (m, 1H), 7.87-7.81 (m, 1H), 7.44 (d, *J* = 4.8 Hz, 1H), 6.87 (d, *J* = 4.8 Hz, 1H), 4.27-4.22 (m, 1H), 4.16-4.12 (m, 1H), 4.05-4.00 (m, 1H), 3.93-3.87 (m, 1H), 3.78-3.73 (m, 1H), 3.58-3.52 (m, 2H), 3.33-3.28 (m, 1H), 2.22-1.18 (m, 1H), 1.79-1.75 (m, 1H), 1.62 (d, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, Chloroform -*d*) δ -71.37 (3F).

Example 137:

(3*S*,4*R*)-4-[(7-{5-[(2*R*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol

Step 1: (3*S*,4*R*)-4-[(7-{5-[(2*R*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate

[00762] To a solution of (3*S*,4*R*)-4-({7-bromopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (150 mg, 0.422 mmol) in dioxane (3 mL) were added bis(pinacolato)diboron (214 mg, 0.844 mmol), PPh_3 (22 mg, 0.084 mmol), $Pd(PPh_3)_2Cl_2$ (30 mg, 0.042 mmol) and KOAc (124 mg, 1.266 mmol). The reaction mixture was stirred for 16 h at 100°C under a nitrogen atmosphere. To this were added 2-bromo-5-[(2*R*)-1,1,1-trifluoropropan-2-yl]pyridine (160 mg, 0.633 mmol), $Pd(dppf)Cl_2$ (34 mg, 0.042 mmol) and Cs_2CO_3 (412 mg, 1.266 mmol) in dioxane (3 mL). The resulting mixture was stirred for additional 2 h at 100 °C under nitrogen atmosphere. The reaction was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-[(7-{5-[(2*R*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate (90 mg, 47%) as yellow oil. MS ESI calculated for $C_{21}H_{22}F_3N_5O_3$ $[M + H]^+$, 450.17; found 450.20.

Example 137:

(3*S*,4*R*)-4-[(7-{5-[(2*R*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol

[00763] A solution of (3*S*,4*R*)-4-[(7-{5-[(2*R*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate (90 mg, 0.200 mmol) and K_2CO_3 (83 mg, 0.600 mmol) in MeOH (2 mL) was stirred for 1 h at room temperature. The resulting mixture was diluted with water (15 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 30% to 50%; detector, UV 254 nm to afford (3*S*,4*R*)-4-[(7-{5-[(2*R*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol (38.1 mg, 46%) as an off-white solid. MS ESI calculated for $C_{19}H_{20}F_3N_5O_2$ $[M + H]^+$, 408.16; found 408.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.70-8.68 (m, 2H), 8.54 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 4.8 Hz, 1H), 6.86 (d, *J* = 5.2 Hz, 1H), 4.90 (br, 1H), 4.27-4.11 (m, 2H), 4.03-4.00 (m, 1H), 3.93-3.86 (m, 1H), 3.75-3.69 (m, 1H), 2.57-

3.50 (m, 2H), 3.33-3.27 (m, 1H), 2.20-2.15 (m, 1H), 1.80-1.69 (m, 1H), 1.60 (d, J = 7.2 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -71.43 (3F).

Example 138:

5-chloro-2-{[(3*R*,4*S*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: *tert*-butyl (3*R*,4*S*)-4-{[5-chloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00764] A solution of 2,5-dichloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine (80 mg, 0.216 mmol), *tert*-butyl (3*R*,4*S*)-4-amino-3-fluoropiperidine-1-carboxylate (142 mg, 0.648 mmol) and DIEA (168 mg, 1.296 mmol) in NMP (1 mL) was stirred for 16 h at 100 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*S*)-4-{[5-chloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (80 mg, 67%) as a light yellow solid. MS ESI calculated for $C_{20}H_{28}ClFIN_5O_2$ $[M + H]^+$, 552.10, found 552.15.

Step 2: *tert*-butyl (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

[00765] A solution of *tert*-butyl (3*R*,4*S*)-4-{[5-chloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (60 mg, 0.109 mmol), $Zn(CN)_2$ (8 mg, 0.065 mmol) and $Pd(PPh_3)_4$ (13 mg, 0.011 mmol) in DMA (1 mL) was stirred for 2 h at 130 °C under nitrogen atmosphere. The resulting mixure was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 70%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (45 mg, 91%) as a light yellow solid. MS ESI calculated for $C_{21}H_{28}ClFN_6O_2$ $[M + H]^+$, 451.19, found 451.30. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 5.21 (d, J = 8.8 Hz, 1H), 4.93-4.80 (m, 1H), 4.55-4.50 (m, 1H), 4.35-4.30 (m, 1H), 4.01-3.95 (m, 1H), 3.12-2.81 (m, 4H), 2.22-2.18 (m, 1H), 1.95-1.82 (m, 2H), 1.50 (s, 9H), 1.02-0.98 (m, 6H).

Step 3: 5-chloro-2-{[(3*R*,4*S*)-3-fluoropiperidin-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride

[00766] A solution of *tert*-butyl (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (45 mg, 0.100 mmol) in DCM (1 mL) and HCl (gas) in 1,4-dioxane (1 mL) was stirred for 2 h at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to afford 5-chloro-2-{[(3*R*,4*S*)-3-fluoropiperidin-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-

carbonitrile hydrochloride (38.5 mg, crude) as a light yellow solid. MS ESI calculated for $C_{16}H_{21}Cl_2FN_6$ $[M - Cl]^+$, 351.14, found 351.25.

Example 138:

5-chloro-2-{[(3*R*,4*S*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00767] A solution of 5-chloro-2-{[(3*R*,4*S*)-3-fluoropiperidin-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (36 mg, 0.103 mmol), $NaHCO_3$ (60 mg, 0.721 mmol) and methanesulfonic anhydride (36 mg, 0.206 mmol) in EtOAc (1 mL) and water (1 mL) was stirred for 40 min at room temperature. The reaction was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford 5-chloro-2-{[(3*R*,4*S*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (34.1 mg, 77%) as a light yellow solid. MS ESI calculated for $C_{17}H_{22}ClFN_6O_2S$ $[M + H]^+$, 429.12; found 429.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 5.29 (d, *J* = 8.4 Hz, 1H), 5.00 (d, *J* = 48.4 Hz, 1H), 4.30-4.23 (m, 1H), 4.08-3.95 (m, 2H), 3.27-3.07 (m, 2H), 2.97 (s, 3H), 2.89 (d, *J* = 7.2 Hz, 2H), 2.25-2.16 (m, 1H), 2.08-1.88 (m, 2H), 1.00 (d, *J* = 6.8 Hz, 6H). ^{19}F NMR (376 MHz, Chloroform -*d*) δ -201.75 (1F).

Example 139:

5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl and 3-methylbutan-2-yl were not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 70/15/15, 1st peak, then CHIRALPAK ID, Hexane/EtOH/DCM = 80/10/10, 1st peak)

Example 140:

5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl and 3-methylbutan-2-yl were not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 70/15/15, 1st peak, then CHIRALPAK ID, Hexane/EtOH/DCM = 80/10/10, 2nd peak)

Example 141:

5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral

configuration of piperidin-4-yl and 3-methylbutan-2-yl were not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 70/15/15, 2nd peak, then CHIRALPAK AD-H, Hexane/EtOH = 85/15, 1st peak)

Example 142:

5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl and 3-methylbutan-2-yl were not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 70/15/15, 2nd peak, then CHIRALPAK AD-H, Hexane/EtOH = 85/15, 2nd peak)

Step 1: *tert*-butyl 4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3,3-difluoropiperidine-1-carboxylate

[00768] To a stirred mixture of 2,5-dichloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (150 mg, 0.391 mmol) and *tert*-butyl 4-amino-3,3-difluoropiperidine-1-carboxylate (461 mg, 1.955 mmol) in NMP (3 mL) was added DIEA (302 mg, 2.346 mmol) at room temperature. The resulting mixture was stirred for 2 days at 100 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 10% to 50%; detector, UV 254 nm to afford *tert*-butyl 4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3,3-difluoropiperidine-1-carboxylate (92 mg, 40%) as a yellow solid. MS ESI calculated for $C_{21}H_{29}ClF_2IN_5O_2[M + H]^+$, 584.10, found 584.35.

Step 2: *tert*-butyl 4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3,3-difluoropiperidine-1-carboxylate

[00769] To a stirred mixture of tert-butyl 4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3,3-difluoropiperidine-1-carboxylate (92 mg, 0.158 mmol) and $Zn(CN)_2$ (6 mg, 0.095 mmol) in DMA (3 mL) was added $Pd(PPh_3)_4$ (36 mg, 0.032 mmol) at room temperature. The resulting mixture was stirred for 2 h at 120 °C under nitrogen atmosphere. The reaction was quenched by the addition of sat. $NaHCO_3$ (10 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford *tert*-butyl 4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3,3-difluoropiperidine-1-carboxylate (67 mg, 88%) as a yellow solid. MS ESI calculated for $C_{22}H_{29}ClF_2N_6O_2$ $[M + H]^+$, 483.20, found 483.20.

Step 3: 5-chloro-2-[(3,3-difluoropiperidin-4-yl)amino]-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride

[00770] To a stirred mixture of *tert*-butyl 4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3,3-difluoropiperidine-1-carboxylate (72 mg, 0.149 mmol) in DCM (2 mL) was added HCl (gas) in 1,4-dioxane (2 mL) dropwise at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford 5-chloro-2-[(3,3-difluoropiperidin-4-yl)amino]-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (60 mg, 95%) as a yellow solid. MS ESI calculated for $C_{17}H_{22}Cl_2F_2N_6$ $[M - Cl]^+$, 383.15, found 383.20.

Step 4: 5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00771] To a mixture of 5-chloro-2-[(3,3-difluoropiperidin-4-yl)amino]-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (65 mg, 0.155 mmol) in EtOAc (3 mL) at were added sat. $NaHCO_3$ (2 mL) and methanesulfonyl methanesulfonate (31 mg, 0.279 mmol) at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The reaction was diluted with water (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (70 mg, crude) as a yellow solid. MS ESI calculated for $C_{18}H_{23}ClF_2N_6O_2S$ $[M + H]^+$, 461.13, found 461.15.

Example 139:

5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl and 3-methylbutan-2-yl were not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 70/15/15, 1st peak, then CHIRALPAK ID, Hexane/EtOH/DCM = 80/10/10, 1st peak)

Example 140:

5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl and 3-methylbutan-2-yl were not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 70/15/15, 1st peak, then CHIRALPAK ID, Hexane/EtOH/DCM = 80/10/10, 2nd peak)

Example 141:

5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl and 3-methylbutan-2-yl were not determined) (CHIRAL

ART Cellulose-SC, Hexane/EtOH/DCM = 70/15/15, 2nd peak, then CHIRALPAK AD-H, Hexane/EtOH = 85/15, 1st peak)

Example 142:

5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl and 3-methylbutan-2-yl were not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 70/15/15, 2nd peak, then CHIRALPAK AD-H, Hexane/EtOH = 85/15, 2nd peak)

[00772] 5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (60 mg) was purified by Prep-Chiral-HPLC with the following conditions: Column: CHIRAL ART Cellulose-SC, 2 x 25 cm, 5 μm; Mobile Phase A: Hexane, Mobile Phase B: EtOH/DCM (1/1); Flow rate: 20 mL/min; Gradient: A:B = 70:30; Wave Length: 254/220 nm.

[00773] The resulting mixture from RT_1: 8.66 min was purified again by Prep-Chiral-HPLC with the following conditions: Column: CHIRALPAK ID, 2 x 25 cm, 5 μm; Mobile Phase A: Hexane, Mobile Phase B: EtOH/DCM (1/1); Flow rate: 20 mL/min; Gradient: A:B = 80:20; Wave Length: 254/220 nm.

[00774] $RT_{1\text{-}1}$: 12.89 min to afford 5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl and 3-methylbutan-2-yl were not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 70/15/15, 1st peak, then CHIRALPAK ID, Hexane/EtOH/DCM = 80/10/10, 1st peak) (7.3 mg, 11%) as a light yellow solid. MS ESI calculated for $C_{18}H_{23}ClF_2N_6O_2S[M + H]^+$, 461.13, found 461.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 5.32 (d, *J* = 8.8 Hz, 1H), 4.34-4.29 (m, 1H), 4.19-4.11 (m, 1H), 3.95-3.91 (m, 1H), 3.28-3.21 (m, 2H), 3.18-3.10 (m, 1H), 2.95 (s, 3H), 2.29-2.16 (m, 2H), 1.93-1.83 (m, 1H), 1.44 (d, *J* = 7.2 Hz, 3H), 1.04 (d, *J* = 6.4 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -110.29&-110.94 (1F), -118.92&-119.56 (1F).

[00775] $RT_{1\text{-}2}$: 15.35 min to afford 5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl and 3-methylbutan-2-yl were not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 70/15/15, 1st peak, then CHIRALPAK ID, Hexane/EtOH/DCM = 80/10/10, 2nd peak) (8.3 mg, 3%) as a light yellow solid. MS ESI calculated for $C_{18}H_{23}ClF_2N_6O_2S[M + H]^+$, 461.13, found 461.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 5.39 (d, *J* = 8.0 Hz, 1H), 4.35-4.30 (m, 1H), 4.15-4.09 (m, 1H), 3.94-3.90 (m, 1H), 3.32-3.13 (m, 3H), 2.95 (s, 3H), 2.27-2.17 (m, 2H), 1.92-1.87 (m, 1H), 1.44

(d, J = 7.2 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -110.35&-111.00 (1F), -118.79&-119.44 (1F).

[00776] The resulting mixture from RT_2: 10.77 min was purified by Prep-HPLC with the following conditions: Column: CHIRALPAK AD-H, 2 x 25 cm, 5 μm; Mobile Phase A: Hexane, Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: A:B = 85:15; Wave Length: 254/220 nm.

[00777] $RT_{2\text{-}1}$: 19.27 min to afford 5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl and 3-methylbutan-2-yl were not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 70/15/15, 2nd peak, then CHIRALPAK AD-H, Hexane/EtOH = 85/15, 1st peak) (8.1 mg, 12%) as a light yellow solid. MS ESI calculated for $C_{18}H_{23}ClF_2N_6O_2S[M + H]^+$, 461.13, found 461.15. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 5.30 (brs, 1H), 4.39-4.29 (m, 1H), 4.22-4.14 (m, 1H), 3.97-3.94 (m, 1H), 3.34-3.23 (m, 2H), 3.19-3.12 (m, 1H), 2.97 (s, 3H), 2.31-2.19 (m, 2H), 1.95-1.85 (m, 1H), 1.47 (d, J = 7.2 Hz, 3H), 1.07 (d, J = 6.4 Hz, 3H), 0.81 (d, J = 6.8 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -110.32&-110.97 (1F), -118.97&-119.62 (1F).

[00778] $RT_{2\text{-}2}$: 23.32 min to afford 5-chloro-2-[(3,3-difluoro-1-methanesulfonylpiperidin-4-yl)amino]-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of piperidin-4-yl and 3-methylbutan-2-yl were not determined) (CHIRAL ART Cellulose-SC, Hexane/EtOH/DCM = 70/15/15, 2nd peak, then CHIRALPAK AD-H, Hexane/EtOH = 85/15, 2nd peak) (6.3 mg, 9%) as a light yellow solid. MS ESI calculated for $C_{18}H_{23}ClF_2N_6O_2S[M + H]^+$, 461.13, found 461.20. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 5.14 (d, J = 8.8 Hz, 1H), 4.38-4.34 (m, 1H), 4.22-4.14 (m, 1H), 3.99-3.95 (m, 1H), 3.31-3.23 (m, 2H), 3.20-3.12 (m, 1H), 2.97 (s, 3H), 2.29-2.19 (m, 2H), 1.96-1.88 (m, 1H), 1.47 (d, J = 7.2 Hz, 3H), 1.056 (d, J = 6.8 Hz, 3H), 0.80 (d, J = 6.4 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -110.51&-111.16 (1F), -119.15&-119.80 (1F).

Example 143:

5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00779] To a stirred solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({7-bromopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (550 mg, 1.211 mmol), trimethyl-1,3,5,2,4,6-trioxatriborinane (221 mg, 1.760 mmol) and Cs_2CO_3 (574 mg, 1.760 mmol) in dioxane (5 mL) and water (1 mL) was added Pd(dppf)Cl_2DCM (72 mg, 0.088 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 100 °C under nitrogen

atmosphere. The resulting mixture was diluted with water (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% $NH_3 \cdot H_2O$), 10% to 50%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (200 mg, 58%) as a yellow solid. MS ESI calculated for $C_{19}H_{27}N_5O_4$ $[M + H]^+$, 490.21, found 490.20. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.49 (s, 1H), 6.73 (d, *J* = 4.8 Hz, 1H), 6.53 (d, *J* = 4.8 Hz, 1H), 5.29 (brs, 1H), 5.01 (s, 1H), 4.09-4.01 (m, 1H), 3.93-3.89 (m, 1H), 3.80-3.71 (m, 1H), 3.38-3.33 (m, 2H), 2.49 (s, 3H), 2.40-2.31 (m, 1H), 2.07 (s, 3H), 1.63-1.58 (m, 1H), 1.49 (s, 9H).

Step 2: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00780] A solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (300 mg, 0.708 mmol) and NCS (63 mg, 0.472 mmol) in DMF (3 mL) was stirred for 16 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% $NH_3 \cdot H_2O$), 10% to 50%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (100 mg, 50%) as a yellow solid. MS ESI calculated for $C_{19}H_{26}ClN_5O_4$ $[M + H]^+$, 424.17, found 424.20. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.53 (s, 1H), 6.45 (s, 1H), 5.32 (brs, 1H), 5.02-4.97 (m, 1H), 4.06-3.87 (m, 2H), 3.80-3.76 (m, 1H), 3.37-3.27 (m, 2H), 2.46 (s, 3H), 2.36-2.32 (m, 1H), 2.07 (s, 3H), 1.62-1.57 (m, 1H), 1.49 (s, 9H).

Step 3: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-iodo-7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00781] A solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (200 mg, 0.472 mmol) and I_2 (299 mg, 1.180 mmol) in DMF (2 mL) was stirred for 16 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-iodo-7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (110 mg, 85%) as a yellow solid. MS ESI calculated for $C_{19}H_{25}ClIN_5O_4$ $[M + H]^+$, 550.06 found 550.20.

Step 4: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-cyano-7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00782] To a stirred solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-iodo-7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (110 mg, 0.200 mmol) and $Zn(CN)_2$ (14 mg, 0.120 mmol) in DMF (1 mL) was added $Zn(CN)_2$ (14 mg, 0.120 mmol) at room temperature. The resulting mixture was stirred for 2 h at 120 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 60% to 80%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-cyano-7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (60 mg, 66.80%) as a yellow solid. MS ESI calculated for $C_{20}H_{25}ClN_6O_4$ $[M + H]^+$, 449.16, found 449.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 5.31 (brs, 1H), 4.97-4.92 (m, 1H), 4.01-3.92 (m, 3H), 3.22-3.16 (m, 2H), 2.58 (s, 3H), 2.38-2.31 (m, 1H), 2.08 (s, 3H), 1.60-1.48 (m, 10H).

Step 5: (3*R*,4*R*)-4-({5-chloro-6-cyano-7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidin-3-yl acetate hydrochloride

[00783] A solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-cyano-7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (60 mg, 0.134 mmol) and HCl (gas)in 1,4-dioxane (2 mL) in DCM (1 mL) was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford (3*R*,4*R*)-4-({5-chloro-6-cyano-7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidin-3-yl acetate hydrochloride (50 mg, 86%) as a yellow oil. MS ESI calculated for $C_{15}H_{18}Cl_2N_6O_2$ $[M + H]^+$, 349.11, found 349.15.

Step 6: (3*R*,4*R*)-4-({5-chloro-6-cyano-7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-difluoromethanesulfonylpiperidin-3-yl acetate

[00784] A solution of (3*R*,4*R*)-4-({5-chloro-6-cyano-7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidin-3-yl acetate hydrochloride (15 mg, 0.043 mmol) and difluoromethanesulfonyl chloride (13 mg, 0.086 mmol) in EtOAc (2 mL) and sat. $NaHCO_3$ (1 mL) was stirred for 40 min at room temperature. The resulting mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford (3*R*,4*R*)-4-({5-chloro-6-cyano-7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-difluoromethanesulfonylpiperidin-3-yl acetate (11 mg, 55%) as a yellow solid. MS ESI calculated for $C_{16}H_{17}ClF_2N_6O_4S$ $[M + H]^+$, 463.07, found 463.10.

Example 143:

5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00785] A solution of (3*R*,4*R*)-4-({5-chloro-6-cyano-7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-difluoromethanesulfonylpiperidin-3-yl acetate (15 mg, 0.032 mmol) and K_2CO_3 (13 mg, 0.096 mmol) in MeOH (2 mL) was stirred for 20 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 50%; detector, UV 254 nm to afford 5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (5.4 mg, 36%) as a white solid. MS ESI calculated for $C_{14}H_{15}ClF_2N_6O_3S$ $[M + H]^+$, 421.06, found 421.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 6.27 (t, *J* = 54.0 Hz, 1H), 5.02 (d, *J* = 6.8 Hz, 1H), 4.17-4.12 (m, 1H), 4.01-3.97 (m, 1H), 3.88-3.77 (m, 2H), 3.43-3.40 (m, 1H), 3.31-3.23 (m, 1H), 3.13-3.07 (m, 1H), 2.58 (s, 3H), 2.32-2.28 (m, 1H), 1.80-1.71 (m, 1H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -121.38 (2F).

Example 144:

5-chloro-7-cyclopropyl-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*S*,4*R*)-4-({7-cyclopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00786] A mixture of (3*S*,4*R*)-4-({7-bromopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (200 mg, 0.563 mmol), cyclopropylboronic acid (145 mg, 1.689 mmol), K_3PO_4 (239 mg, 1.126 mmol) and Pd(dppf)Cl_2DCM (46 mg, 0.056 mmol) in dioxane (5 mL) was stirred for 2 h at 100 °C under nitrogen atmosphere. The reaction was quenched by the addition of water (50 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-({7-cyclopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (70 mg, 39%) as a yellow solid. MS ESI calculated for $C_{16}H_{20}N_4O_3$ $[M + H]^+$, 317.15; found 317.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.46 (s, 1H), 6.75-6.61 (m, 1H), 6.28 (d, *J* = 4.8 Hz, 1H), 5.16 (d, *J* = 7.2 Hz, 1H), 5.03-4.97 (m, 1H), 4.11-4.01 (m, 2H), 4.00-3.95 (m, 1H), 3.66-3.60 (m, 1H), 3.53-3.40 (m, 1H), 2.50-2.43 (m, 1H), 2.40-2.33 (m, 1H), 2.07 (s, 3H), 1.73-1.67 (m, 1H), 1.16-1.05 (m, 2H), 0.95-0.84 (m, 2H).

Step 2: (3*S*,4*R*)-4-({5-chloro-7-cyclopropyl-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00787] A mixture of (3*S*,4*R*)-4-({7-cyclopropyl-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (65 mg, 0.147 mmol) and 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (29 mg, 0.147 mmol) in CH_3CN (6 mL) was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure and purified by Prep-TLC (PE/EtOAc 1/1) to afford

(3*S*,4*R*)-4-({5-chloro-7-cyclopropyl-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (50 mg, 71%) as yellow oil. MS ESI calculated for $C_{16}H_{19}ClN_4O_3$ $[M + H]^+$, 351.11, found 351.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.51 (d, *J* = 6.9 Hz, 1H), 6.20 (s, 1H), 5.31 (d, *J* = 12.4 Hz, 1H), 5.03-4.97 (m, 1H), 4.08-4.02 (m, 2H), 3.99-3.93 (m, 1H), 3.65-3.60 (m, 1H), 3.50-3.45 (m, 1H), 2.48-2.40 (m, 1H), 2.37-2.31 (m, 1H), 2.07 (s, 3H), 1.75-1.68 (m, 1H), 1.16-1.03 (m, 2H), 0.89-0.82 (m, 2H).

Step 3: (3*S*,4*R*)-4-({5-chloro-7-cyclopropyl-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00788] A mixture of (3*S*,4*R*)-4-({5-chloro-7-cyclopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (110 mg, 0.314 mmol) and I_2 (29 mg, 0.116 mmol) in DMF (2 mL) was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (5 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EtOAc 1/1) to afford (3*S*,4*R*)-4-({5-chloro-7-cyclopropyl-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (20 mg, 13%) as a yellow solid. MS ESI calculated for $C_{16}H_{18}ClIN_4O_3$ $[M + H]^+$, 477.01, found 477.00.

Step 4: (3*S*,4*R*)-4-({5-chloro-6-cyano-7-cyclopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00789] A mixture of (3*S*,4*R*)-4-({5-chloro-7-cyclopropyl-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (20 mg, 0.042 mmol), $Zn(CN)_2$ (3 mg, 0.025 mmol) and $Pd(PPh_3)_4$ (5 mg, 0.004 mmol) in DMF (0.2 mL) was stirred for 2 h at 120 °C under nitrogen atmosphere. The crude product was purified by reverse phase flash with the following conditions: C18 column; mobile phase, CH_3CN in water (plus 5 mmol/L NH_4HCO_3); 40% to 60%; Flow rate: 25 mL/min; Detector: 220/254 nm to afford (3*S*,4*R*)-4-({5-chloro-6-cyano-7-cyclopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (6 mg, 38%) as yellow oil. MS ESI calculated for $C_{17}H_{18}ClN_5O_3$ $[M + H]^+$, 376.11, found 376.15.

Step 5: 5-chloro-7-cyclopropyl-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00790] A mixture of (3*S*,4*R*)-4-({5-chloro-6-cyano-7-cyclopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (6 mg, 0.016 mmol) and K_2CO_3 (7 mg, 0.048 mmol) in MeOH (0.5 mL) was stirred for 30 min at room temperature. The resulting mixture was purified by reverse phase flash with the following conditions: C18 column; mobile phase, CH_3CN in water (5 mmol/L NH_4HCO_3); 25% to 50%; Flow rate: 25 mL/min; Detector: 220/254 nm to afford 5-chloro-7-cyclopropyl-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-

carbonitrile (2.3 mg, 43%) as an off-white solid. MS ESI calculated for $C_{15}H_{16}ClN_5O_2$ $[M + H]^+$, 334.10, found 334.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 5.14 (brs, 1H), 4.12-4.07 (m, 1H), 4.03-3.98 (m, 1H), 3.86-3.78 (m, 1H), 3.74-3.70 (m, 1H), 3.55-3.48 (m, 1H), 3.30-3.24 (m, 1H), 2.24-2.14 (m, 2H), 1.75-1.70 (m, 1H), 1.35-1.18 (m, 4H).

Example 145:

5-chloro-7-(2,2-difluorocyclopropyl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*S*,4*R*)-4-{[7-(2,2-difluorocyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00791] To a stirred solution of (3*S*,4*R*)-4-({7-bromopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (500 mg, 1.408 mmol) and potassium (2,2-difluorocyclopropyl)trifluoroboranuide (518 mg, 2.816 mmol) in dioxane (10 mL) and water (2 mL) were added Cs_2CO_3 (1375 mg, 4.224 mmol) and 3rd Gen RuPhos Palladacycle (117 mg, 0.141 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 100 °C under nitrogen atmosphere. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-{[7-(2,2-difluorocyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (180 mg, 36%) as yellow oil. MS ESI calculated for $C_{16}H_{18}F_2N_4O_3$ $[M + H]^+$, 353.13, found 353.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.57 (s, 1H), 6.70 (d, J = 4.8 Hz, 1H), 6.51 (d, J = 4.8 Hz, 1H), 5.08-4.88 (m, 2H), 4.10-4.01 (m, 2H), 3.99-3.91 (m, 1H), 3.69-3.56 (m, 1H), 3.53-3.39 (m, 1H), 3.22-3.10 (m, 1H), 2.55-2.40 (m, 1H), 2.10-1.95 (m, 4H), 1.74-1.64 (m, 2H).

Step 2: (3*S*,4*R*)-4-{[5-chloro-7-(2,2-difluorocyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00792] A solution of (3*S*,4*R*)-4-{[7-(2,2-difluorocyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (130 mg, 0.369 mmol) and NCS (54 mg, 0.406 mmol) in DMF (3 mL) was stirred for 16 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 20% to 60%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-7-(2,2-difluorocyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (85 mg, 59%) as a yellow solid. MS ESI calculated for $C_{16}H_{17}ClF_2N_4O_3$ $[M + H]^+$, 387.10, found 387.15.

Step 3: (3*S*,4*R*)-4-{[5-chloro-7-(2,2-difluorocyclopropyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00793] A solution of (3*S*,4*R*)-4-{[5-chloro-7-(2,2-difluorocyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (80 mg, 0.207 mmol) and I_2 (210 mg, 0.828 mmol) in DMF (2 mL) was stirred for 16 h at room temperature. The reaction was quenched with sat. $Na_2S_2O_3$ (30 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 20% to 60%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-7-(2,2-difluorocyclopropyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (60 mg, 56%) as a yellow solid. MS ESI calculated for $C_{16}H_{16}ClF_2IN_4O_3$ $[M + H]^+$, 512.99, found 513.05.

Step 4: (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(2,2-difluorocyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00794] To a stirred solution of (3*S*,4*R*)-4-{[5-chloro-7-(2,2-difluorocyclopropyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (60 mg, 0.117 mmol) and $Zn(CN)_2$ (8 mg, 0.070 mmol) in DMF (1 mL) was added $Pd(PPh_3)_4$ (13 mg, 0.012 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 120 °C under nitrogen atmosphere. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 20% to 60%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(2,2-difluorocyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (20 mg, 41%) as a yellow solid. MS ESI calculated for $C_{17}H_{16}ClF_2N_5O_3$ $[M + H]^+$, 412.09, found 412.15.

Example 145:

5-chloro-7-(2,2-difluorocyclopropyl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00795] A mixture of (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(2,2-difluorocyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (20 mg, 0.049 mmol) and K_2CO_3 (20 mg, 0.147 mmol) in MeOH (1 mL) was stirred for 30 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 20% to 70%; detector, UV 254 nm to afford 5-chloro-7-(2,2-difluorocyclopropyl)-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (6.5 mg, 35%) as an off-white solid. MS ESI calculated for

$C_{15}H_{14}ClF_2N_5O_2$ $[M + H]^+$, 368.08, found 370.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.76 (s, 1H), 5.15 (brs, 1H), 4.12-4.07 (m, 1H), 4.03-3.98 (m, 1H), 3.89-3.82 (m, 1H), 3.75-3.70 (m, 1H), 3.57-3.50 (m, 1H), 3.32-3.26 (m, 1H), 2.96-2.90 (m, 1H), 2.29-2.13 (m, 3H), 1.74-1.66 (m, 1H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -128.85--129.80 (1F), -137.63--138.64 (1F).

Example 146:

5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(1,1,2,2,2-pentafluoroethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*S*,4*R*)-4-({7-bromo-5-chloro-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00796] A solution of (3*S*,4*R*)-4-({7-bromo-5-chloropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (750 mg, 1.925 mmol) and I_2 (1.9 g, 7.700 mmol) in DMF (15 mL) was stirred for 16 h at room temperature. The reaction was quenched with sat. $Na_2S_2O_3$ (50 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 30% to 70%; detector, UV 254 nm to afford (3*S*,4*R*)-4-({7-bromo-5-chloro-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (850 mg, 85%) as a yellow solid. MS ESI calculated for $C_{13}H_{13}BrClIN_4O_3$ $[M + H]^+$, 514.89, 516.89, found 514.95, 516.95.

Step 2: (3*S*,4*R*)-4-({7-bromo-5-chloro-6-cyanopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00797] To a stirred solution of (3*S*,4*R*)-4-({7-bromo-5-chloro-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (800 mg, 1.552 mmol) and $Zn(CN)_2$ (182 mg, 1.552 mmol) in DMF (16 mL) was added $Pd(PPh_3)_4$ (179 mg, 0.155 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 130 °C under nitrogen atmosphere. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford (3*S*,4*R*)-4-({7-bromo-5-chloro-6-cyanopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (100 mg, 15%) as a yellow solid. MS ESI calculated for $C_{14}H_{13}BrClN_5O_3$ $[M + H]^+$, 413.99, 415.99, found 414.00; 416.00. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.66 (s, 1H), 5.45 (d, *J* = 7.2 Hz, 1H), 5.01-4.93 (m, 1H), 4.10-3.97 (m, 3H), 3.62-3.53 (m, 1H), 3.47-3.38 (m, 1H), 2.53-2.42 (m, 1H), 2.08 (s, 3H), 1.74-1.68 (m, 1H).

Step 3: (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1,1,2,2,2-pentafluoroethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

[00798] A mixture of trimethyl(1,1,2,2,2-pentafluoroethyl)silane (74 mg, 0.386 mmol) and AgF (49 mg, 0.386 mmol) in DMF (2 mL) was stirred for 20 min at room temperature under nitrogen atmosphere. To this was added Cu power (49 mg, 0.772 mmol) at room temperature. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. To this was added (3*S*,4*R*)-4-({7-bromo-5-chloro-6-cyanopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (80 mg, 0.193 mmol) at room temperature. The resulting mixture was stirred for 2 h at 80 °C under nitrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with MeOH (3 x 5 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 30% to 60%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1,1,2,2,2-pentafluoroethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (40 mg, 45%) as a yellow solid. MS ESI calculated for $C_{16}H_{13}ClF_5N_5O_3$ $[M + H]^+$, 454.06, found 454.05.

Example 146:

5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(1,1,2,2,2-pentafluoroethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00799] A mixture of (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1,1,2,2,2-pentafluoroethyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (30 mg, 0.066 mmol) and K_2CO_3 (27 mg, 0.198 mmol) in MeOH (1 mL) was stirred for 1 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 20% to 50%; detector, UV 254 nm to afford 5-chloro-2-{[(3*S*,4*R*)-3-hydroxyoxan-4-yl]amino}-7-(1,1,2,2,2-pentafluoroethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (15.2 mg, 55%) as an off-white solid. MS ESI calculated for $C_{14}H_{11}ClF_5N_5O_2$ $[M + H]^+$, 412.05, found 412.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.89 (s, 1H), 5.31 (d, *J* = 5.6 Hz, 1H), 4.11-4.06 (m, 1H), 4.02-3.96 (m, 1H), 3.78-3.66 (m, 2H), 3.55-3.48 (m, 1H), 3.31-3.24 (m, 1H), 2.26-2.20 (m, 1H), 1.72-1.60 (m, 1H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -83.16 (3F), -112.43 (2F).

Example 147:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-trifluoromethanesulfonylpiperidin-4-yl]amino}-7-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*R*,4*R*)-4-({5-chloro-6-cyano-7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-difluoromethanesulfonylpiperidin-3-yl acetate

[00800] A solution of (3*R*,4*R*)-4-({5-chloro-6-cyano-7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidin-3-yl acetate (15 mg, 0.043 mmol) and trifluoromethanesulfonyl chloride (14 mg, 0.086 mmol) in EtOAc (2 mL) and sat. $NaHCO_3$ (1 mL) was stirred for 40 min at room temperature. The resulting mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford (3*R*,4*R*)-4-({5-chloro-6-cyano-7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-difluoromethanesulfonylpiperidin-3-yl acetate (6 mg, 30%) as a yellow solid. MS ESI calculated for $C_{16}H_{16}ClF_3N_6O_4S$ $[M + H]^+$, 481.06, found 481.15.

Example 147:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-trifluoromethanesulfonylpiperidin-4-yl]amino}-7-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00801] A solution of (3*R*,4*R*)-4-({5-chloro-6-cyano-7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-trifluoromethanesulfonylpiperidin-3-yl acetate (15 mg, 0.031 mmol) and K_2CO_3 (13 mg, 0.093 mmol) in MeOH (2 mL) was stirred for 20 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 50%; detector, UV 254 nm to afford 5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-trifluoromethanesulfonylpiperidin-4-yl]amino}-7-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (2 mg, 14%) as a white solid. MS ESI calculated for $C_{14}H_{14}ClF_3N_6O_3S$ $[M + H]^+$, 439.05, found 439.00. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 5.06 (d, *J* = 6.4 Hz, 1H), 4.16-4.12 (m, 1H), 4.02-3.98 (m, 1H), 3.88-3.76 (m, 2H), 3.28-3.20 (m, 1H), 3.09-3.03 (m, 1H), 2.58 (s, 3H), 2.35-2.29 (m, 1H), 1.83-1.76 (m, 1H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -75.57 (3F).

Example 148:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*R*,4*R*)-4-({5-chloro-6-cyano-7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-methanesulfonylpiperidin-3-yl acetate

[00802] A solution of (3*R*,4*R*)-4-({5-chloro-6-cyano-7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidin-3-yl acetate (15 mg, 0.043 mmol) and methanesulfonic anhydride (15 mg, 0.086 mmo) in EtOAc (1 mL) and sat. $NaHCO_3$ (1 mL) was stirred for 40 min at room temperature. The resulting mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was

purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford (3*R*,4*R*)-4-({5-chloro-6-cyano-7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-methanesulfonylpiperidin-3-yl acetate (17 mg, 93%) as a yellow solid. MS ESI calculated for $C_{16}H_{19}ClN_6O_4S$ $[M + H]^+$, 427.09, found 427.15.

Example 148:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00803] A solution of (3*R*,4*R*)-4-({5-chloro-6-cyano-7-methylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-methanesulfonylpiperidin-3-yl acetate (15 mg, 0.035 mmol) and K_2CO_3 (14 mg, 0.105 mmol) in MeOH (2 mL) was stirred for 20 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 50%; detector, UV 254 nm to afford 5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (3.6 mg, 24%) as a white solid. MS ESI calculated for $C_{14}H_{17}ClN_6O_3S$ $[M + H]^+$, 385.08, found 385.05. ^1H NMR (400 MHz, DMSO-d_6) δ 8.96 (s, 1H), 7.44 (brs, 1H), 5.27 (brs, 1H), 3.66-3.58 (m, 3H), 3.51-3.47 (m, 1H), 2.91-2.86 (m, 4H), 2.71-2.67 (m, 1H), 2.49 (s, 3H), 2.14-2.07 (m, 1H), 1.56-1.49 (m, 1H).

Example 149:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-ethylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({7-ethylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00804] To a stirred solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({7-bromopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (265 mg, 0.583 mmol) and potassium ethyltrifluoro-lambda4-borane (120 mg, 0.880 mmol) and Cs_2CO_3 (430 mg, 1.320 mmol) in toluene (4 mL) and water (1 mL) was added 2nd Gen RuPhos-PdCl (34 mg, 0.044 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 100 °C under nitrogen atmosphere. The resulting mixture was diluted with EtOAc (30 mL) and washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% $NH_3 \cdot H_2O$), 40% to 50%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({7-ethylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (100 mg, 56%) as a yellow solid. MS ESI calculated for $C_{20}H_{29}N_5O_4$ $[M + H]^+$, 404.22, found 404.25.

Step 2: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-ethylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00805] A solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({7-ethylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (150 mg, 0.372 mmol) and NCS (50 mg, 0.372 mmol) in DMF (2 mL) was stirred for 16 h at room temperature. The reaxtion mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% $NH_3{\cdot}H_2O$), 10% to 50%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-ethylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (60 mg, 37%) as a yellow solid. MS ESI calculated for $C_{20}H_{28}ClN_5O_4$ $[M + H]^+$, 438.18, found 438.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.54 (s, 1H), 6.47 (s, 1H), 5.22 (brs, 1H), 4.99-4.92 (m, 1H), 3.99-3.80 (m, 2H), 3.82-3.76 (m, 1H), 3.33-3.21 (m, 2H), 2.89 (q, *J* = 7.6 Hz, 2H), 2.36-2.30 (m, 1H), 2.07 (s, 3H), 1.93-1.87 (m, 1H), 1.62-1.55 (m, 1H), 1.49 (s, 9H), 1.32 (t, *J* = 7.6 Hz, 3H).

Step 3: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-ethyl-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00806] A solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-ethylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (100 mg, 0.228 mmol) and I_2 (290 mg, 1.140 mmol) in DMF (2 mL) was stirred for 16 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% $NH_3{\cdot}H_2O$), 10% to 50%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-ethyl-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (75 mg, 58%) as a yellow solid.MS ESI calculated for $C_{20}H_{27}ClIN_5O_4$ $[M + H]^+$, 564.08 found 564.25.

Step 4: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-cyano-7-ethylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00807] To a stirred solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-ethyl-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (75 mg, 0.133 mmol) and $Zn(CN)_2$ (5 mg, 0.080 mmol) in DMF (1 mL) was added $Pd(PPh_3)_4$ (15 mg, 0.013 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 120 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 50%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-cyano-7-ethylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (50 mg, 81%) as a yellow solid. MS ESI calculated for $C_{21}H_{27}ClN_6O_4$ $[M + H]^+$, 463.18, found 463.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 5.26 (brs, 1H), 4.97-4.90 (m, 1H), 4.08-4.00 (m, 1H), 3.98-

3.90 (m, 2H), 3.22-3.10 (m 2H), 3.05 (q, J = 7.6 Hz, 2H), 2.38-2.30 (m, 1H), 2.08 (s, 3H), 1.62-1.50 (m, 10H), 1.36 (t, J = 7.6 Hz, 3H).

Step 5: (3*R*,4*R*)-4-({5-chloro-6-cyano-7-ethylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidin-3-yl acetate hydrochloride

[00808] A solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-cyano-7-ethylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (50 mg, 0.108 mmol) and HCl (gas) in 1,4-dioxane (2 mL) in DCM (1 mL) was stirred for 40 min at room temperature. The resulting mixture was concentrated under reduced pressure to afford (3*R*,4*R*)-4-({5-chloro-6-cyano-7-ethylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidin-3-yl acetate hydrochloride (40 mg, 82%) as yellow oil. MS ESI calculated for $C_{16}H_{20}Cl_2N_6O_2$ $[M - Cl]^+$, 363.13, found 363.15.

Step 6: (3*R*,4*R*)-4-({5-chloro-6-cyano-7-ethylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-methanesulfonylpiperidin-3-yl acetate

[00809] A solution of (3*R*,4*R*)-4-({5-chloro-6-cyano-7-ethylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidin-3-yl acetate hydrochloride (30 mg, 0.083 mmol) and methanesulfonic anhydride (29 mg, 0.166 mmol) in EtOAc (1 mL) and sat. $NaHCO_3$ (1 mL) was stirred for 40 min at room temperature. The resulting mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (10/1) to afford (3*R*,4*R*)-4-({5-chloro-6-cyano-7-ethylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-methanesulfonylpiperidin-3-yl acetate (20 mg, 55%) as a yellow solid. MS ESI calculated for $C_{17}H_{21}ClN_6O_4S$ $[M + H]^+$, 441.10, found 441.20.

Example 149:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-ethylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00810] A solution of (3*R*,4*R*)-4-({5-chloro-6-cyano-7-ethylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-methanesulfonylpiperidin-3-yl acetate (20 mg, 0.047 mmol) and K_2CO_3 (19 mg, 0.141 mmol) in MeOH (1 mL) was stirred for 20 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 50%; detector, UV 254 nm to afford 5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-ethylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (4 mg, 20%) as a white solid. MS ESI calculated for $C_{15}H_{19}ClN_6O_3S$ $[M + H]^+$, 399.09, found 399.10. ^1H NMR (400 MHz, DMSO-d_6) δ 8.97 (s, 1H), 7.43 (d, J = 7.6 Hz, 1H), 5.26 (d, J = 3.6 Hz, 1H), 3.66-3.58 (m, 3H), 3.51-3.47 (m, 1H), 2.98-2.86 (m, 6H), 2.72-2.67 (m, 1H), 2.14-2.08 (m, 1H), 1.56-1.50 (m, 1H), 1.28 (t, J = 7.6 Hz, 3H).

Example 150:

(3*S*,4*R*)-4-({7-[5-(1-ethylcyclopropyl)pyridin-2-yl]-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol

Step 1: methyl 1-(6-chloropyridin-3-yl)cyclopropane-1-carboxylate

[00811] To a stirred solution of methyl 2-(6-chloropyridin-3-yl)acetate (4 g, 21.551 mmol) in DMF (100 mL) was added NaH (2.1 g, 53.877 mmol, 60%) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at 0 °C under nitrogen atmosphere. To this was added dibromoethane (6.1 g, 32.326 mmol) dropwise at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched with sat. NH_4Cl (200 mL). The resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (4/1) to afford methyl 1-(6-chloropyridin-3-yl)cyclopropane-1-carboxylate (3.3 g, 72%) as a colorless oil. MS ESI calculated for $C_{10}H_{10}ClNO_2$ $[M + H]^+$, 212.04, found 211.85. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.37 (d, *J* = 2.4 Hz, 1H), 7.65 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 3.66 (s, 3H), 1.72-1.68 (m, 2H), 1.22-1.19 (m, 2H).

Step 2: [1-(6-chloropyridin-3-yl)cyclopropyl]methanol

[00812] To a stirred solution of methyl 1-(6-chloropyridin-3-yl)cyclopropane-1-carboxylate (3.3 g, 15.592 mmol) in MeOH (100 mL) was added $NaBH_4$ (3.0 g, 77.960 mmol) at 0 °C. The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was diluted with water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford [1-(6-chloropyridin-3-yl)cyclopropyl]methanol (1.1 g, 38%) as a colorless oil. MS ESI calculated for $C_9H_{10}ClNO$ $[M + H]^+$, 184.05, found 184.05. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.39 (d, *J* = 2.4 Hz, 1H), 7.69 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 3.70 (s, 2H), 2.22 (brs, 1H), 0.98-0.89 (m, 4H).

Step 3: 1-(6-chloropyridin-3-yl)cyclopropane-1-carbaldehyde

[00813] To a stirred solution of [1-(6-chloropyridin-3-yl)cyclopropyl]methanol (1.1 g, 5.990 mmol) in DCM (30 mL) was added Dess-Martin reagent (5.1 g, 11.980 mmol) at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (3 x 50 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (4/1) to afford 1-(6-chloropyridin-3-yl)cyclopropane-1-carbaldehyde (850 mg, 78%) as a colorless oil.

MS ESI calculated for C_9H_8ClNO $[M + H]^+$, 182.03, found 181.90. ^1H NMR (400 MHz, Chloroform-*d*) δ 9.01 (s, 1H), 8.33 (d, *J* = 2.4 Hz, 1H), 7.62 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 1.83-1.51 (m, 2H), 1.59-1.36 (m, 2H).

Step 4: 2-chloro-5-(1-ethynylcyclopropyl)pyridine

[00814] To a stirred solution of 1-(6-chloropyridin-3-yl)cyclopropane-1-carbaldehyde (350 mg, 1.927 mmol) and dimethyl (1-diazo-2-oxopropyl)phosphonate (740 mg, 3.854 mmol) in MeOH (10 mL) was added K_2CO_3 (532 mg, 3.854 mmol) at room temperature. The resulting mixture was stirred for 1 h at room temperature. The reaction was quenched with sat. NH_4Cl (100 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford 2-chloro-5-(1-ethynylcyclopropyl)pyridine (300 mg, 87%) as an off-white solid. MS ESI calculated for $C_{10}H_8ClN$ $[M + H]^+$, 178.03, found 178.05. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.38 (d, *J* = 2.4 Hz, 1H), 7.61 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 2.16 (s, 1H), 1.58-1.52 (m, 2H), 1.30-1.25 (m, 2H).

Step 5: 2-chloro-5-(1-ethylcyclopropyl)pyridine

[00815] To a solution of 2-chloro-5-(1-ethynylcyclopropyl)pyridine (340 mg, 1.914 mmol) in EtOAc (20 mL) was added PtO_2 (43 mg, 0.191 mmol) under nitrogen atmosphere. The mixture was hydrogenated at room temperature for 1 h under hydrogen atmosphere (1 atm). The resulting mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford 2-chloro-5-(1-ethylcyclopropyl)pyridine (280 mg, 80%) as yellow oil. MS ESI calculated for $C_{10}H_{12}ClN$ $[M + H]^+$, 182.07, found 182.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.32 (d, *J* = 2.4 Hz, 1H), 7.57 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.31-7.22 (m, 1H), 1.59 (q, *J* = 7.2 Hz, 2H), 0.86 (t, *J* = 7.2 Hz, 3H), 0.83-0.70 (m, 4H).

Step 6: (3*S*,4*R*)-4-({7-[5-(1-ethylcyclopropyl)pyridin-2-yl]-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate

[00816] To a stirred solution of (3*S*,4*R*)-4-({7-bromo-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (70 mg, 0.188 mmol) and bis(pinacolato)diboron (95 mg, 0.376 mmol) in dioxane (2 mL) were added PPh_3 (10 mg, 0.038 mmol), $Pd(PPh_3)_2Cl_2$ (13 mg, 0.019 mmol) and KOAc (55 mg, 0.564 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 100 °C under nitrogen atmosphere. To this were added water (0.4 mL), $Pd(dppf)Cl_2DCM$ (15 mg, 0.019 mmol) and Cs_2CO_3 (122 mg, 0.376 mmol) at room temperature. The resulting mixture was stirred for 2 h at 100 °C under nitrogen

atmosphere. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 20% to 70%; detector, UV 254 nm to afford (3*S*,4*R*)-4-({7-[5-(1-ethylcyclopropyl)pyridin-2-yl]-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (35 mg, 42%) as a yellow solid. MS ESI calculated for $C_{23}H_{26}FN_5O_3$ $[M + H]^+$, 440.20, found 440.20.

Example 150:

(3*S*,4*R*)-4-({7-[5-(1-ethylcyclopropyl)pyridin-2-yl]-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol

[00817] A mixture of (3*S*,4*R*)-4-({7-[5-(1-ethylcyclopropyl)pyridin-2-yl]-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (35 mg, 0.080 mmol) and K_2CO_3 (33 mg, 0.240 mmol) in MeOH (1 mL) was stirred for 1 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 20% to 70%; detector, UV 254 nm to afford (3*S*,4*R*)-4-({7-[5-(1-ethylcyclopropyl)pyridin-2-yl]-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol (12.2 mg, 38%) as a yellow solid. MS ESI calculated for $C_{21}H_{24}FN_5O_2$ $[M + H]^+$, 398.19, found 398.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.72 (s, 1H), 8.63 (s, 1H), 8.44 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 6.4 Hz, 1H), 7.04 (s, 1H), 4.89 (brs, 1H), 4.16-4.10 (m, 1H), 4.05-3.84 (m, 3H), 3.76-3.66 (m, 1H), 3.58-3.50 (m, 1H), 3.33-3.26 (m, 1H), 2.22-2.14 (m, 1H), 1.79-1.59 (m, 3H), 0.94-0.80 (m, 7H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -159.86 (1F).

Example 153:

5-chloro-2-{[(3*R*,4*S*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: *tert*-butyl (3*R*,4*S*)-4-({5-chloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate

[00818] To a stirred solution of 2,5-dichloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine (60 mg, 0.26 mmol) and *tert*-butyl (3*R*,4*S*)-4-amino-3-fluoropiperidine-1-carboxylate (114 mg, 0.52 mmol) in NMP (1 mL) was added DIEA (202 mg, 1.56 mmol) at room temperature. The resulting mixture was stirred for 16 h at 120 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% TFA), 45% to 65%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*S*)-4-({5-chloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate (89 mg, 83%) as a light yellow solid. MS ESI calculated for $C_{19}H_{27}ClFN_5O_2$ $[M + H]^+$, 412.18, found 412.25.

Step 2: *tert*-butyl (3*R*,4*S*)-4-({5-chloro-6-iodo-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate

[00819] To a stirred solution of *tert*-butyl (3*R*,4*S*)-4-({5-chloro-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate (85 mg, 0.20 mmol) in DMF (1 mL) was added I_2 (209 mg, 0.82 mmol) at room temperature. The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was diluted with EtOAc (100 mL) washed with brine (20 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% TFA), 70% to 90%; detector, UV 254 nm to afford to afford *tert*-butyl (3*R*,4*S*)-4-({5-chloro-6-iodo-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate (55 mg, 49%) as a light yellow solid. MS ESI calculated for $C_{19}H_{26}ClFIN_5O_2$ $[M + H]^+$, 538.08, found 538.10.

Step 3: *tert*-butyl (3*R*,4*S*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate

[00820] To a stirred solution of *tert*-butyl (3*R*,4*S*)-4-({5-chloro-6-iodo-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate (10 mg, 0.02 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.01 mmol) in DMA (0.5 mL) was added $Zn(CN)_2$ (6 mg, 0.05 mmol). The resulting mixture was stirred for 2 h at 120 °C under nitrogen atmosphere. The resulting mixture was diluted with EtOAc (100 mL), washed with brine (20 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (2/1) to afford tert-butyl (3*R*,4*S*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate (30 mg, 82%) as a light yellow solid. MS ESI calculated for $C_{20}H_{26}ClFN_6O_2$ $[M + H]^+$, 437.18, found 437.15.

Step 4: 5-chloro-2-{[(3*R*,4*S*)-3-fluoropiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride

[00821] A solution of *tert*-butyl (3*R*,4*S*)-4-({5-chloro-6-cyano-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-3-fluoropiperidine-1-carboxylate (32 mg, 0.07 mmol) in HCl (gas) in 1,4-dioxane (1 mL) and DCM (1 mL) was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford 5-chloro-2-{[(3*R*,4*S*)-3-fluoropiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (30 mg , crude) as a light yellow solid. MS ESI calculated for $C_{15}H_{19}Cl_2FN_6$ $[M - Cl]^+$, 337.13, found 337.10.

Example 153:

5-chloro-2-{[(3*R*,4*S*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00822] A solution of 5-chloro-2-{[(3*R*,4*S*)-3-fluoropiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (30 mg, 0.08 mmol) and methanesulfonyl methanesulfonate (14 mg, 0.08 mmol) in EtOAc (2 mL) and sat. $NaHCO_3$ (1 mL) was stirred for 1 h at room temperature. The resulting mixture was diluted with EtOAc (30 mL), washed with brine (30 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 20% to 70%; detector, UV 254 nm to afford 5-chloro-2-{[(3*R*,4*S*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-isopropylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (19.4 mg, 58%) as a light yellow solid. MS ESI calculated for $C_{16}H_{20}ClFN_6O_2S$ $[M + H]^+$, 415.10, found 415.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 5.25 (d, *J* = 8.8 Hz, 1H), 4.95 (d, *J* = 48.4 Hz, 1H), 4.30-4.22 (m, 1H), 4.04-3.99 (m, 2H), 3.68-3.60 (m, 1H), 3.27-3.07 (m, 2H), 2.96 (s, 3H), 2.09-1.91 (m, 2H), 1.47 (d, *J* = 7.2 Hz, 6H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -201.75 (1F).

Example 154:

5-chloro-2-{[(3*R*,4*S*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/^{i}PrOH = 70/30, 1st peak)

Example 155:

5-chloro-2-{[(3*R*,4*S*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/^{i}PrOH = 70/30, 2nd peak)

Step 1: *tert*-butyl (3*R*,4*S*)-4-((5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)-3-fluoropiperidine-1-carboxylate

[00823] To a stirred mixture of 2,5-dichloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (120 mg, 0.465 mmol) and *tert*-butyl (3*R*,4*S*)-4-amino-3-fluoropiperidine-1-carboxylate (405 mg, 1.860 mmol) in NMP (1 mL) was added DIEA (360 mg, 2.790 mmol). The resulting mixture was stirred for 16 h at 100 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 60% to 80%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*S*)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate

(130 mg, 63%) as yellow oil. MS ESI calculated for $C_{21}H_{31}ClFN_5O_2$ $[M + H]^+$, 439.22, found 440.30.

Step 2: *tert*-butyl (3*R*,4*S*)-4-((5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)-3-fluoropiperidine-1-carboxylate

[00824] To a stirred mixture of *tert*-butyl (3*R*,4*S*)-4-{[5-chloro-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (130 mg, 0.295 mmol) in DMF (1 mL) was added I_2 (299 mg, 1.180 mmol) at room temperature. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 50% to 80%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*S*)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (120 mg, 71%) as a yellow solid. MS ESI calculated for $C_{21}H_{30}ClFIN_5O_2$ $[M + H]^+$, 566.11, found 566.30.

Step 3: *tert*-butyl (3*R*,4*S*)-4-((5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)-3-fluoropiperidine-1-carboxylate

[00825] To a stirred mixture of *tert*-butyl (3*R*,4*S*)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (110 mg, 0.194 mmol) and $Pd(PPh_3)_4$ (22 mg, 0.019 mmol) in DMF (1 mL) was added $Zn(CN)_2$ (27 mg, 0.233 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 120 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (80 mg, 88%) as a yellow solid. MS ESI calculated for $C_{22}H_{30}ClFN_6O_2$ $[M + H]^+$, 464.21, found 465.30. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.66 (s, 1H), 5.20 (brs, 1H), 4.92-4.76 (m, 1H), 4.53-4.46 (m, 2H), 3.95-3.90 (m, 1H), 3.26-3.19 (m, 1H),3.05-2.93 (m, 2H), 2.23-2.18 (m, 1H), 1.93-1.85 (m, 2H), 1.61 (s, 9H), 1.45-1.42 (m, 3H), 1.03 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H).

Step 4: 5-chloro-2-(((3*R*,4*S*)-3-fluoro-1-(methylsulfonyl)piperidin-4-yl)amino)-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00826] To a stirred mixture of *tert*-butyl (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-fluoropiperidine-1-carboxylate (70 mg, 0.151 mmol) in DCM (1 mL) was added HCl (gas) in 1,4-dioxane (1 mL) dropwise at room temperature. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure. To this were added sat. $NaHCO_3$ (1 mL),

EtOAc (1 mL), and methanesulfonyl methanesulfonate (39 mg, 0.226 mmol). The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was diluted with EtOAc (50 mL), washed with brine (10 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (1/1) to afford 5-chloro-2-{[(3*R*,4*S*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (65 mg, 97%) as a yellow solid. MS ESI calculated for $C_{18}H_{24}ClFN_6O_2S$ $[M + H]^+$, 443.14, found 443.15.

Example 154:

5-chloro-2-{[(3*R*,4*S*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/^{i}PrOH = 70/30, 1st peak)

Example 155:

5-chloro-2-{[(3*R*,4*S*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/^{i}PrOH = 70/30, 2nd peak)

[00827] 5-chloro-2-{[(3*R*,4*S*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile (70 mg) was purified by Prep-Chiral-HPLC with the following conditions: Column: CHIRALPAK AD-H, 2 x 25 cm, 5 μm; Mobile Phase A: Hexane, Mobile Phase B: *i*-PrOH; Flow rate: 20 mL/min; Gradient: A:B = 70:30; Wave Length: 254/220 nm.

[00828] RT_1: 9.73 min to afford 5-chloro-2-{[(3*R*,4*S*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/^{i}PrOH = 70/30, 1st peak) (14.9 mg, 21%) as an off-white solid. MS ESI calculated for $C_{18}H_{24}ClFN_6O_2S$ $[M + H]^+$, 443.14, found 443.25. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 5.24 (d, *J* = 8.8 Hz, 1H), 4.94 (d, *J* = 48.4 Hz, 1H), 4.30-4.23 (m, 1H), 4.04-3.95 (m, 2H), 3.28-3.06 (m, 3H), 2.96 (s, 3H), 2.26-2.16 (m, 1H), 2.08-1.91 (m, 2H), 1.46 (d, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).

[00829] RT_2: 12.05 min to afford 5-chloro-2-{[(3*R*,4*S*)-3-fluoro-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/^{i}PrOH = 70/30, 2nd peak) (12.5 mg, 18%) as an off-white solid. MS ESI calculated for $C_{18}H_{24}ClFN_6O_2S$ $[M + H]^+$, 443.14, found 443.25. ^{1}H NMR (400 MHz,

Chloroform-*d*) δ 8.69 (s, 1H), 5.24 (d, *J* = 8.4 Hz, 1H), 4.93 (d, *J* = 48.4 Hz, 1H), 4.29-4.22 (m, 1H), 4.04-3.95 (m, 2H), 3.28-3.07 (m, 3H), 2.96 (s, 3H), 2.24-2.18 (m, 1H), 2.06-1.92 (m, 2H), 1.46 (d, *J* = 7.2 Hz, 3H), 1.05 (d, *J* = 6.4 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).

Example 156:

5-chloro-7-(2-methylpropyl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: 5-chloro-6-iodo-7-(2-methylpropyl)-*N*-(oxan-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-amine

[00830] To a stirred solution of 2,5-dichloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine (60 mg, 0.162 mmol) and oxan-4-amine (49 mg, 0.486 mmol) in NMP (1 mL) was added DIEA (105 mg, 0.810 mmol). The resulting mixture was stirred for 16 h at 80 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 70%; detector, UV 254 nm to afford 5-chloro-6-iodo-7-(2-methylpropyl)-*N*-(oxan-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-amine (45 mg, 63%) as a light yellow solid. MS ESI calculated for $C_{15}H_{20}ClIN_4O$ $[M + H]^+$, 435.04, found 435.05.

Example 156:

5-chloro-7-(2-methylpropyl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00831] To a stirred solution of 5-chloro-6-iodo-7-(2-methylpropyl)-*N*-(oxan-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-amine (45 mg, 0.104 mmol) and $Zn(CN)_2$ (7 mg, 0.062 mmol) in DMA (2 mL) was added $Pd(PPh_3)_4$ (12 mg, 0.010 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 120 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 30% to 60%; detector, UV 254 nm to afford 5-chloro-7-(2-methylpropyl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (21 mg, 62%) as a light yellow solid. MS ESI calculated for $C_{16}H_{20}ClN_5O$ $[M + H]^+$, 334.14, found 334.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 4.96-4.94 (m, 1H), 4.06-4.02 (m, 2H), 3.91-3.87 (m, 1H), 3.60-3.53 (m, 2H), 2.89 (d, *J* = 7.2 Hz, 2H), 2.27-2.18 (m, 1H), 2.17-2.09 (m, 2H), 1.67-1.61 (m, 2H), 1.00 (d, *J* = 6.4 Hz, 6H).

Example 157:

5-chloro-7-(1-methylcyclobutyl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: 5-chloro-6-iodo-7-(1-methylcyclobutyl)-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-amine

[00832] A mixture of 2,5-dichloro-6-iodo-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (60 mg, 0.157 mmol), DIEA (122 mg, 0.942 mmol) and oxan-4-amine (48 mg, 0.471 mmol) in NMP (1 mL) was stirred for 16 h at 80 °C. The resulting mixture was purified by reversed-phase

chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford 5-chloro-6-iodo-7-(1-methylcyclobutyl)-N-(oxan-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-amine (60 mg, 86%) as a yellow solid. MS ESI calculated for $C_{16}H_{20}ClIN_4O$ $[M + H]^+$, 447.04, found 447.05.

Example 157:

5-chloro-7-(1-methylcyclobutyl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00833] A mixture of 5-chloro-6-iodo-7-(1-methylcyclobutyl)-*N*-(oxan-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-amine (60 mg, 0.134 mmol), $Pd(PPh_3)_4$ (16 mg, 0.013 mmol) and $Zn(CN)_2$ (9 mg, 0.080 mmol) in DMF (1 mL) was stirred for 2 h at 120 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 45% to 65%; detector, UV 254 nm to afford 5-chloro-7-(1-methylcyclobutyl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (16.8 mg, 36%) as an off-white solid. MS ESI calculated for $C_{17}H_{20}ClN_5O$ $[M + H]^+$, 346.14, found 346.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.65 (s, 1H), 4.86 (d, J = 6.8 Hz, 1H), 4.04-4.02 (m, 2H), 3.83-3.74 (m, 1H), 3.57-3.51 (m, 2H), 2.80-2.69 (m, 2H), 2.30-2.22 (m, 3H), 2.13-2.07 (m, 2H), 1.97-1.92 (m, 1H), 1.65-1.46 (m, 5H).

Example 158:

5-chloro-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: 5-chloro-*N*-[(3*S*,4*R*)-3-fluorooxan-4-yl]-6-iodo-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-amine

[00834] A mixture of 2,5-dichloro-6-iodo-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (60 mg, 0.157 mmol), (3*S*,4*R*)-3-fluorooxan-4-amine hydrochloride (73 mg, 0.471 mmol) and DIEA (122 mg, 0.942 mmol) in NMP (2 mL) was stirred for 16 h at 80 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 55%; detector, UV 254 nm to afford 5-chloro-*N*-[(3*S*,4*R*)-3-fluorooxan-4-yl]-6-iodo-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-amine (33 mg, 45%) as a brown solid. MS ESI calculated for $C_{16}H_{19}ClFIN_4O$ $[M + H]^+$, 465.03, found 465.10.

Example 158:

5-chloro-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00835] To a stirred solution of 5-chloro-*N*-[(3*S*,4*R*)-3-fluorooxan-4-yl]-6-iodo-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-amine (30 mg, 0.065 mmol) and $Zn(CN)_2$ (5 mg,

0.043 mmol) in DMF (1 mL) was added $Pd(PPh_3)_4$ (7 mg, 0.006 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 120 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 50% to 70%; detector, UV 254 nm to afford 5-chloro-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}-7-(1-methylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (4.7 mg, 20%) as a light yellow solid. MS ESI calculated for $C_{17}H_{19}ClFN_5O$ $[M + H]^+$, 364.13, found 364.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 5.06 (d, *J* = 6.0 Hz, 1H), 4.64-4.50 (m, 1H), 4.13-3.89 (m, 3H), 3.66-3.55 (m, 2H), 2.77-2.70 (m, 2H), 2.45-2.41 (m, 1H), 2.33-2.24 (m, 3H), 1.99-1.91 (m, 1H), 1.72-1.62 (m, 4H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -193.53 (1F).

Example 159:

5-chloro-2-{[(3*S*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (Lux 5um Cellulose-4, Hexane/EtOH = 60/40, 1st peak)

Example 160:

5-chloro-2-{[(3*S*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (Lux 5um Cellulose-4, Hexane/EtOH = 60/40, 2nd peak)

Step 1: *tert*-butyl (3*S*,4*S*)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate

[00836] A solution of 2,5-dichloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (100 mg, 0.260 mmol), *tert*-butyl (3*S*,4*S*)-4-amino-3-hydroxypiperidine-1-carboxylate (169 mg, 0.780 mmol) and DIEA (202 mg, 1.560 mmol) in NMP (1 mL) was stirred for 2 h at 60 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 30% to 50%; detector, UV 254 nm to afford *tert*-butyl (3*S*,4*S*)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (75 mg, 51%) as a light yellow solid. MS ESI calculated for $C_{21}H_{31}ClIN_5O_3$ $[M + H]^+$, 564.12, found 564.10.

Step 2: *tert*-butyl (3*S*,4*S*)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00837] A solution of *tert*-butyl (3*S*,4*S*)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (75 mg, 0.133 mmol), Ac_2O (20 mg, 0.200 mmol) and TEA (40 mg, 0.399 mmol) in DCM (1 mL) was stirred for 16 h at 50 °C.

The resulting mixture was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford *tert*-butyl (3*S*,4*S*)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (70 mg, crude) as a light yellow solid. MS ESI calculated for $C_{23}H_{33}ClIN_5O_4$ $[M + H]^+$, 606.13, found 606.30.

Step 3: *tert*-butyl (3*S*,4*S*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00838] A solution of *tert*-butyl (3*S*,4*S*)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(3-methylbutan-2-*yl*)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (55 mg, 0.091 mmol), $Zn(CN)_2$ (6 mg, 0.055 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) in DMF (1 mL) was stirred for 2 h at 120 °C under nitrogen atmosphere. The mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford *tert*-butyl (3*S*,4*S*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-*yl*]amino}piperidine-1-carboxylate (40 mg, 87%) as a light yellow solid. MS ESI calculated for $C_{24}H_{33}ClN_6O_4$ $[M + H]^+$, 505.23, found 505.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.66 (s, 1H), 5.30 (brs, 1H), 4.97-4.85 (m, 1H), 4.09-3.79 (m, 3H), 3.35-3.14 (m, 3H), 2.38-2.17 (m, 2H), 2.09-2.07 (m, 3H), 1.61-1.50 (m, 10H), 1.47 (d, J = 7.2 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H).

Step 4: (3*S*,4*S*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride

[00839] A solution of *tert*-butyl (3*S*,4*S*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (40 mg, 0.079 mmol) in HCl (gas) in 1,4-dioxane (1 mL) and DCM (1 mL) was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford (3*S*,4*S*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (34 mg, crude) as a light yellow solid. MS ESI calculated for $C_{19}H_{26}Cl_2N_6O_2$ $[M - Cl]^+$, 405.17, found 405.15.

Step 5: (3*S*,4*S*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-*yl*]amino}-1-methanesulfonylpiperidin-3-yl acetate

[00840] A solution of (3*S*,4*S*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (33 mg, 0.075 mmol), $NaHCO_3$ (44 mg, 0.525 mmol) and methanesulfonic anhydride (26 mg, 0.150 mmol) in EtOAc (2 mL) and water (2 mL) was stirred for 40 min at room temperature. The reaction was diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following

conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford (3*S*,4*S*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (33 mg, 91%) as a light yellow solid. MS ESI calculated for $C_{20}H_{27}ClN_6O_4S$ $[M + H]^+$, 483.15, found 483.15.

Step 6: 5-chloro-2-{[(3*S*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00841] A solution of (3*S*,4*S*)-4-{[5-chloro-6-cyano-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (33 mg, 0.068 mmol) and K_2CO_3 (28 mg, 0.204 mmol) in MeOH (1 mL) was stirred for 30 min at room temperature. The mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford 5-chloro-2-{[(3*S*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (30 mg, 99%) as a light yellow solid. MS ESI calculated for $C_{18}H_{25}ClN_6O_3S$ $[M + H]^+$, 441.14, found 441.15.

Example 159:

5-chloro-2-{[(3*S*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (Lux 5um Cellulose-4, Hexane/EtOH = 60/40, 1st peak)

Example 160:

5-chloro-2-{[(3*S*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (Lux 5um Cellulose-4, Hexane/EtOH = 60/40, 2nd peak)

[00842] 5-chloro-2-{[(3*S*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (35 mg) was resolved by Prep-Chiral-HPLC with the following conditions: Column: Lux 5um Cellulose-4, 2.12 x 25 cm, 5 μm; Mobile Phase A: Hexane, Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: A:B = 60:40; Wave Length: 254/220 nm.

[00843] RT_1: 14.17 min to afford 5-chloro-2-{[(3*S*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (Lux 5um Cellulose-4, Hexane/EtOH = 60/40, 1st peak) (6.8 mg, 19%) as an off-white solid. MS ESI calculated for $C_{18}H_{25}ClN_6O_3S$ $[M + H]^+$, 441.14; found 441.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 5.09 (brs, 1H), 4.00-3.96 (m, 1H), 3.88-3.70 (m, 3H), 3.26-3.22

(m, 1H), 2.98-2.89 (m, 4H), 2.83-2.80 (m, 1H), 2.33-2.19 (m, 2H), 1.79-1.74 (m, 1H), 1.47 (d, *J* = 7.2 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.4 Hz, 3H).

[00844] RT_2: 17.01 min to afford 5-chloro-2-{[(3*S*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (Lux 5um Cellulose-4, Hexane/EtOH = 60/40, 2nd peak) (7.6 mg, 21%) as an off-white solid. MS ESI calculated for $C_{18}H_{25}ClN_6O_3S$ $[M + H]^+$, 441.14; found 441.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.74 (s, 1H), 5.17 (brs, 1H), 4.01-3.96 (m, 1H), 3.87-3.74 (m, 3H), 3.29-3.21 (m, 1H), 2.98-2.89 (m, 4H), 2.83-2.77 (m, 1H), 2.34-2.18 (m, 2H), 1.80-1.70 (m, 1H), 1.47 (d, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H).

Example 161:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: 2,4-dichloro-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine

[00845] To a stirred solution of 2,4-dichloropyrrolo[2,1-*f*][1,2,4]triazine (800 mg, 4.255 mmol), 2-ethyl-2-methylbutanoic acid (1.66 g, 12.765 mmol) and $AgNO_3$ (1.45 g, 8.510 mmol) in CH_3CN (24 mL) and water (12 mL) was added $(NH_4)_2S_2O_8$ (4.85 g, 21.275 mmol) in water (12 mL) dropwise at 50 °C. The resulting mixture was stirred for 2 h at 50 °C. The reaction was diluted with water (100 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford 2,4-dichloro-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine (820 mg, 70%) as light yellow oil. MS ESI calculated for $C_{12}H_{15}Cl_2N_3$ $[M + H]^+$, 272.06, found 272.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.04 (d, *J* = 4.8, 1H), 6.82 (d, *J* = 4.8, 1H), 2.35-2.20 (m, 2H), 1.81-1.71 (m, 2H), 1.43 (s, 3H), 0.66-0.62 (m, 6H).

Step 2: 2-chloro-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine

[00846] A solution of 2,4-dichloro-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine (890 mg, 3.270 mmol) and $NaBH_4$ (198 mg, 5.232 mmol) in THF (10 mL) and *i*-PrOH (1 mL) was stirred for 2 h at room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (3 x 50 mL). The filtrate was concentrated under reduced pressure. To the residue was added DDQ (653 mg, 2.878 mmol) in DCM (5 mL). The resulting mixture was stirred for 30 min at room temperature. The resulting mixture was diluted with sat. $NaHCO_3$ (50 mL). The resulting mixture was extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under

reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford 2-chloro-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine (450 mg, 98%) as light yellow oil. MS ESI calculated for $C_{12}H_{16}ClN_3$ $[M + H]^+$, 238.10, found 238.05. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 6.92 (d, J = 4.8 Hz, 1H), 6.82 (d, J = 4.8 Hz, 1H), 2.35-2.25 (m, 2H), 1.80-1.73 (m, 2H), 1.43 (s, 3H), 0.63 (t, J = 7.2 Hz, 6H).

Step 3: 2,5-dichloro-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine

[00847] A solution of 2-chloro-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine (440 mg, 1.851 mmol) and 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (365 mg, 1.851 mmol) in CH_3CN (5 mL) was stirred for 1 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford 2,5-dichloro-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine (280 mg, 55%) as a light yellow solid. MS ESI calculated for $C_{12}H_{15}Cl_2N_3$ $[M + H]^+$, 272.06, found 272.05. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.75 (s, 1H), 6.73 (s, 1H), 2.30-2.21 (m, 2H), 1.79-1.70 (m, 1H), 1.39 (s, 3H), 0.65 (t, J = 7.2 Hz, 6H).

Step 4: *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate

[00848] A solution of 2,5-dichloro-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine (220 mg, 0.808 mmol), *tert*-butyl (3*R*,4*R*)-4-amino-3-hydroxypiperidine-1-carboxylate (524 mg, 2.424 mmol) and DIEA (627 mg, 4.848 mmol) in NMP (3 mL) was stirred for 16 h at 100 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (210 mg, 57%) as a light yellow solid. MS ESI calculated for $C_{22}H_{34}ClN_5O_3$ $[M + H]^+$, 452.24, found 452.25.

Step 5: *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-iodo-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate

[00849] A solution of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (210 mg, 0.465 mmol) and I_2 (590 mg, 2.325 mmol) in DMF (3 mL) was stirred for 16 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 50% to 80%; detector, UV 254 nm to afford tert-butyl (3*R*,4*R*)-4-{[5-chloro-6-iodo-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (200 mg, 74%) as a light yellow solid. MS ESI calculated for $C_{22}H_{33}ClIN_5O_3$ $[M + H]^+$, 578.13, found 578.20.

Step 6: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00850] A solution of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-6-iodo-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (240 mg, 0.415 mmol), Ac_2O (64 mg, 0.622 mmol) and TEA (126 mg, 1.245 mmol) in DCM (3 mL) was stirred for 16 h at 50 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford *tert*-butyl (3R,4R)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(3-methylpentan-3-yl)pyrrolo[2,1-f][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (210 mg, 81%) as a light yellow solid. MS ESI calculated for $C_{24}H_{35}ClIN_5O_4$ $[M + H]^+$, 620.14, found 620.20.

Step 7: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00851] A solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (200 mg, 0.323 mmol), $Zn(CN)_2$ (23 mg, 0.194 mmol) and $Pd(PPh_3)_4$ (37 mg, 0.032 mmol) in DMA (3 mL) was stirred for 2 h at 120 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (130 mg, 77%) as a light yellow solid. MS ESI calculated for $C_{25}H_{35}ClN_6O_4$ $[M + H]^+$, 519.24, found 519.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 5.34 (brs, 1H), 4.91-4.86 (m, 1H), 4.06-3.98 (m, 1H), 3.91-3.84 (m, 2H), 3.23-3.16 (m, 2H), 2.45-2.40 (m, 2H), 2.34-2.29 (m, 1H), 2.08 (s, 3H), 1.71-1.55 (m, 6H), 1.50 (s, 9H), 0.75-0.70 (m, 6H).

Step 8: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride

[00852] A solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (130 mg, 0.250 mmol) in HCl (gas) in 1,4-dioxane (2 mL) and DCM (2 mL) was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (110 mg, crude) as a light yellow solid. MS ESI calculated for $C_{20}H_{28}Cl_2N_6O_2$ $[M - Cl]^+$, 419.19, found 419.20.

Step 9: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate

[00853] A solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (110 mg, 0.242 mmol), $NaHCO_3$ (142 mg, 1.694 mmol) and methanesulfonic anhydride (84 mg, 0.484 mmol) in EtOAc (2 mL) and water (2 mL) was stirred for 40 min at room temperature. The reaction was diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (105 mg, 87%) as a light yellow solid. MS ESI calculated for $C_{21}H_{29}ClN_6O_4S$ $[M + H]^+$, 497.17, found 497.25.

Example 161:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00854] A solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (100 mg, 0.201 mmol) and K_2CO_3 (83 mg, 0.603 mmol) in MeOH (2 mL) was stirred for 30 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 50% to 70%; detector, UV 254 nm to afford 5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(3-methylpentan-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (66.3 mg, 71%) as an off-white solid. MS ESI calculated for $C_{19}H_{27}ClN_6O_3S$ $[M + H]^+$, 455.16; found 455.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 5.05 (d, *J* = 7.2 Hz, 1H), 3.98-3.94 (m, 1H), 3.88-3.70 (m, 3H), 3.00-2.93 (m, 1H), 2.90-2.82 (m, 4H), 2.48-2.33 (m, 3H), 1.76-1.62 (m, 6H), 0.72 (t, *J* = 7.2 Hz, 6H).

Example 162:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: 2,4-dichloro-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine

[00855] A solution of 2,4-dichloropyrrolo[2,1-*f*][1,2,4]triazine (1 g, 5.319 mmol) and 2,2-dimethyl butyric acid (1.85 g, 15.957 mmol) and Ag_2CO_3 (2.93 g, 10.638 mmol) in CH_3CN (10 mL) and water (5 mL) was stirred for 10 min at room temperature. To this was added $(NH_4)_2S_2O_8$ (6.07 g, 26.595 mmol) in water (5 mL) dropwise at room temperature. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The

combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (10/1) to afford 2,4-dichloro-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (700 mg, 51%) as yellow oil. MS ESI calculated for $C_{11}H_{13}Cl_2N_3$ $[M + H]^+$, 258.05; found 258.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.03 (d, *J* = 4.8 Hz, 1H), 6.82 (d, *J* = 4.8 Hz, 1H), 2.07-2.01 (m, 2H), 1.49 (s, 6H), 0.66 (t, *J* = 7.2 Hz, 3H).

Step 2: 2-chloro-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine

[00856] A mixture of 2,4-dichloro-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (700 mg, 2.712 mmol) and $NaBH_4$ (164 mg, 4.339 mmol) in THF (5 mL) and *i*-PrOH (5 mL) was stirred for 4 h at room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (3 x 30 mL). The filtrate was concentrated under reduced pressure. To this was added DDQ (885 mg, 3.899 mmol) in DCM (10 mL). The resulting mixture was stirred for 1 h at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (50 mL) at room temperature. The resulting mixture was extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford 2-chloro-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (500 mg, 92%) as a yellow solid. MS ESI calculated for $C_{11}H_{14}ClN_3$ $[M + H]^+$, 224.09, found 224.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.73 (s, 1H), 6.94 (d, *J* = 4.8 Hz, 1H), 6.83 (d, *J* = 4.8 Hz, 1H), 2.04 (q, *J* = 7.2 Hz, 2H), 1.50 (s, 6H), 0.65 (t, *J* = 7.2 Hz, 3H).

Step 3: 2,5-dichloro-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine

[00857] A mixture of 2-chloro-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (500 mg, 2.235 mmol) and 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (264 mg, 1.341 mmol) in CH_3CN (5 mL) was stirred for 1 h at room temperature. The resulting mixture was purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford 2,5-dichloro-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (350 mg, 60%) as yellow oil. MS ESI calculated for $C_{11}H_{13}Cl_2N_3$ $[M + H]^+$, 258.05, found 258.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.77 (s, 1H), 6.74 (s, 1H), 2.02 (q, *J* = 7.2 Hz, 2H), 1.47 (s, 6H), 0.67 (t, *J* = 7.2 Hz, 3H).

Step 4: *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate

[00858] A mixture of 2,5-dichloro-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (320 mg, 1.240 mmol), *tert*-butyl (3*R*,4*R*)-4-amino-3-hydroxypiperidine-1-carboxylate hydrochloride (940 mg, 3.719 mmol) and DIEA (641 mg, 4.959 mmol) in NMP (5 mL) was stirred for 16 h at 80 °C.

The reaction was quenched by the addition of water (50 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (450 mg, 83%) as a yellow solid. MS ESI calculated for $C_{21}H_{32}ClN_5O_3$ $[M + H]^+$, 438.22, found 438.20.

Step 5: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00859] A mixture of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (450 mg, 1.027 mmol), Ac_2O (157 mg, 1.538 mmol) and TEA (416 mg, 4.111 mmol) in DCM (5 mL) was stirred for 16 h at 50 °C. The resulting mixture was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (450 mg, 91%) as a yellow solid. MS ESI calculated for $C_{23}H_{34}ClN_5O_4$ $[M + H]^+$, 480.23, found 480.25.

Step 6: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00860] A mixture of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (440 mg, 0.917 mmol) and I_2 (931 mg, 3.668 mmol) in DMF (5 mL) was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (aq.) (50 mL) at room temperature. The resulting mixture was extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (380 mg, 68%) as a yellow solid. MS ESI calculated for $C_{23}H_{33}ClIN_5O_4$ $[M + H]^+$, 606.13, found 606.25.

Step 7: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00861] A mixture of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-iodo-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (100 mg, 0.165 mmol), $Zn(CN)_2$ (11 mg, 0.099 mmol) and $Pd(PPh_3)_4$ (19 mg, 0.017 mmol) in DMA (2 mL) was stirred for 2 h at 120 °C under nitrogen atmosphere. The reaction was quenched by the addition of water (20 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined

organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (2/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (65 mg, 78%) as a yellow solid. MS ESI calculated for $C_{24}H_{33}ClN_6O_4$ $[M + H]^+$, 505.23, found 505.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 5.51 (brs, 1H), 4.93-4.86 (m, 1H), 4.06-4.00 (m, 1H), 3.90-3.83 (m, 2H), 3.22-3.15 (m, 2H), 2.35-2.28 (m, 1H), 2.07-2.02 (m, 6H), 1.63 (s, 6H) 1.49 (s, 9H), 0.72 (t, J = 7.2 Hz, 3H).

Step 8: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate

[00862] A mixture of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (80 mg, 0.158 mmol) and HCl (gas) in 1,4-dioxane (1 mL) in DCM (1 mL) was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure. To this were added methanesulfonic anhydride (51 mg, 0.294 mmol) in EtOAc (2 mL) and sat. $NaHCO_3$ (2 mL). The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (65 mg, crude) as a yellow solid. MS ESI calculated for $C_{20}H_{27}ClN_6O_4S$ $[M + H]^+$, 483.15, found 483.15.

Example 162:

5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00863] A mixture of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (65 mg, 0.135 mmol) and K_2CO_3 (56 mg, 0.405 mmol) in MeOH (0.5 mL) was stirred for 1 h at room temperature. The resulting mixture was purified by reverse phase flash with the following conditions: C18 column; mobile phase, CH_3CN in water (5 mM NH_4HCO_3); 40% to 60%; Flow rate: 25 mL/min; Detector: 220/254 nm to afford 5-chloro-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}-7-(2-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (46.1 mg, 76%) as a yellow solid. MS ESI calculated for $C_{18}H_{25}ClN_6O_3S$ $[M + H]^+$,441.14, found 441.30. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 5.16 (brs, 1H), 3.99-3.93 (m, 1H), 3.89-3.83 (m, 1H), 3.79-3.71

(m, 2H), 3.00-2.93 (m, 1H), 2.90-2.83 (m, 4H), 2.39-2.34 (m, 1H), 2.09-2.03 (m, 2H), 1.76-1.70 (m, 1H), 1.63 (s, 6H), 0.72 (t, J = 7.6 Hz, 3H).

Example 163:

5-chloro-7-(1-ethylcyclopropyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: methyl 1-{2-chloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl}cyclopropane-1-carboxylate

[00864] To a stirred solution of zinc (0.77 g, 11.732 mmol) in DMA (40 mL) were added 1,2-dibromoethane (1.50 g, 7.985 mmol) and TMSCl (0.60 g, 5.523 mmol) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. Then to thise was added methyl 1-bromocyclopropane-1-carboxylate (5.20 g, 29.048 mmol). The resulting mixture was stirred for 2 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down. To this were added 7-bromo-2-chloropyrrolo[2,1-*f*][1,2,4]triazine (4 g, 17.207 mmol), $Pd_2(dba)_3$ (1.58 g, 1.721 mmol) and CTC-Q-Phos (2.44 g, 3.441 mmol) in THF (120 mL) at room temperature. The resulting mixture was stirred for 1 h at room temperature. The reaction was quenched with water (60 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (60 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford methyl 1-{2-chloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl}cyclopropane-1-carboxylate (3.60 g, 83%) as a brown yellow solid. MS ESI calculated for $C_{11}H_{10}ClN_3O_2$ $[M + H]^+$, 252.05; found 251.95. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.77 (s, 1H), 6.91 (d, J = 4.4 Hz, 1H), 6.86 (d, J = 4.4 Hz, 1H), 3.64 (s, 3H), 1.86-1.82 (m, 2H), 1.35-1.31 (m, 2H).

Step 2: (1-{2-chloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl}cyclopropyl)methanol

[00865] To a stirred solution of methyl 1-{2-chloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl}cyclopropane-1-carboxylate (3.60 g, 14.304 mmol) in THF (40 mL) was added $LiAlH_4$ (28.6 mL, 71.520 mmol) in portions at 0 °C. The resulting mixture was stirred for 2 h at 0 °C. To this was added $Na_2SO_4.10H_2O$ (15 g) at 0 °C. The resulting mixture was filtered, the filter cake was washed with EtOAc (3 x 30 mL). The filtrate was concentrated under reduced pressure. To the residue was added DDQ (4.87 g, 21.456 mmol) in DCM (40 mL). The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was diluted with water (50 mL) and extracted with DCM (3 x 75 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (1-{2-chloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl}cyclopropyl)methanol (2.0 g, 62%) as a yellow solid. MS ESI calculated for $C_{10}H_{10}ClN_3O$ $[M + H]^+$, 224.05; found 224.00. ^{1}H NMR

(400 MHz, Chloroform-*d*) δ 8.73 (s, 1H), 6.92 (d, *J* = 4.8 Hz, 1H), 6.84 (d, *J* = 4.8 Hz, 1H), 3.84 (s, 2H), 1.15-1.06 (m, 4H).

Step 3: 1-{2-chloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl}cyclopropane-1-carbaldehyde

[00866] A solution of (1-{2-chloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl}cyclopropyl)methanol (3.00 g, 13.413 mmol) and Dess-Martin wreagent (22.76 g, 53.652 mmol) in DCM (30 mL) was stirred for 3 h at room temperature. The reaction was quenched with sat. $NaHCO_3$ (15 mL) at 0 °C. The resulting mixture was extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 1-{2-chloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl}cyclopropane-1-carbaldehyde (2.0 g, 67%) as a yellow solid. MS ESI calculated for $C_{10}H_8ClN_3O$ $[M + H]^+$, 222.04; found 222.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 9.22 (s, 1H), 8.81 (s, 1H), 6.95 (d, *J* = 4.8 Hz, 1H), 6.89 (d, *J* = 4.8 Hz, 1H), 1.90-1.78 (m, 2H), 1.62-1.52 (m, 2H).

Step 4: 2-chloro-7-(1-ethynylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazine

[00867] To a stirred solution of 1-{2-chloropyrrolo[2,1-*f*][1,2,4]triazin-7-yl}cyclopropane-1-carbaldehyde (1.20 g, 5.414 mmol) and K_2CO_3 (1.50 g, 10.828 mmol) in MeOH (25 mL) was added dimethyl (1-diazo-2-oxopropyl)phosphonate (2.08 g, 10.828 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (20 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford 2-chloro-7-(1-ethynylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazine (800 mg, 67%) as a light yellow solid. MS ESI calculated for $C_{11}H_8ClN_3$ $[M + H]^+$, 218.04; found 218.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.75 (s, 1H), 6.96 (d, *J* = 4.8 Hz, 1H), 6.89 (d, *J* = 4.8 Hz, 1H), 2.03 (s, 1H), 1.64-1.57 (m, 2H), 1.57-1.52 (m, 2H).

Step 5: 2-chloro-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazine

[00868] To a solution of 2-chloro-7-(1-ethynylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazine (1.30 g, 5.973 mmol) in EtOAc (30 mL) was added PtO_2 (0.14 g, 0.597 mmol) under nitrogen atmosphere. The mixture was hydrogenated at room temperature for 1 h under hydrogen atmosphere (~1 atm). The resulting mixture was filtered. The filtrate was concentrated under reduced pressure. To the residue was added DDQ (2.03 g, 8.960 mmol) in DCM (30 mL). The resulting mixture was stirred for 1 h at room temperature. The reaction was quenched with sat. $NaHCO_3$ (10 mL). The resulting mixture was extracted with DCM (3 x 30 mL). The combined organic layers were

washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford 2-chloro-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazine (650 mg, 49%) as yellow oil. MS ESI calculated for $C_{11}H_{12}ClN_3$ $[M + H]^+$, 222.07; found 222.05. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 6.87 (d, *J* = 4.8 Hz, 1H), 6.79 (d, *J* = 4.8 Hz, 1H), 1.79 (q, *J* = 7.2 Hz, 2H), 0.98-0.91 (m, 2H), 0.90-0.85 (m, 2H), 0.81 (t, *J* = 7.2 Hz, 3H).

Step 6: 2,5-dichloro-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazine

[00869] A solution of 2-chloro-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazine (650 mg, 2.932 mmol) and NCS (411 mg, 3.079 mmol) in DMF (10 mL) was stirred for 16 h at room temperature. The reaction was quenched with water (15 mL). The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford 2,5-dichloro-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazine (650 mg, 86%) as a yellow solid. MS ESI calculated for $C_{11}H_{11}Cl_2N_3$ $[M + H]^+$, 256.03; found 256.05. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.75 (s, 1H), 6.72 (s, 1H), 1.77 (q, *J* = 7.2 Hz, 2H), 0.96-0.93 (m, 2H), 0.91-0.86 (m, 2H), 0.83 (t, *J* = 7.2 Hz, 3H).

Step 7: 2,5-dichloro-7-(1-ethylcyclopropyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazine

[00870] A solution of 2,5-dichloro-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazine (575 mg, 2.245 mmol) and I_2 (2.28 g, 8.980 mmolv) in DMF (12 mL) was stirred for 16 h at room temperature. The reaction was quenched with sat. $Na_2S_2O_3$ (10 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford 2,5-dichloro-7-(1-ethylcyclopropyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazine (400 mg, 35%) as yellow oil. MS ESI calculated for $C_{11}H_{10}Cl_2IN_3$ $[M + H]^+$, 381.93; found 382.05. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.76 (s, 1H), 1.80-1.69 (m, 2H), 1.08-1.05 (m, 2H), 1.03-0.99 (m, 2H), 0.96-0.89 (m, 3H).

Step 8: *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclopropyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate

[00871] To a stirred solution of 2,5-dichloro-7-(1-ethylcyclopropyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazine (400 mg, 0.806 mmol) in NMP (8 mL) were added *tert*-butyl (3*R*,4*R*)-4-amino-3-hydroxypiperidine-1-carboxylate (523 mg, 2.418 mmol) and DIEA (521 mg, 4.030 mmol). The resulting mixture was stirred for 16 h at 100 °C. The resulting mixture was diluted with EtOAc

(50 mL) and washed with water (3 x 15 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclopropyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (350 mg, 77%) as a Brown yellow solid. MS ESI calculated for $C_{21}H_{29}ClIN_5O_3$ [M + H]$^+$, 562.10; found 562.15.

Step 9: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-7-(1-ethylcyclopropyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00872] To a stirred solution of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclopropyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (350 mg, 0.623 mmol) in DCM (8 mL) were added Ac_2O (95 mg, 0.934 mmol) and TEA (315 mg, 3.115 mmol). The resulting mixture was stirred for 16 h at 50 °C. The resulting mixture was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-7-(1-ethylcyclopropyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (300 mg, 79%) as yellow oil. MS ESI calculated for $C_{23}H_{31}ClIN_5O_4$ [M + H]$^+$, 604.11; found 604.15.

Step 10: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

[00873] To a stirred mixture of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-7-(1-ethylcyclopropyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (300 mg, 0.497 mmol) in DMA (6 mL) were added $Zn(CN)_2$ (35 mg, 0.298 mmol) and $Pd(PPh_3)_4$ (57 mg, 0.050 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred for 2 h at 120°C under nitrogen atmosphere. The reaction was quenched by the addition of water (50 mL). The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (130 mg, 52%) as a light yellow solid. MS ESI calculated for $C_{24}H_{31}ClN_6O_4$ [M + H]$^+$, 503.21; found 503.25. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 5.32 (brs, 1H), 5.03-4.95 (m, 1H), 4.10-3.95 (m, 1H), 3.94-3.84 (m, 2H), 3.20-3.12 (m, 2H), 2.42-2.33 (m, 1H), 2.09 (s, 3H), 1.78-1.63 (m, 3H), 1.50 (s, 9H), 1.08-0.99 (m, 2H), 0.95-0.89 (m, 5H).

Step 11: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride

[00874] To a stirred solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (130 mg, 0.258 mmol) in DCM (2 mL) was added HCl (gas) in 1,4-dioxane (2 mL) dropwise at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (100 mg, 88%) as a yellow solid. MS ESI calculated for $C_{19}H_{24}Cl_2N_6O_2$ $[M - Cl]^+$, 403.16; found 403.15.

Step 12: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate

[00875] To a stirred solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (30 mg, 0.068 mmol) were added sat. $NaHCO_3$ (1 mL) and methanesulfonic anhydride (35 mg, 0.204 mmol) in EtOAc (1 mL). The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (1/1) to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (20 mg, 60%) as light yellow solid. MS ESI calculated for $C_{20}H_{25}ClN_6O_4S$ $[M + H]^+$, 481.13; found 481.35.

Example 163:

5-chloro-7-(1-ethylcyclopropyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00876] A solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (20 mg, 0.042 mmol) and K_2CO_3 (17 mg, 0.126 mmo) in MeOH (1 mL) was stirred for 40 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 35% to 55%; detector, UV 254 nm to afford 5-chloro-7-(1-ethylcyclopropyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (9 mg, 51%) as an off-white solid. MS ESI calculated for $C_{18}H_{23}ClN_6O_3S$ $[M + H]^+$, 439.12; found 439.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 5.14 (d, *J* = 5.6 Hz, 1H), 4.04-3.99 (m, 1H), 3.88-3.82 (m, 2H), 3.73-3.70 (m, 1H), 2.93-2.86 (m, 4H), 2.75-2.70 (m, 1H), 2.33-2.29 (m, 1H), 1.83-1.73 (m, 2H), 1.65-1.60 (m, 1H), 1.09-1.06 (m, 1H), 1.00-0.91 (m, 6H).

Example 164:

5-chloro-7-(1-ethylcyclopropyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-trifluoromethanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: 3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-trifluoromethanesulfonylpiperidin-3-yl acetate

[00877] To a stirred solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (40 mg, 0.091 mmol) was added sat. $NaHCO_3$ (1 mL) and trifluoromethanesulfonyl chloride (92 mg, 0.546 mmol) in EtOAc (1.5 mL). The resulting mixture was stirred for 4 h at room temperature. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 40% to 60%; detector, UV 254 nm to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-trifluoromethanesulfonylpiperidin-3-yl acetate (14 mg, 28%) as a light yellow solid. MS ESI calculated for $C_{20}H_{22}ClF_3N_6O_4S$ $[M + H]^+$, 535.11; found 535.35.

Example 164:

5-chloro-7-(1-ethylcyclopropyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-trifluoromethanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00878] A solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-trifluoromethanesulfonylpiperidin-3-yl acetate (14 mg, 0.026 mmol) and K_2CO_3 (10 mg, 0.078 mmol) in MeOH (1 mL) was stirred for 40 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 45% to 65%; detector, UV 254 nm to afford 5-chloro-7-(1-ethylcyclopropyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-trifluoromethanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (3.5 mg, 27%) as an off-white solid. MS ESI calculated for $C_{18}H_{20}ClF_3N_6O_3S$ $[M + H]^+$, 493.10; found 493.30. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.72 (s, 1H), 5.24 (brs, 1H), 4.16-4.13 (m, 1H), 4.05-3.97 (m, 1H), 3.86-3.76 (m, 2H), 3.24-3.18 (m, 1H), 3.08-2.96 (m, 1H), 2.39-2.25 (m, 1H), 1.84-1.71 (m, 2H), 1.67-1.58 (m, 1H), 1.12-1.05 (m, 1H), 1.02-0.89 (m, 6H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -75.54 (3F).

Example 165:

5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-difluoromethanesulfonylpiperidin-3-yl acetate

[00879] To a stirred solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (40 mg, 0.091 mmol) was added sat. $NaHCO_3$ (1 mL) and difluoromethanesulfonyl chloride (41 mg, 0.273 mmol) in EtOAc (1.5 mL). The resulting mixture was stirred for 4 h at room temperature. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 35% to 60%; detector, UV 254 nm to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-difluoromethanesulfonylpiperidin-3-yl acetate (18 mg, 38%) as a light yellow solid. MS ESI calculated for $C_{20}H_{23}ClF_2N_6O_4S$ $[M + H]^+$, 517.12; found 517.15.

Example 165:

5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00880] A solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-difluoromethanesulfonylpiperidin-3-yl acetate (18 mg, 0.035 mmol) and K_2CO_3 (14 mg, 0.105 mmol) in MeOH (1 mL) was stirred for 40 min at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10mM NH_4HCO_3), 30% to 55% gradient in 8 min; detector, UV 254 nm to afford 5-chloro-2-{[(3*R*,4*R*)-1-difluoromethanesulfonyl-3-hydroxypiperidin-4-yl]amino}-7-(1-ethylcyclopropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (6 mg, 36%) as an off-white solid. MS ESI calculated for $C_{18}H_{21}ClF_2N_6O_3S$ $[M + H]^+$, 475.11; found 475.25. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 6.26 (t, *J* = 54.0 Hz, 1H), 5.12 (brs, 1H), 4.18-4.13 (m, 1H), 4.02-3.98 (m, 1H), 3.85-3.75 (m, 2H), 3.27-3.21 (m, 1H), 3.08-3.02 (m, 1H), 2.32-2.27 (m, 1H), 1.85-1.71 (m, 2H), 1.67-1.57 (m, 1H), 1.09-0.91 (m, 7H).^{19}F NMR (377 MHz, Chloroform-*d*) δ -121.41 (2F).

Example 166:

5-chloro-7-cyclopropyl-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({7-cyclopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00881] A mixture of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({7-bromopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (200 mg, 0.44 mmol), cyclopropylboronic acid (113 mg, 1.32 mmol), K_3PO_4 (187 mg, 0.88 mmol) and $Pd(dppf)Cl_2$·DCM (36 mg, 0.04 mmol) in dioxane (2 mL) and water (0.4 mL) was stirred for 16 h at 100 °C under nitrogen atmosphere. The resulting mixture was diluted with water (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({7-cyclopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (90 mg, 49%) as a light yellow solid. Exact Mass calculated for $C_{21}H_{29}N_5O_4$ $[M + H]^+$, 416.22, found 416.20.

Step 2: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-cyclopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00882] To a stirred solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({7-cyclopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (97 mg, 0.20 mmol) in DMF (1 mL) was added NCS (29 mg, 0.22 mmol) at room temperature. The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% TFA), 50% to 70%; detector, UV 254 nm to afford to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-cyclopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (75 mg, 82%) as a light yellow solid. Exact Mass calculated for $C_{21}H_{28}ClN_5O_4$ $[M + H]^+$, 450.18, found 450.20.

Step 3: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-cyclopropyl-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00883] A solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-cyclopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (77 mg, 0.17 mmol) and NIS (58 mg, 0.26 mmol) in DMF (0.8 mL) was stirred for 1 h at room temperature. The resulting mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-cyclopropyl-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (40 mg, 40%) as a light yellow solid. Exact Mass calculated for $C_{21}H_{27}ClIN_5O_4$ $[M + H]^+$, 576.08, found 576.15.

Step 4: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-cyano-7-cyclopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate

[00884] To a stirred solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-7-cyclopropyl-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (42 mg, 0.07 mmol) and $Zn(CN)_2$ (5 mg, 0.04 mmol) in DMA (2 mL) was added $Pd(PPh_3)_4$ (8 mg, 0.01 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was irradiated with microwave radiation for 4 h at 130 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 30% to 60%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-cyano-7-cyclopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (30 mg, 87%) as a light yellow solid. Exact Mass calculated for $C_{22}H_{27}ClN_6O_4$ [M + H]$^+$, 475.18, found 475.30. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.63 (s, 1H), 5.18 (brs, 1H), 4.95-4.91 (m, 1H), 4.07-4.02 (m, 1H), 3.93-3.88 (m, 2H), 3.18-3.12 (m, 2H), 2.38-2.24 (m, 2H), 2.07 (s, 3H), 1.59-1.49 (m, 10H), 1.42-1.12 (m, 4H).

Step 5: (3*R*,4*R*)-4-({5-chloro-6-cyano-7-cyclopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-methanesulfonylpiperidin-3-yl acetate

[00885] To a stirred solution of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-({5-chloro-6-cyano-7-cyclopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)piperidine-1-carboxylate (30 mg, 0.06 mmol) and HCl (gas) in 1,4-dioxane (0.5 mL) in DCM (1 mL) at room temperature. The resulting mixture was stirred for 1 h at room temperature. The mixture was concentrated under reduced pressure. To this were added sat. $NaHCO_3$ (1 mL) and methanesulfonic anhydride (19 mg, 0.11 mmol) in EtOAc (1 mL). The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford (3*R*,4*R*)-4-({5-chloro-6-cyano-7-cyclopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-methanesulfonylpiperidin-3-yl acetate (20 mg, crude) as yellow solid. Exact Mass calculated for $C_{18}H_{21}ClN_6O_4S$ [M + H]$^+$, 453.10, found 453.15.

Example 166:

5-chloro-7-cyclopropyl-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00886] To a stirred solution of (3*R*,4*R*)-4-({5-chloro-6-cyano-7-cyclopropylpyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)-1-methanesulfonylpiperidin-3-yl acetate (20 mg, 0.04 mmol) and K_2CO_3 (12 mg, 0.09 mmol) in MeOH (1 mL) at room temperature. The resulting mixture was stirred for 1 h at room temperature. The mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 30% to 50%; detector, UV 254 nm to afford to afford 5-chloro-7-cyclopropyl-2-{[(3*R*,4*R*)-3-hydroxy-1-

methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (2 mg, 11%) as a light yellow solid. Exact Mass calculated for $C_{16}H_{19}ClN_6O_3S$ [M + H]$^+$, 411.09, found 411.10. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (s, 1H), 7.42 (d, J = 7.2 Hz, 1H), 5.28 (brs, 1H), 3.65-3.59 (m, 3H), 3.51-3.47 (m, 1H), 2.91-2.86 (m, 4H), 2.68-2.65 (m, 1H), 2.30-2.26 (m, 1H), 2.17-2.12 (m, 1H), 1.56-1.49 (m, 1H), 1.27-1.20 (m, 2H), 1.15-1.12 (m, 2H).

Example 167:

5-chloro-7-(3-methylbutan-2-yl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/^{i}PrOH = 97/3, 1st peak)

Example 168:

5-chloro-7-(3-methylbutan-2-yl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/^{i}PrOH = 97/3, 2nd peak)

Step 1: 5-chloro-6-iodo-7-(3-methylbutan-2-yl)-*N*-(oxan-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-amine

[00887] To a stirred solution of 2,5-dichloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (100 mg, 0.260 mmol) and oxan-4-amine (79 mg, 0.780 mmol) in NMP (2 mL) was added DIEA (168 mg, 1.300 mmol). The resulting mixture was stirred for 16 h at 80 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 70%; detector, UV 254 nm to afford 5-chloro-6-iodo-7-(3-methylbutan-2-yl)-*N*-(oxan-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-amine (90 mg, 77%) as light yellow solid. MS ESI calculated for $C_{16}H_{22}ClIN_4O$ [M + H]$^+$, 449.05, found 449.05.

Step 2: 5-chloro-7-(3-methylbutan-2-yl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00888] To a stirred solution of 5-chloro-6-iodo-7-(3-methylbutan-2-yl)-*N*-(oxan-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-amine (90 mg, 0.201 mmol) and $Zn(CN)_2$ (14 mg, 0.121 mmol) in DMA (2 mL) was added $Pd(PPh_3)_4$ (23 mg, 0.020 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 120 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 40% to 70%; detector, UV 254 nm to afford 5-chloro-7-(3-methylbutan-2-yl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (55 mg, 78%) as a light yellow solid. MS ESI calculated for $C_{17}H_{22}ClN_5O$ [M + H]$^+$, 348.15, found 348.15.

Example 167:

5-chloro-7-(3-methylbutan-2-yl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/^{i}PrOH = 97/3, 1st peak)

Example 168:

5-chloro-7-(3-methylbutan-2-yl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/^{i}PrOH = 97/3, 2nd peak)

[00889] 5-chloro-7-(3-methylbutan-2-yl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (55 mg) was resolved by Prep-Chiral-HPLC with the following conditions: Column: CHIRALPAK AD-H, 2 x 25 cm, 5 μm; Mobile Phase A: Hexane, Mobile Phase B: *i*-PrOH; Flow rate: 20 mL/min; Gradient: A:B = 97:3; Wave Length: 254/220 nm.

[00890] RT_1: 19.28 min to afford 5-chloro-7-(3-methylbutan-2-yl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/^{i}PrOH = 97/3, 1st peak) (16 mg, 29%) as a white solid . MS ESI calculated for $C_{17}H_{22}ClN_5O$ $[M + H]^+$, 348.15, found 348.20. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.66 (s, 1H), 4.91 (d, *J* = 6.8 Hz, 1H), 4.06-4.02 (m, 2H), 3.91-3.84 (m, 1H), 3.61-3.58 (m, 2H), 3.30-3.22 (m, 1H), 2.29-2.20 (m, 1H), 2.13-2.09 (m, 2H), 1.68-1.56 (m, 2H), 1.47 (d, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).

[00891] RT_2: 21.87 min to afford 5-chloro-7-(3-methylbutan-2-yl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/^{i}PrOH = 97/3, 2nd peak) (14 mg, 25%) as a white solid. MS ESI calculated for $C_{17}H_{22}ClN_5O$ $[M + H]^+$, 348.15, found 348.20. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.66 (s, 1H), 4.90 (d, *J* = 7.2 Hz, 1H), 4.06-4.02 (m, 2H), 3.91-3.84 (m, 1H), 3.61-3.54 (m, 2H), 3.30-3.22 (m, 1H), 2.29-2.20 (m, 1H), 2.13-2.09 (m, 2H), 1.68-1.57 (m, 2H), 1.47 (d, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.4 Hz, 3H).

Example 169:

5-chloro-7-(1-ethylcyclopropyl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: 5-chloro-7-(1-ethylcyclopropyl)-6-iodo-*N*-(oxan-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-amine

[00892] To a stirred solution of 2,5-dichloro-7-(1-ethylcyclopropyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazine (100 mg, 0.262 mmol) and oxan-4-amine (79 mg, 0.786 mmol) in NMP (1.5 mL) was added DIEA (135 mg, 1.048 mmol). The resulting mixture was stirred for 16 h at 120 °C. The resulting

mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 40% to 60%; detector, UV 254 nm to afford 5-chloro-7-(1-ethylcyclopropyl)-6-iodo-*N*-(oxan-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-amine (110 mg, 94%) as a yellow solid. MS ESI calculated for $C_{16}H_{20}ClIN_4O$ $[M + H]^+$, 447.04, found 447.10.

Example 169:

5-chloro-7-(1-ethylcyclopropyl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00893] To a stirred solution of 5-chloro-7-(1-ethylcyclopropyl)-6-iodo-*N*-(oxan-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-amine (80 mg, 0.179 mmol) and $Zn(CN)_2$ (13 mg, 0.107 mmol) in DMA (1.5 mL) was added $Pd(PPh_3)_4$ (21 mg, 0.018 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 120 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford 5-chloro-7-(1-ethylcyclopropyl)-2-(oxan-4-ylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (36.4 mg, 59%) as a white solid. MS ESI calculated for $C_{17}H_{20}ClN_5O$ $[M + H]^+$, 346.14, found 346.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 4.94 (d, *J* = 6.8 Hz, 1H), 4.08-4.02 (m, 2H), 3.94-3.88 (m, 1H), 3.61-3.54 (m, 2H), 2.17-2.13 (m, 2H), 1.73-1.59 (m, 4H), 1.05-1.03 (m, 2H), 0.97-0.91 (m, 5H).

Example 170:

5-chloro-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: 5-chloro-*N*-[(3*S*,4*R*)-3-fluorooxan-4-yl]-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-amine

[00894] A mixture of 2,5-dichloro-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine (60 mg, 0.162 mmol), (3*S*,4*R*)-3-fluorooxan-4-amine hydrochloride (76 mg, 0.486 mmol) and DIEA (105 mg, 0.810 mmol) in NMP (1 mL) was stirred for 16 h at 80 °C. The reaction was quenched by the addition of water (20 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (1/1) to afford 5-chloro-*N*-[(3*S*,4*R*)-3-fluorooxan-4-yl]-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-amine (35 mg, 47%) as a yellow solid. MS ESI calculated for $C_{15}H_{19}ClFIN_4O$ $[M + H]^+$, 453.03; found 453.05.

Example 170:

5-chloro-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00895] A mixture of 5-chloro-*N*-[(3*S*,4*R*)-3-fluorooxan-4-yl]-6-iodo-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-amine (35 mg, 0.077 mmol), $Zn(CN)_2$ (5 mg, 0.046 mmol) and $Pd(PPh_3)_4$ (9 mg, 0.008 mmol) in DMA (0.5 mL) was stirred for 2 h at 120 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (5 mM NH_4HCO_3); 45% to 70%; Detector: 220/254 nm to afford 5-chloro-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}-7-(2-methylpropyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (6.1 mg, 22%) as a yellow solid. MS ESI calculated for $C_{16}H_{19}ClN_4O_3$ $[M + H]^+$, 352.13, found 352.20. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 5.27 (brs, 1H), 4.60-4.48 (m, 1H), 4.15-4.08 (m, 2H), 3.95-3.91 (m, 1H), 3.65-3.55 (m, 2H), 2.91 (d, *J* = 7.2 Hz, 2H), 2.44-2.39 (m, 1H), 2.26-2.19 (m, 1H), 1.74-1.68 (m, 1H), 1.02-1.00 (m, 6H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -193.56 (1F).

Example 171:

5-chloro-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 95/5, 1st peak)

Example 172:

5-chloro-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 95/5, 2nd peak)

Step 1: 5-chloro-*N*-[(3*S*,4*R*)-3-fluorooxan-4-yl]-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-amine

[00896] A mixture of 2,5-dichloro-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (100 mg, 0.260 mmol), (3*S*,4*R*)-3-fluorooxan-4-amine hydrochloride (61 mg, 0.390 mmol) and DIEA (168 mg, 1.300 mmol) in DMSO (2 mL) was stirred for 16 h at 80 °C. The reaction was quenched by the addition of water (20 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (1/1) to afford 5-chloro-*N*-[(3*S*,4*R*)-3-fluorooxan-4-yl]-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-amine (80 mg, 65%) as yellow oil. MS ESI calculated for $C_{16}H_{21}ClFIN_4O$ $[M + H]^+$, 467.04; found 467.05.

Step 2: 5-chloro-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00897] A mixture of 5-chloro-*N*-[(3*S*,4*R*)-3-fluorooxan-4-yl]-6-iodo-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-amine (85 mg, 0.182 mmol), $Zn(CN)_2$ (13 mg, 0.109 mmol) and $Pd(PPh_3)_4$ (21 mg, 0.018 mmol) in DMA (2 mL) was stirred for 2 h at 120 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (5 mM NH_4HCO_3); 45% to 70%; Detector: 220/254 nm to afford 5-chloro-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (60 mg, 90%) as a yellow solid. MS ESI calculated for $C_{17}H_{21}ClFN_5O$ $[M + H]^+$, 366.14, found 366.20.

Example 171:

5-chloro-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 95/5, 1st peak)

Example 172:

5-chloro-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 95/5, 2nd peak)

[00898] 5-chloro-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (60 mg) was resolved by Prep-Chiral-HPLC with the following conditions: Column: CHIRALPAK AD-H, 2 x 25 cm, 5 μm; Mobile Phase A: Hexane, Mobile Phase B: *i*-PrOH; Flow rate: 20 mL/min; Gradient: A:B = 95:5; Wave Length: 254/220 nm.

[00899] RT_1: 16.37 min to afford 5-chloro-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH = 95/5, 1st peak) (22.4 mg, 37%) as a yellow solid. MS ESI calculated for $C_{17}H_{21}ClFN_5O$ $[M + H]^+$, 366.14, found 366.15. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 5.11 (brs, 1H), 4.63-4.46 (m, 1H), 4.13-4.06 (m, 2H), 3.96-3.87 (m, 1H), 3.67-3.56 (m, 2H), 3.32-3.22 (m, 1H), 2.44-2.38 (m, 1H), 2.26-2.21 (m, 1H), 1.74-1.66 (m, 1H), 1.47 (d, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -193.43 (1F).

[00900] RT_2: 18.95 min to afford 5-chloro-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}-7-(3-methylbutan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (single diastereoisomer, absolute chiral configuration of 3-methylbutan-2-yl was not determined) (CHIRALPAK AD-H, Hexane/EtOH

= 95/5, 2nd peak) (21.6 mg, 36%) as a yellow solid. MS ESI calculated for $C_{17}H_{21}ClFN_5O$ [M + H]$^+$, 366.14, found 366.20. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 5.11 (brs, 1H), 4.63-4.47 (m, 1H), 4.15-4.08 (m, 2H), 3.93-3.90 (m, 1H), 3.66-3.56 (m, 2H), 3.30-3.25 (m, 1H), 2.44-2.39 (m, 1H), 2.27-2.22 (m, 1H), 1.73-1.64 (m, 1H), 1.47 (d, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -193.52 (1F).

Example 173:

5-chloro-7-(1-ethylcyclopropyl)-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

Step 1: 5-chloro-7-(1-ethylcyclopropyl)-*N*-[(3*S*,4*R*)-3-fluorooxan-4-yl]-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-amine

[00901] To a stirred solution of 2,5-dichloro-7-(1-ethylcyclopropyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazine (50 mg, 0.131 mmol) and (3*S*,4*R*)-3-fluorooxan-4-amine hydrochloride (61 mg, 0.393 mmol) in DMSO (1 mL) was added DIEA (84 mg, 0.655 mmol). The resulting mixture was stirred for 16 h at 80 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 30% to 70%; detector, UV 254 nm to afford 5-chloro-7-(1-ethylcyclopropyl)-*N*-[(3*S*,4*R*)-3-fluorooxan-4-yl]-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-amine (40 mg, 66%) as a yellow solid. MS ESI calculated for $C_{16}H_{19}ClFIN_4O$ [M + H]$^+$, 465.03, found 465.10.

Example 173:

5-chloro-7-(1-ethylcyclopropyl)-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

[00902] To a stirred solution of 5-chloro-7-(1-ethylcyclopropyl)-*N*-[(3*S*,4*R*)-3-fluorooxan-4-yl]-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-amine (30 mg, 0.065 mmol) and $Zn(CN)_2$ (4 mg, 0.039 mmol) in DMA (1 mL) was added $Pd(PPh_3)_4$ (7 mg, 0.007 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 120 °C under nitrogen atmosphere. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mM NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford 5-chloro-7-(1-ethylcyclopropyl)-2-{[(3*S*,4*R*)-3-fluorooxan-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (5.4 mg, 23%) as a yellow solid. MS ESI calculated for $C_{17}H_{19}ClFN_5O$ [M + H]$^+$, 364.13, found 364.10. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 5.19 (d, *J* = 6.0 Hz, 1H), 4.67-4.53 (m, 1H), 4.13-4.06 (m, 2H), 3.92-3.89 (m, 1H), 3.64-

3.54 (m, 2H), 2.48-2.43 (m, 1H), 1.75-1.63 (m, 3H), 1.06-0.86 (m, 7H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -193.70 (1F).

II. Biological Evaluation

CDK4/Cyclin D1 Mobility Shift Assay

[00903] Small molecule inhibition of CDK4/Cyclin D1 kinase activity was evaluated using a fluorescence-based microfluidic mobility shift assay. CDK4/Cyclin D1 catalyzes the production of ADP from ATP during phosphoryl transfer to the substrate peptide, FLPeptide34 (5-FAM-RRRFRPASPLRGPPK-COOH) (Perkin Elmer, 760643). CDK4/Cyclin D1 (Thermo Fisher, PR8064A) at 3 nM was prepared with 10 mM MgCl and 1 M ATP in a buffer containing 40 mM HEPES, 1 mM EGTA, 0.01% Brij-35, 0.05% BSA, and 1 mM DTT and pre-incubated at room temperature for 30 min prior to the start of the reaction. 3 micromolar of the substrate was added to start the reaction. The mobility shift assay electrophoretically separates the fluorescently labeled peptides (substrate and phosphorylated product) following the 30 minute kinase reaction. The reaction was terminated by addition of 0.5 M EDTA. Both substrate and product were measured and the ratio of these values used to generate % conversion of substrate to product by the LabChip EZ reader (Perkin Elmer). IC50 values were calculated using the inhibition of conversion ratio using Dotmatics Knowledge Solutions Studies curve fitting (Dotmatics, Bishops Stortford, UK, CM23) and are presented in Table 2.

CDK6/Cyclin D3 Mobility Shift Assay

[00904] Small molecule inhibition of CDK6/Cyclin D3 kinase activity was evaluated using a fluorescence-based microfluidic mobility shift assay. CDK6/Cyclin D3 catalyzes the production of ADP from ATP during phosphoryl transfer to the substrate peptide, FLPeptide34 (5-FAM-RRRFRPASPLRGPPK-COOH) (Perkin Elmer, 760643). CDK6/Cyclin D3 (Carna, 04-107) at 5 nM was prepared with 10 mM MgCl and 100 micromolar ATP in a buffer containing 50 mM HEPES, 1 mM EGTA, 0.01% Brij-35, 0.05% BSA, and 2 mM DTT and pre-incubated at room temperature for 30 min prior to the start of the reaction. 1.5 micromolar of the substrate is added to start the reaction. The mobility shift assay electrophoretically separates the fluorescently labeled peptides (substrate and phosphorylated product) following the 120 minute kinase reaction. The reaction was terminated by addition of 0.5 M EDTA. Both substrate and product were measured and the ratio of these values used to generate % conversion of substrate to product by the LabChip EZ reader (Perkin Elmer). IC50 values were calculated using the inhibition of conversion ratio using Dotmatics Knowledge Solutions Studies curve fitting (Dotmatics, Bishops Stortford, UK, CM23) and are presented in Table 2.

CDK2/Cyclin E1 Mobility Shift Assay

[00905] Small molecule inhibition of CDK2/Cyclin E1 kinase activity was evaluated using a fluorescence-based microfluidic mobility shift assay. CDK2/Cyclin E1 catalyzes the production of ADP from ATP during phosphoryl transfer to the substrate peptide, FLPeptide18 (5-FAM-QSPKKG-CONH2) (Perkin Elmer, 760362). CDK2/Cyclin E1 (Eurofin, 14-475) at 2 nM was prepared with 10 mM MgCl and 100 micromolar ATP in a buffer containing 50 mM HEPES, 1 mM EGTA, 0.01% Brij-35, 0.05% BSA, and 2 mM DTT and pre-incubated at room temperature for 30 min prior to the start of the reaction. 1.5 micromolar of the substrate is added to start the reaction. The mobility shift assay electrophoretically separates the fluorescently labeled peptides (substrate and phosphorylated product) following the 120 minute kinase reaction. The reaction was terminated by addition of 0.5 M EDTA. Both substrate and product were measured and the ratio of these values used to generate % conversion of substrate to product by the LabChip EZ reader (Perkin Elmer). IC50 values were calculated using the inhibition of conversion ratio using Dotmatics Knowledge Solutions Studies curve fitting (Dotmatics, Bishops Stortford, UK, CM23) and are presented in Table 2.

Phopho-Serine 807/811 Rb HTRF Assay

[00906] WM3629 cells were seeded at 20,000 cells per well in a 96 well plate, respectively, in 90 microliers growth media and allowed to adhere to the plate at 37 °C with 5% CO_2 overnight. The following day, compounds were serially diluted from a 10 mM top dose for a 10-point 3-fold dilution curve in DMSO. Following a 100-fold dilution in growth media, a further 10-fold dilution was made into the cell plate for a final volume of 100 microliter and 0.1% DMSO. Compounds and cells were incubated together for 18 hours at 37 °C with 5% CO_2. Samples were prepared by addition of supplemented HTRF lysis buffer followed by shaking for 45 minutes at room temperature and further homogenization by manual trituration. Phosphorylation at serine 807/811 was assessed using an HTRF sandwich assay (Cisbio, 64RBS807PEH). The specific signal modulates positively in proportion to phospho-Rb (Ser807/811). Specific Eu3+-Cryptate (donor) and d2 (acceptor) labeled antibodies were added to the cell lysate and incubated overnight at room temperature. Specific signal was measured at 665nm and 620nm on a Perkin Elmer Envision 2105 and the ratios used to calculate IC50 values within the Dotmatics Knowledge Solutions Studies curve fitting environment (Dotmatics, Bishops Stortford, UK, CM23) and are presented in Table 2.

MCF7 Cyquant Assay

[00907] Cells are plated at densities of 2500 cells/well into 96-well poly-D-lysine coated plates and allowed to adhere overnight in an incubator at 37° C and 5% CO2. The following day, compounds were serially diluted from a 10 mM top dose for a 9-point 3-fold dilution curve in DMSO. Following a 100-fold dilution in growth media, a further 10-fold dilution was made into

the cell plate for a final volume of 150ul and 0.1% DMSO. . Compounds and cells were incubated together for 6 days at 37° C with 5% CO2. CyQuant (Invitrogen, C35011) detection buffer was prepared according to manufacturer's directions and the 2x solution added to the cells in culture. Following a 60 minute incubation of the detection reagent with cells at 37° C, fluorescence is read using the standard "green" filter set on the Envision reader. Specific signal was used to calculate IC50 values within the Dotmatics Knowledge Solutions Studies curve fitting environment (Dotmatics, Bishops Stortford, UK, CM23) and are presented in Table 2.

Table 2

Synthetic Chemistry Example	CDK4 (CycD1) IC_{50}	CDK6 (CycD3) IC_{50}	CDK2 (CycE1) IC_{50}	MCF7 (CyQuant) IC_{50}	WM3629 (pRb) IC_{50}
1	A	A	B	--	A
2	A	A	C	--	B
3	A	A	>3uM	--	B
4	A	A	A	--	A
5	A	A	A	--	A
6	A	A	A	--	B
7	A	A	A	B	A
8	B	A	>3uM	--	C
9	A	A	A	--	A
10	A	A	B	--	C
11	A	A	C	--	C
12	A	A	A	--	B
13	A	A	>3uM	--	B
14	A	A	C	--	B
15	A	A	>3uM	--	B
16	A	A	>3uM	--	B
17	A	A	B	--	B
18	A	A	A	--	B
19	A	A	A	A	A
20	A	A	A	--	A
21	A	A	B	--	B
22	A	A	B	--	A
23	A	A	C	--	B
24	A	A	B	--	B
25	A	A	A	--	A
26	A	A	B	--	B
27	A	A	C	--	B
28	A	A	B	--	B
29	A	A	A	--	A

Synthetic Chemistry Example	CDK4 (CycD1) IC_{50}	CDK6 (CycD3) IC_{50}	CDK2 (CycE1) IC_{50}	MCF7 (CyQuant) IC_{50}	WM3629 (pRb) IC_{50}
30	A	A	A	--	A
31	A	A	B	--	B
32	A	A	B	--	B
33	A	A	B	--	B
34	A	A	B	--	A
35	A	A	A	A	A
36	A	A	C	--	B
37	A	B	B	--	C
38	A	A	A	A	A
39	A	A	A	--	A
40	A	A	B	--	B
41	A	A	A	A	A
42	A	A	A	--	A
43	A	A	A	--	B
44	A	A	A	--	A
45	A	A	A	--	A
46	A	A	A	--	B
47	A	A	A	--	A
48	A	A	A	--	C
49	A	A	A	A	A
50	A	A	A	--	A
51	A	A	A	--	A
52	A	A	B	--	B
53	A	A	A	--	A
54	A	A	B	--	A
55	A	A	A	A	--
56	A	A	A	A	--
57	A	A	A	A	--
58	A	A	A	A	--
59	A	A	A	B	--
60	A	A	A	A	--
61	A	A	A	A	A
62	A	A	A	A	A
63	A	A	A	A	--
64	A	A	A	A	--
66	A	A	A	A	--
67	A	A	A	C	--
68	A	A	A	C	--

Synthetic Chemistry Example	CDK4 (CycD1) IC_{50}	CDK6 (CycD3) IC_{50}	CDK2 (CycE1) IC_{50}	MCF7 (CyQuant) IC_{50}	WM3629 (pRb) IC_{50}
69	A	A	A	A	A
70	A	A	A	A	A
71	A	A	A	A	--
75	A	A	A	A	A
76	A	A	A	B	--
77	A	A	A	B	--
78	A	A	A	C	--
79	A	A	B	C	--
80	A	B	A	B	B
81	B	B	B	C	--
82	B	B	B	C	--
83	B	B	B	C	--
84	A	A	A	A	--
85	A	A	A	A	A
86	A	A	A	A	A
87	A	A	A	B	--
88	A	A	A	B	A
89	A	A	A	B	B
90	A	A	A	B	A
91	A	A	A	B	--
92	--	--	--	B	--
93	--	--	--	A	A
94	--	--	--	A	A
95	--	--	--	A	A
96	--	--	--	A	A
97	--	--	--	B	--
98	--	--	--	A	A
99	--	--	--	A	--
100	--	--	--	B	--
101	--	--	--	A	--
102	--	--	--	B	--
103	--	--	--	B	--
104	--	--	--	>1uM	--
106	--	--	--	A	A
107	--	--	--	A	A
108	--	--	--	A	A
109	--	--	--	A	A
110	--	--	--	B	--

Synthetic Chemistry Example	CDK4 (CycD1) IC_{50}	CDK6 (CycD3) IC_{50}	CDK2 (CycE1) IC_{50}	MCF7 (CyQuant) IC_{50}	WM3629 (pRb) IC_{50}
111	--	--	--	A	A
112	--	--	--	A	A
113	--	--	--	>1uM	--
114	--	--	--	B	--
115	--	--	--	B	--
116	--	--	--	>1uM	--
117	--	--	--	A	--
118	--	--	--	A	--
119	--	--	--	>1uM	--
120	--	--	--	A	--
121	--	--	--	A	--
122	--	--	--	>1uM	--
123	--	--	--	A	--
124	--	--	--	A	--
125	--	--	--	B	--
126	--	--	--	A	--
127	--	--	--	B	--
128	--	--	--	A	--
129	--	--	--	A	--
130	--	--	--	A	--
131	--	--	--	B	--
132	--	--	--	B	--
133	--	--	--	A	--
134	--	--	--	A	--
135	--	--	--	A	--
136	--	--	--	B	--
137	--	--	--	B	--
138	--	--	--	A	--
139	--	--	--	--	A
140	--	--	--	--	A
141	--	--	--	--	A
142	--	--	--	--	B
143	--	--	--	--	A
144	--	--	--	--	A
145	--	--	--	--	A
146	--	--	--	--	B
147	--	--	--	--	B
148	--	--	--	--	A

Synthetic Chemistry Example	CDK4 (CycD1) IC_{50}	CDK6 (CycD3) IC_{50}	CDK2 (CycE1) IC_{50}	MCF7 (CyQuant) IC_{50}	WM3629 (pRb) IC_{50}
149	--	--	--	--	A
150	--	--	--	--	A
153	--	--	--	--	A
154	--	--	--	--	A
155	--	--	--	--	A
156	--	--	--	--	B
157	--	--	--	--	B
158	--	--	--	--	B
159	--	--	--	--	--
160	--	--	--	--	--
161	--	--	--	--	--
162	--	--	--	--	--
163	--	--	--	--	--
164	--	--	--	--	--
165	--	--	--	--	--
166	--	--	--	--	--
167	--	--	--	--	--
168	--	--	--	--	--
169	--	--	--	--	--
170	--	--	--	--	--
171	--	--	--	--	--
172	--	--	--	--	--
173	--	--	--	--	--

Note: Assay IC_{50} data are designated within the following ranges:
A: ≤ 0.10 μM
B: > 0.10 μM to ≤ 1.0 μM
C: > 1.0 μM to ≤ 10 μM
D: > 10 μM to 30 μM

[00908] AssayQuant CDK4 assay

[00909] CDK4/Cyclin D1 Mobility Shift Assay

[00910] Small molecule inhibition of CDK4/Cyclin D1 kinase activity was evaluated using a fluorescence-based phosphosensor (AssayQuant Technologies). The sensing mechanism exploits a synthetic α-amino acid that relays information on the phosphorylation state of the kinase substrates. Upon phosphorylation of the substrate, fluorescence is turned on. CDK4/Cyclin D1 catalyzes the phosphoryl transfer to the substrate peptide (AQT0258), leading to an increase in fluorescence that is directly proportional to the amount of phosphorylated substrate. CDK4/Cyclin D1 (Thermo Fisher, PR8064A) at 2.5 nM was prepared with 10uM substrate in a buffer containing 10mM MgCl2, 54 mM HEPES, 0.55 mM EGTA, 0.01% Brij-35,

0.02% BSA, 1 mM DTT and 1% glycerol and pre-incubated at room temperature for 30 min prior to the start of the reaction. 400uM ATP is added to start the reaction. The reaction is allowed to run for 180 minutes at room temperature, then fluorescence read on the EnSight Reader. IC50 values were calculated using the inhibition of conversion ratio using Dotmatics Knowledge Solutions Studies curve fitting (Dotmatics, Bishops Stortford, UK, CM23) and are presented in Table 3.

Table 3

Synthetic Chemistry Example	CDK4 (Assay Quant) (CycD1) IC_{50}
92	A
93	A
94	A
95	A
96	A
97	A
98	A
99	A
100	A
101	A
102	A
103	A
104	B
106	A
107	A
108	A
109	A
110	A
111	A
112	A
113	A
114	A
115	A
116	A
117	A
118	A
119	A
120	A
121	A
122	A

Synthetic Chemistry Example	CDK4 (Assay Quant) (CycD1) IC_{50}
123	A
124	A
125	A
126	A
127	A
128	A
129	A
130	A
131	A
132	A
133	A
134	A
135	A
136	A
137	A
138	A
139	A
140	A
141	A
142	A
143	A
144	A
145	A
146	A
147	A
148	A
149	A
150	A
153	A
154	A
155	A
156	A
157	A
158	A
159	--
160	--
161	--
162	--

Synthetic Chemistry Example	CDK4 (Assay Quant) (CycD1) IC_{50}
163	--
164	--
165	--
166	--
167	--
168	--
169	--
170	--
171	--
172	--
173	--

Note: Assay IC_{50} data are designated within the following ranges:
A: ≤ 0.10 μM
B: > 0.10 μM to ≤ 1.0 μM
C: > 1.0 μM to ≤ 10 μM
D: > 10 μM to 30 μM

III. Preparation of Pharmaceutical Dosage Forms

[00911] Example 1: Oral capsule

[00912] The active ingredient is a compound of Table 1, or a pharmaceutically acceptable salt or solvate thereof. A capsule for oral administration is prepared by mixing 1-1000 mg of active ingredient with starch or other suitable powder blend. The mixture is incorporated into an oral dosage unit such as a hard gelatin capsule, which is suitable for oral administration.

[00913] Example 2: Solution for injection

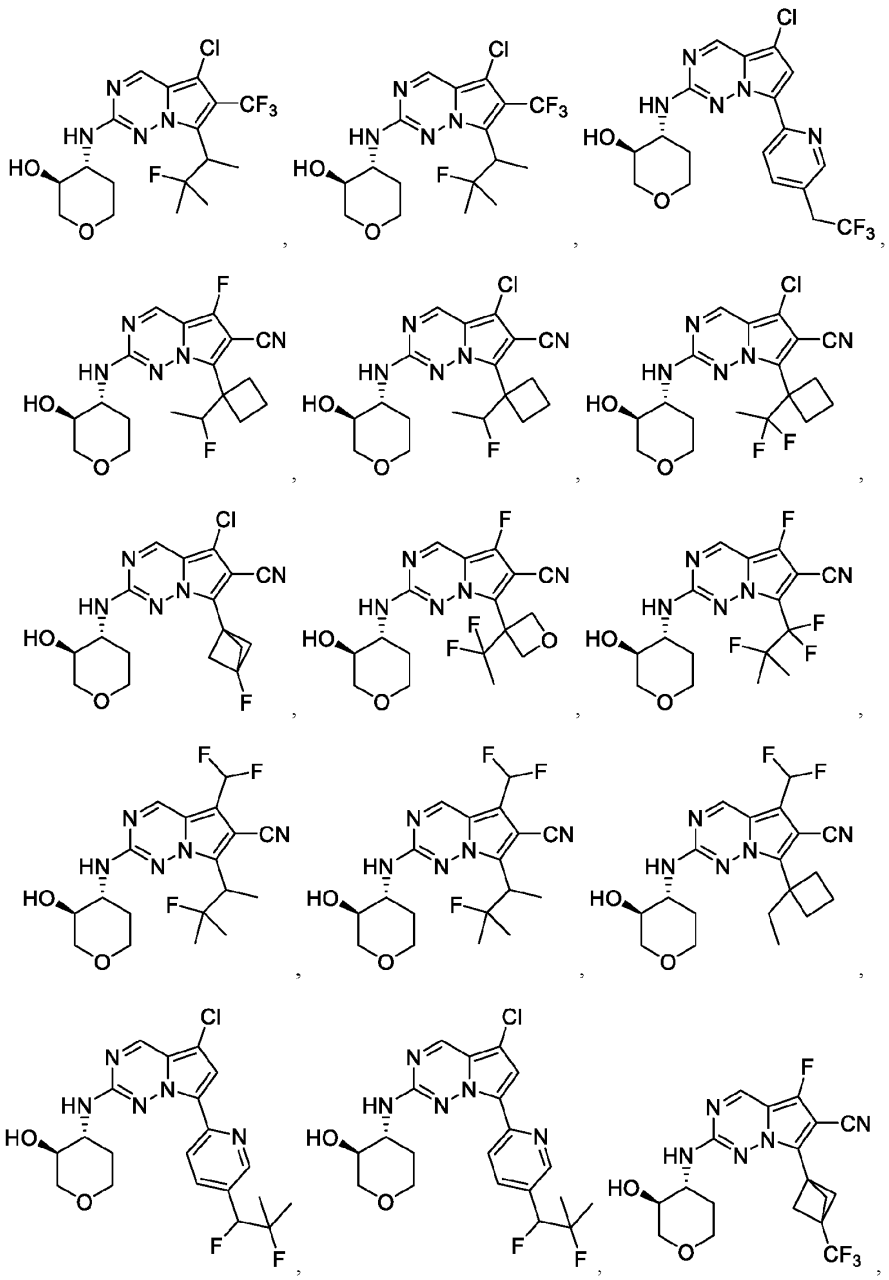
[00914] The active ingredient is a compound of Table 1, or a pharmaceutically acceptable salt or solvate thereof, and is formulated as a solution in sesame oil at a concentration of 50 mg-eq/mL.

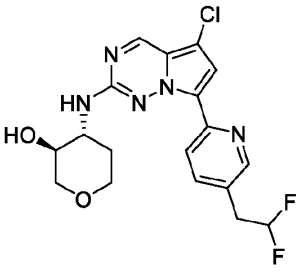
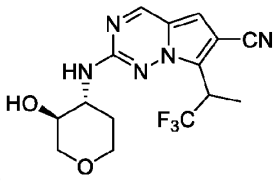
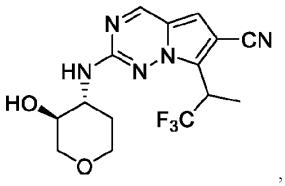
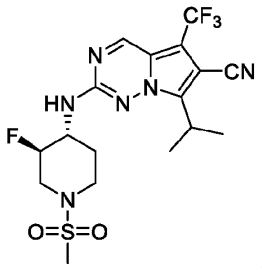
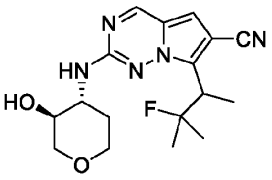
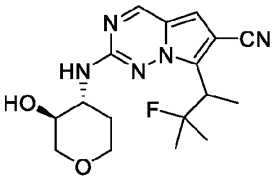
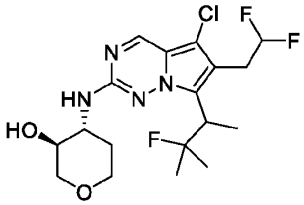
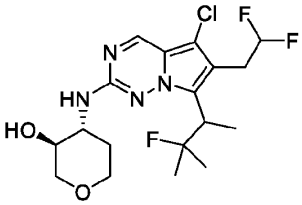
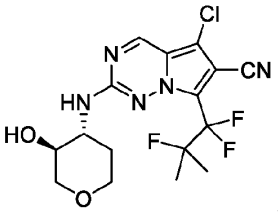
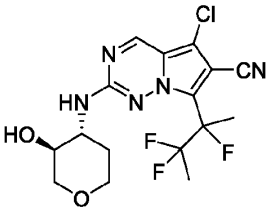
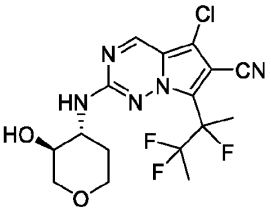
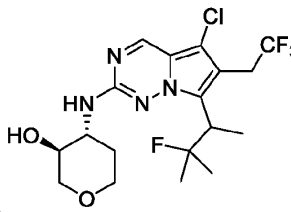
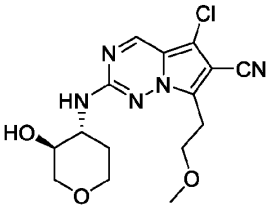
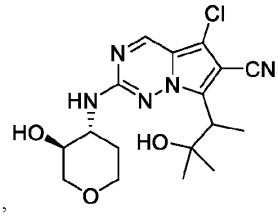
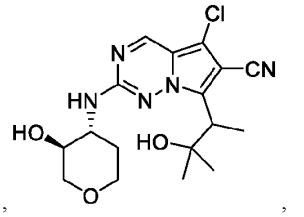
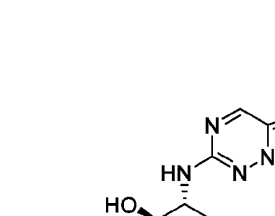
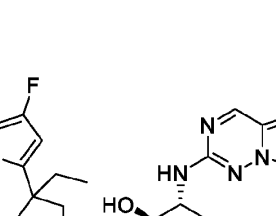
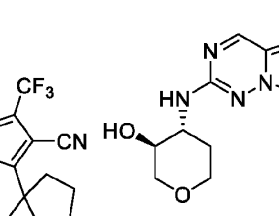
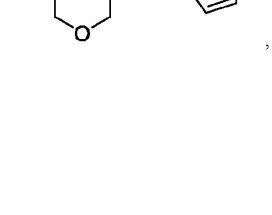
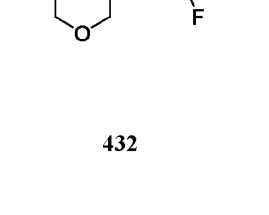
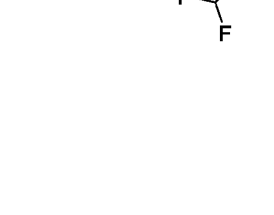
[00915] The examples and embodiments described herein are for illustrative purposes only and various modifications or changes suggested to persons skilled in the art are to be included within the spirit and purview of this application and scope of the appended claims.

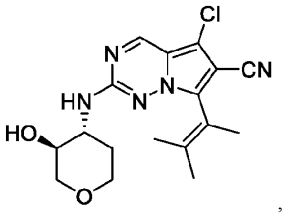
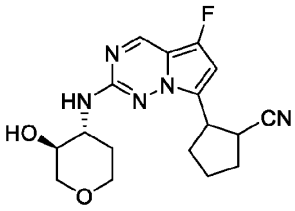
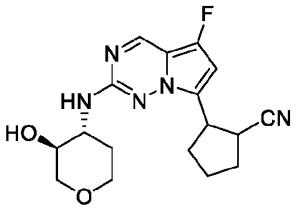
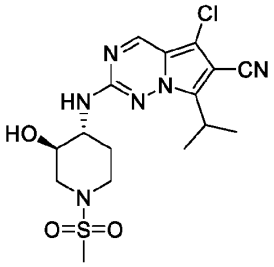
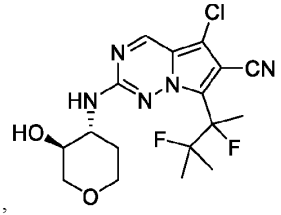
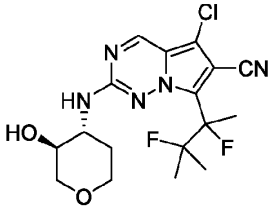
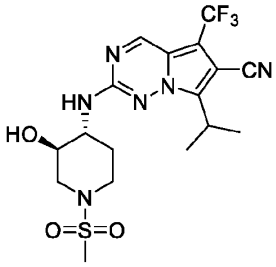
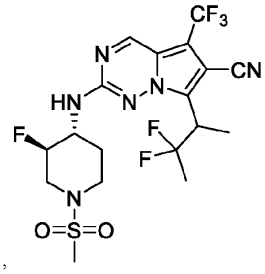
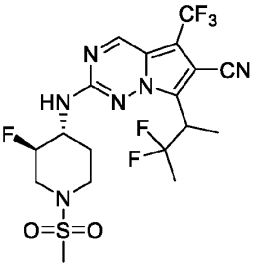
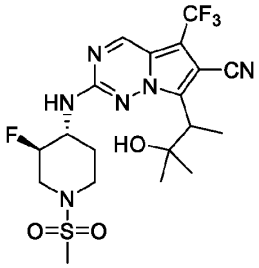
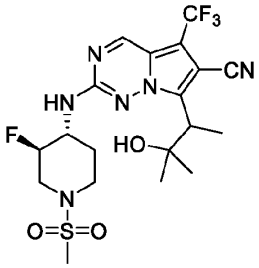
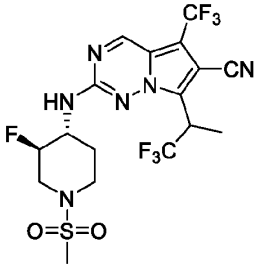
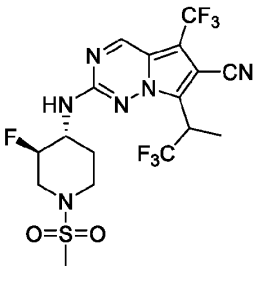
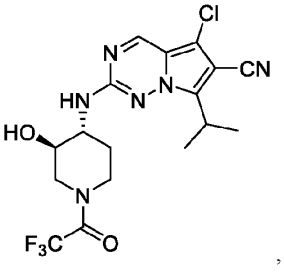
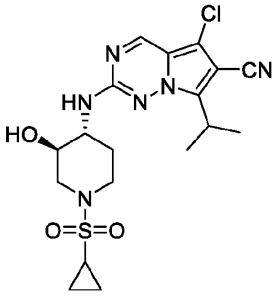
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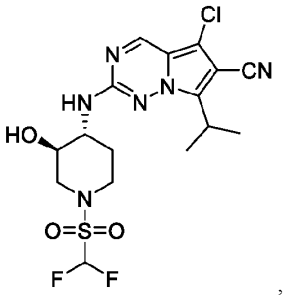
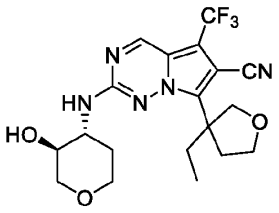
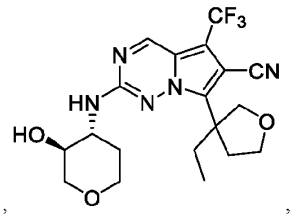
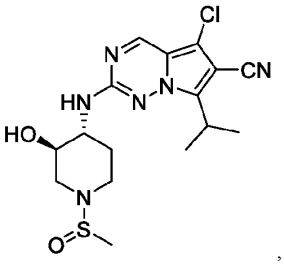
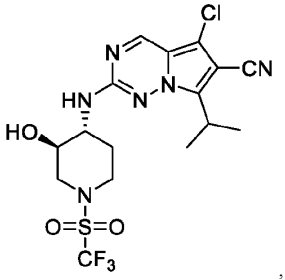
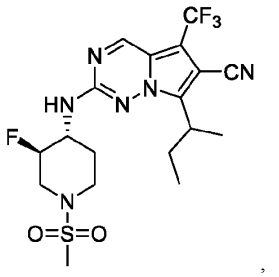
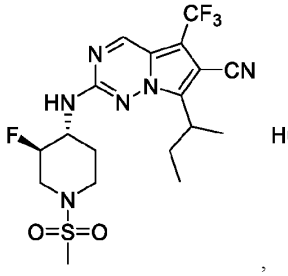
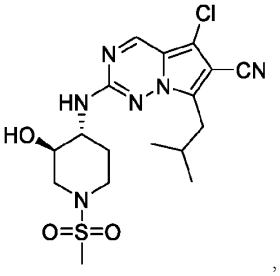
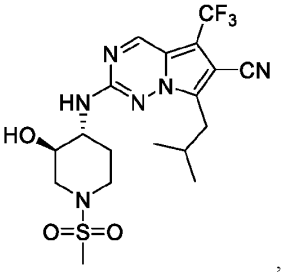
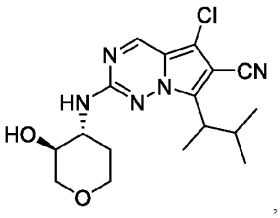
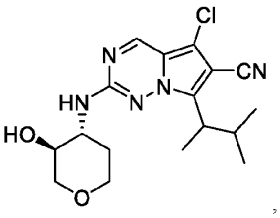
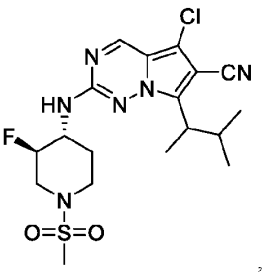
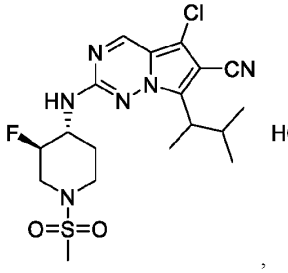
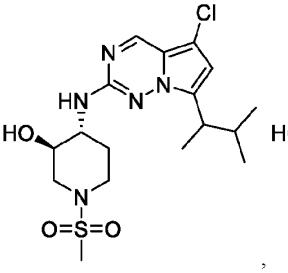
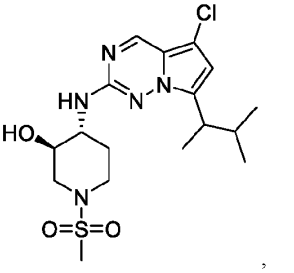
We claim:

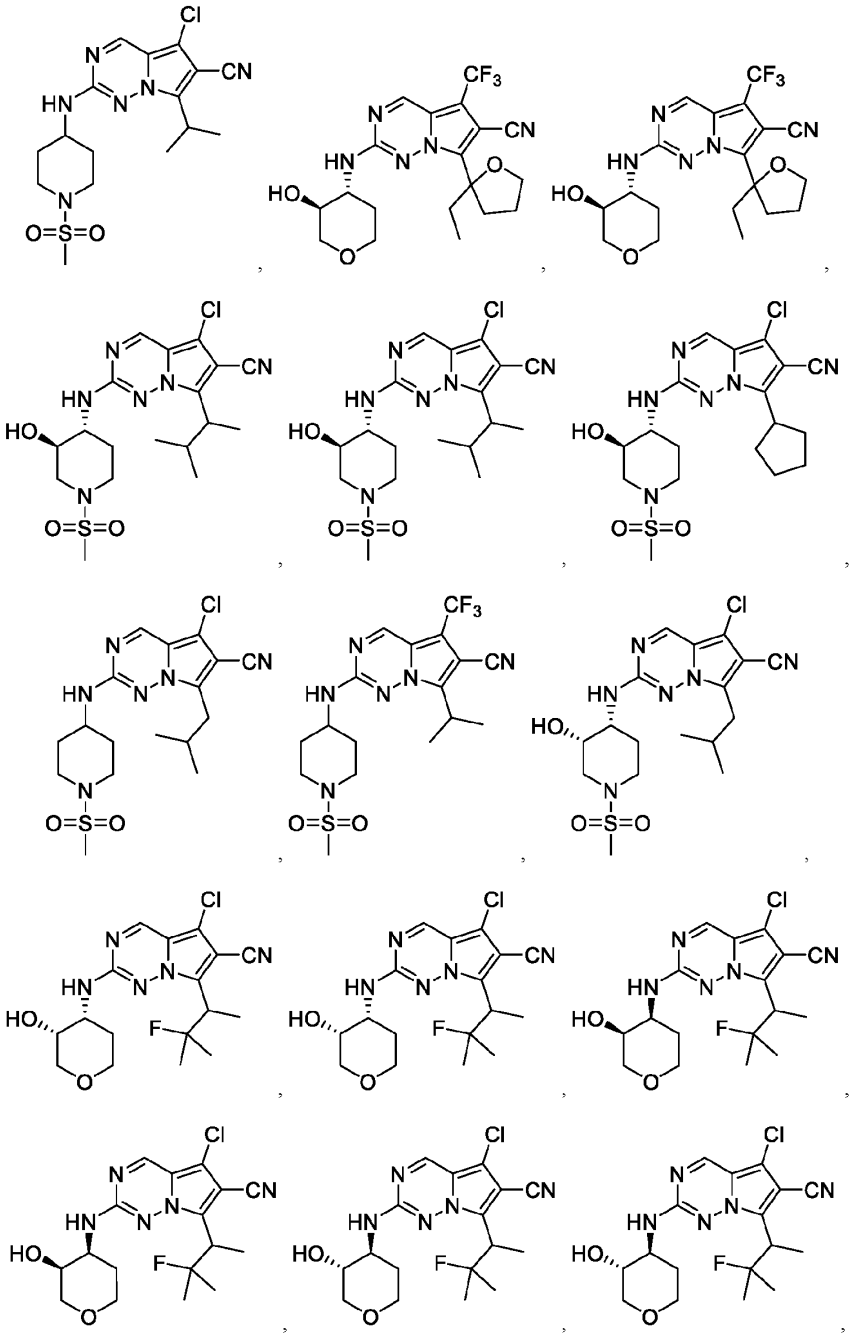
1. A compound, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, having a structure selected from the group consisting of:

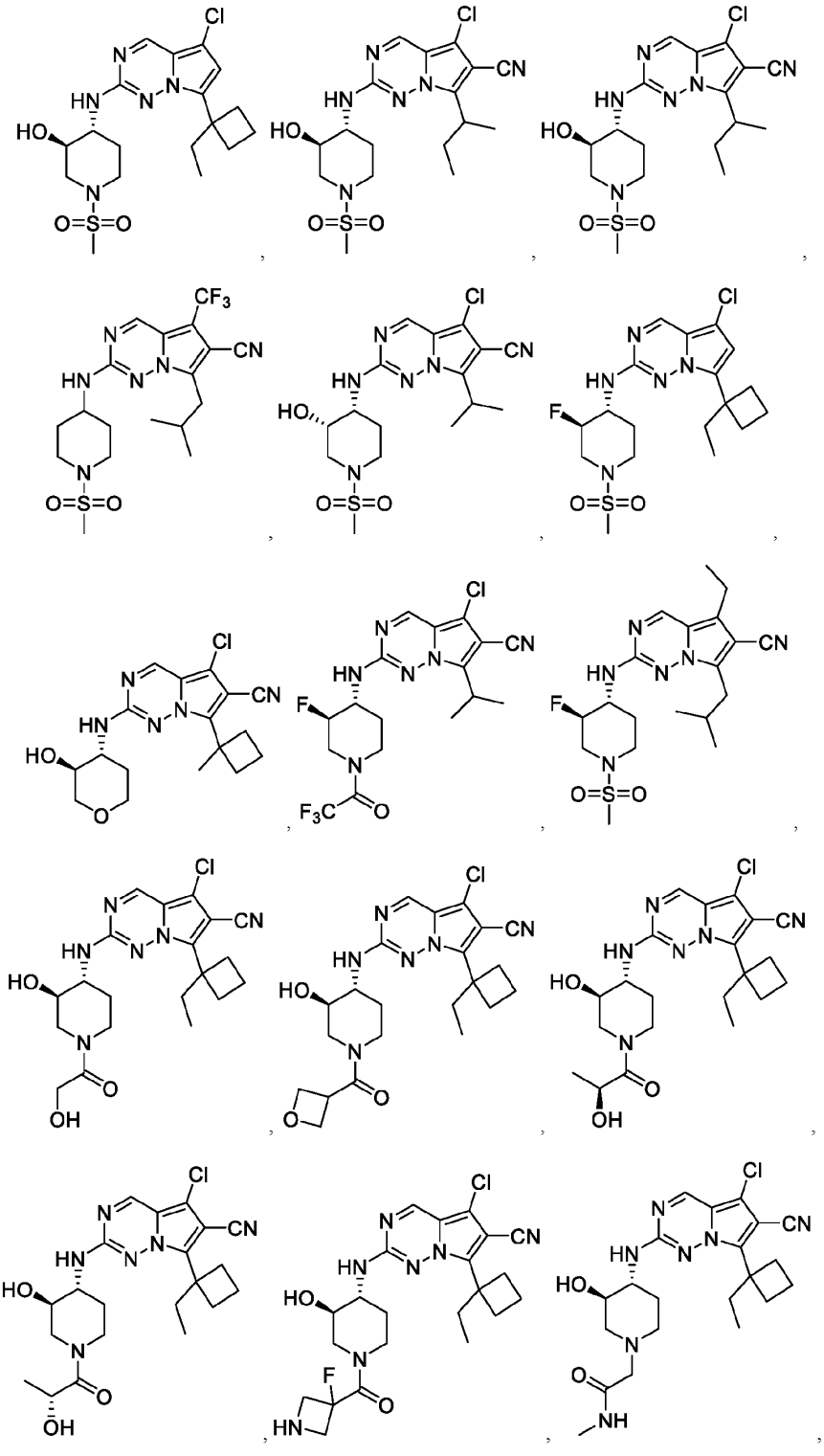


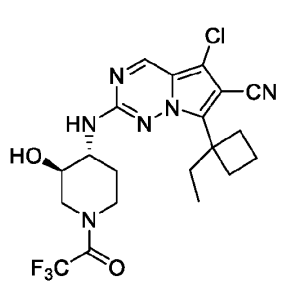
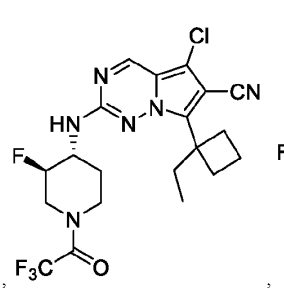
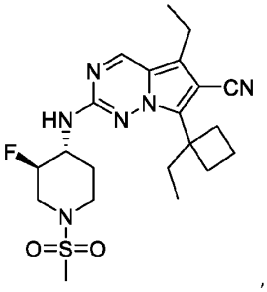
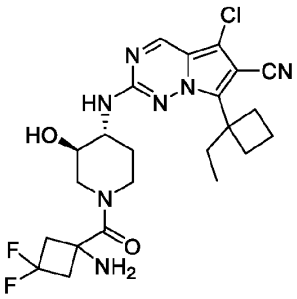
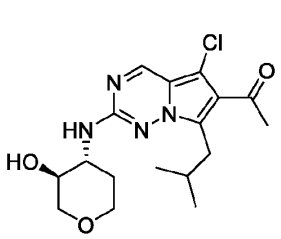
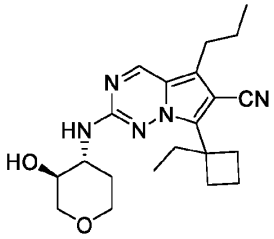
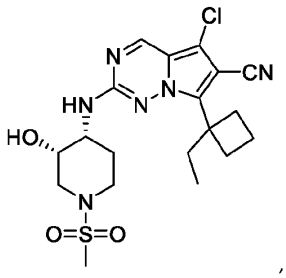
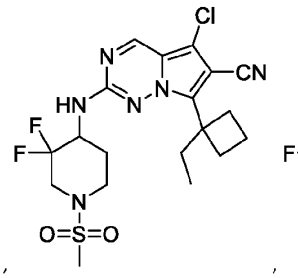
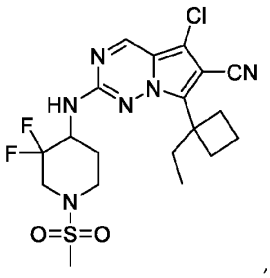
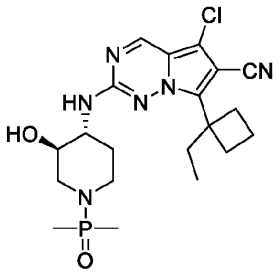
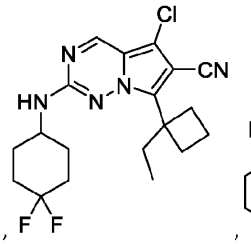
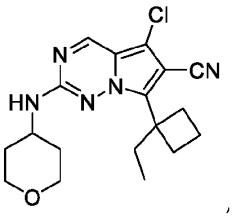
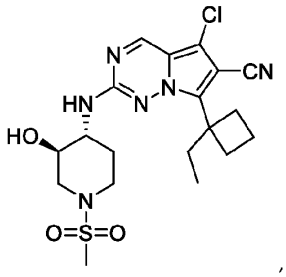
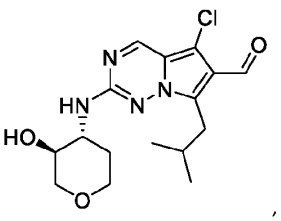
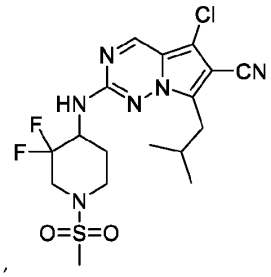






















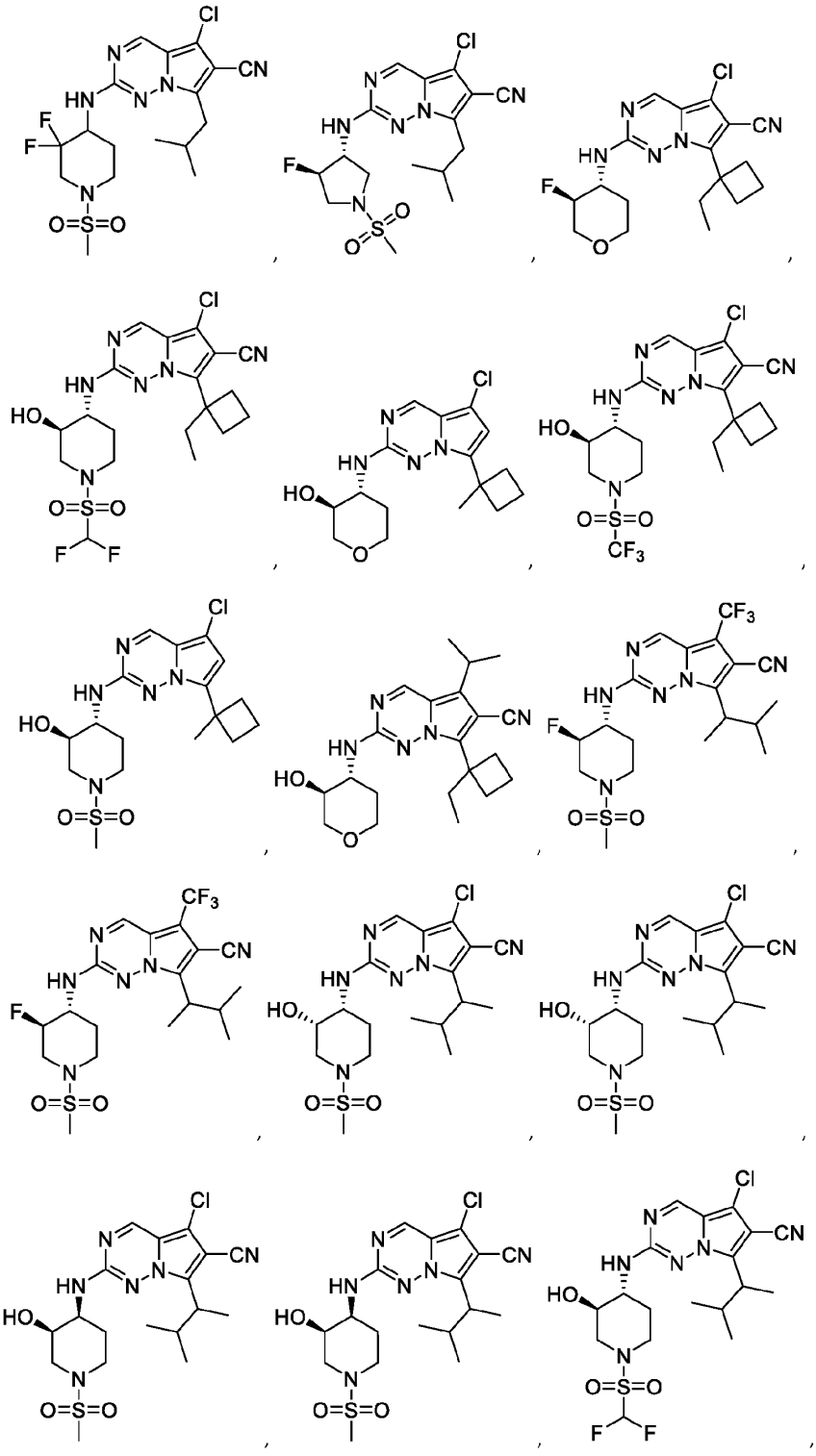
















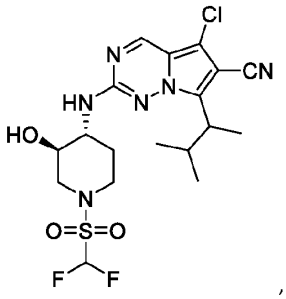
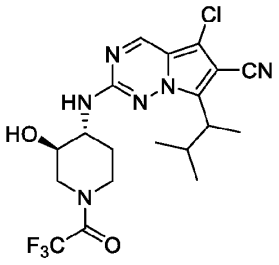
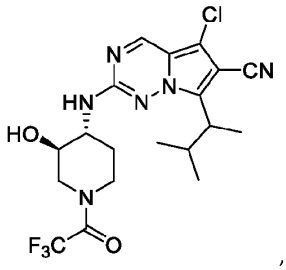
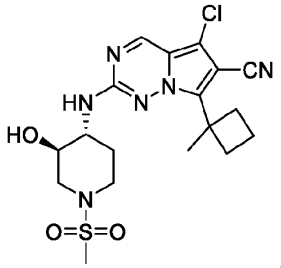
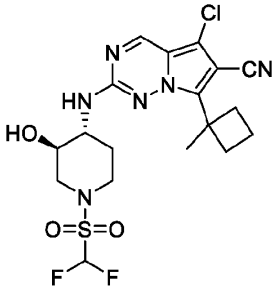
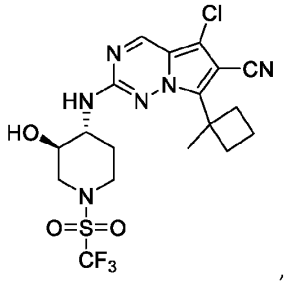
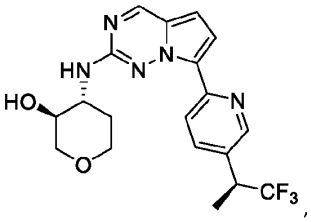
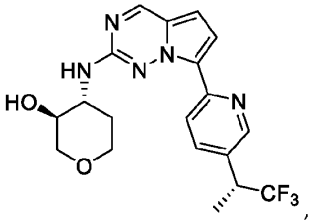
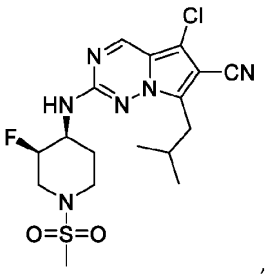
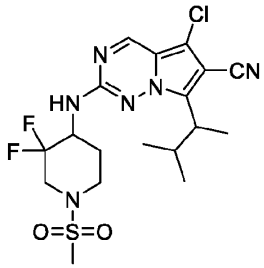
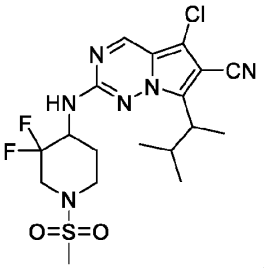
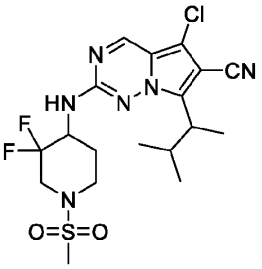
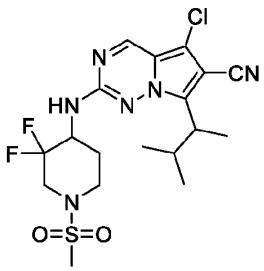
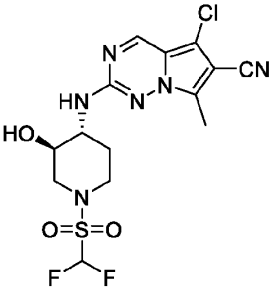
















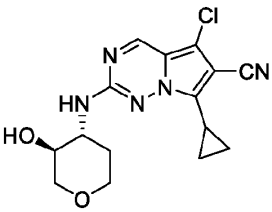


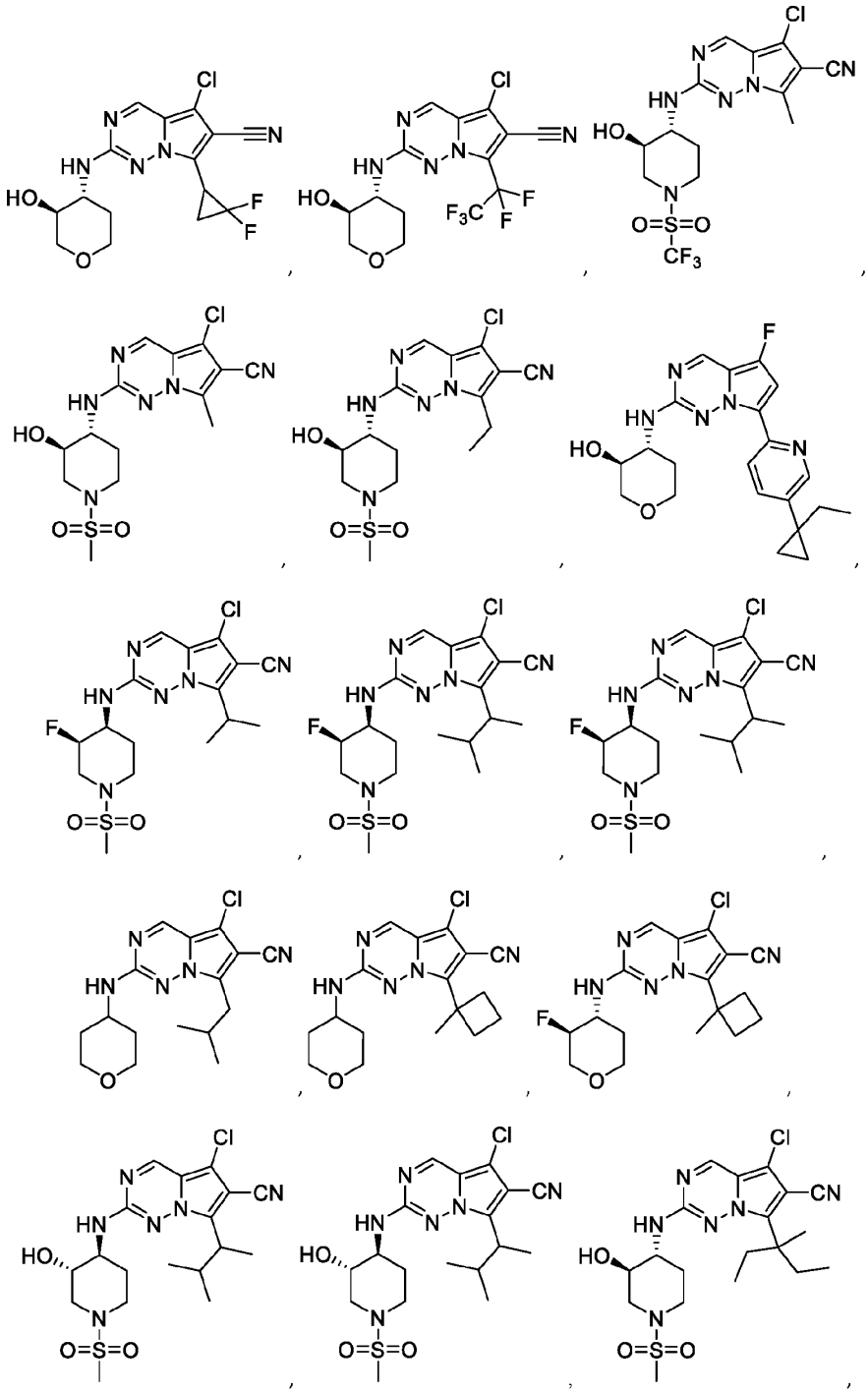


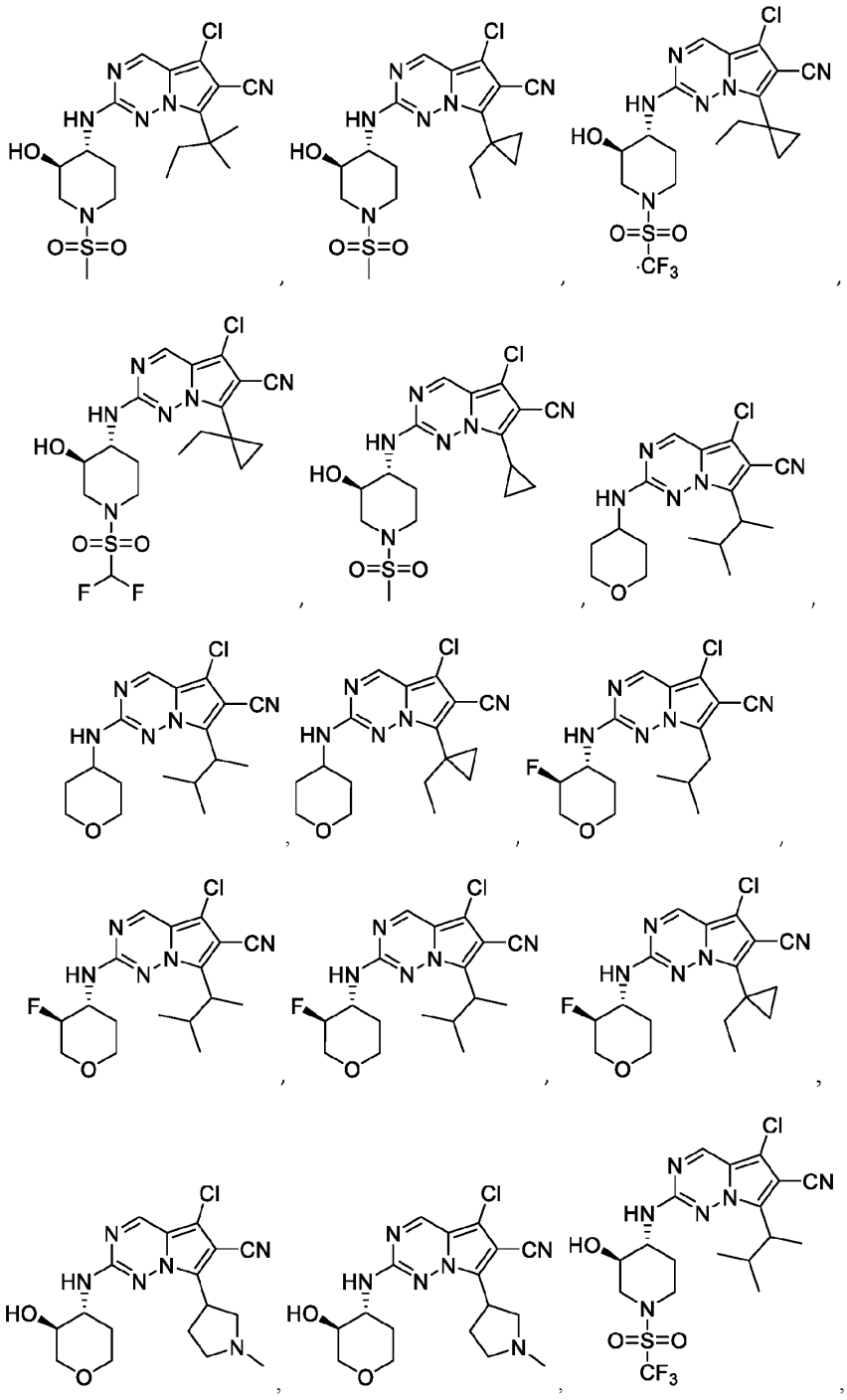
















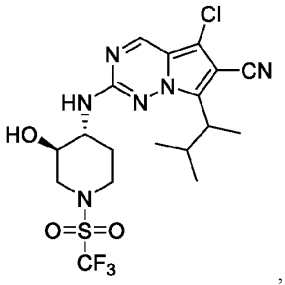
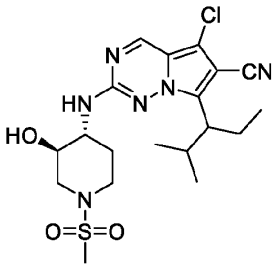
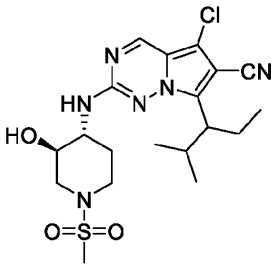
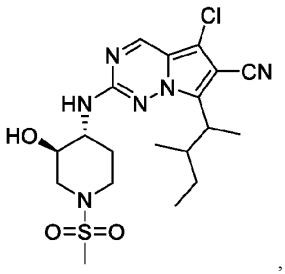
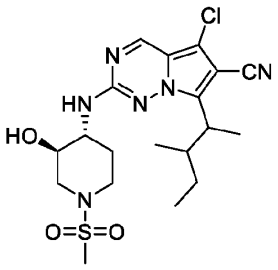
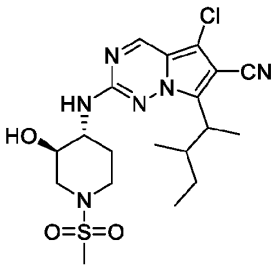
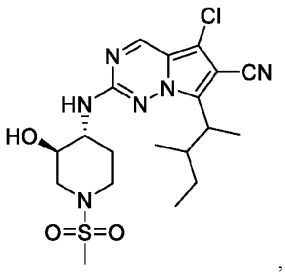
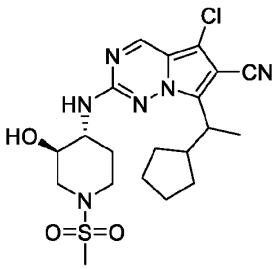
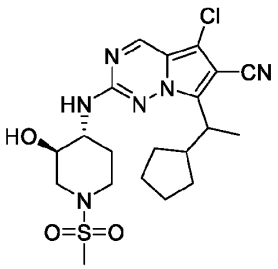
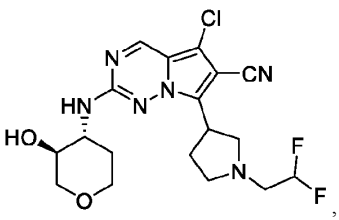
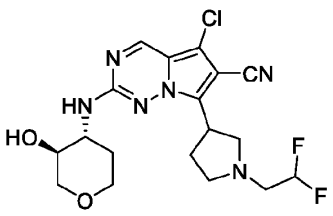
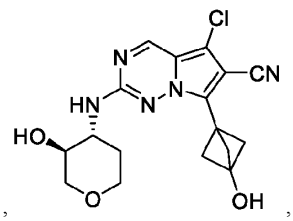
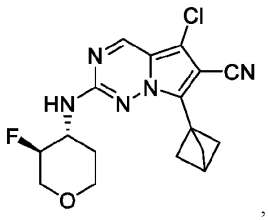
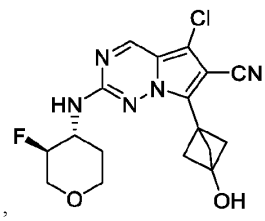
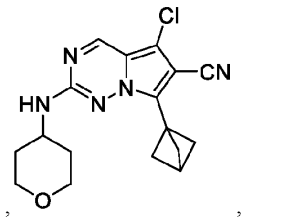


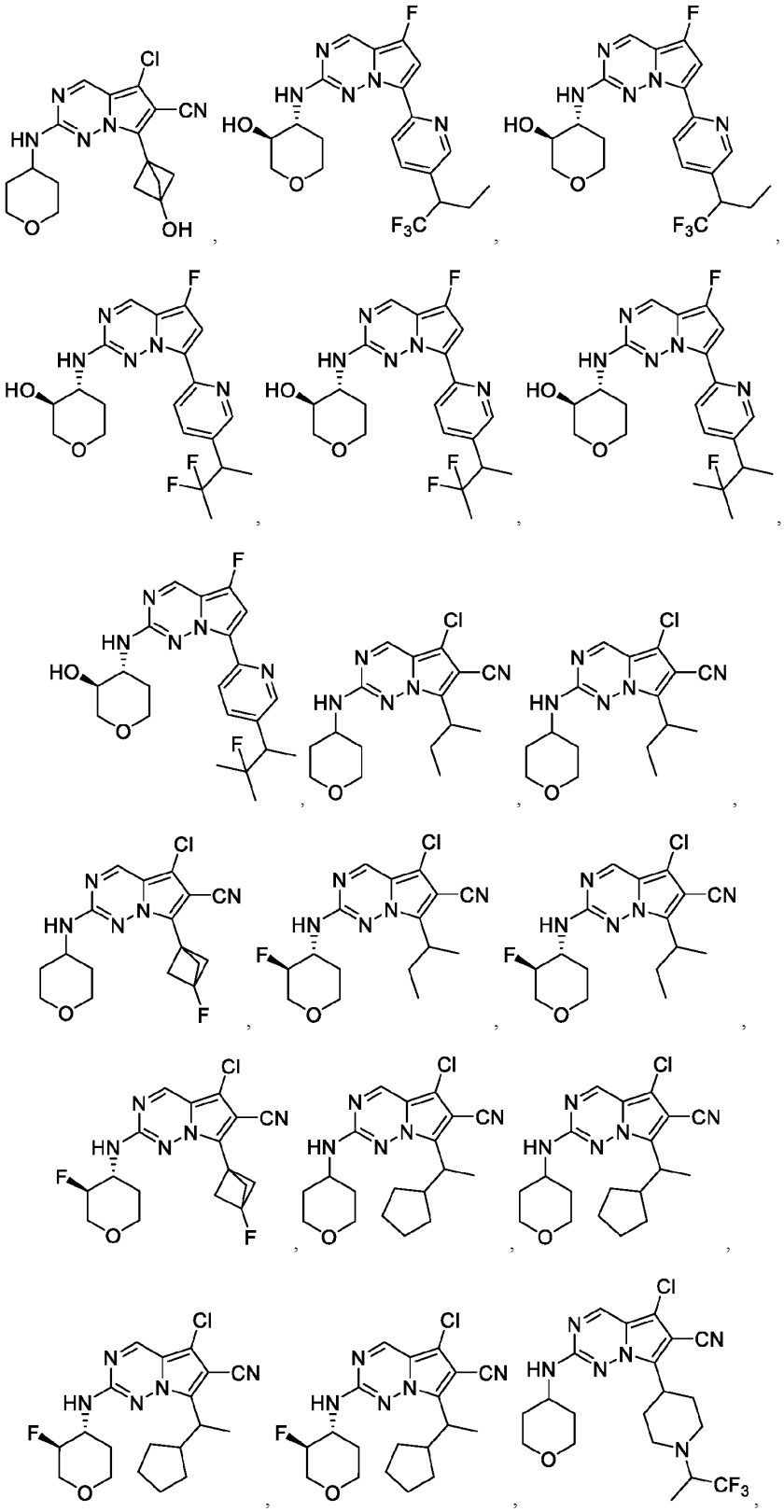















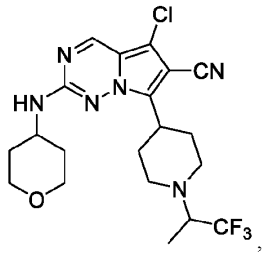
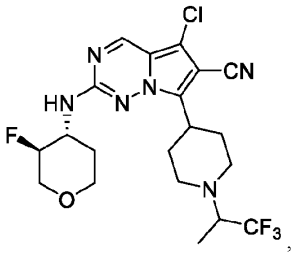
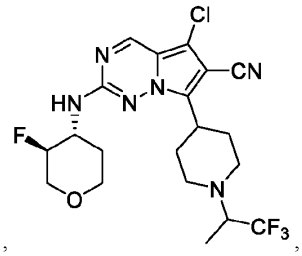
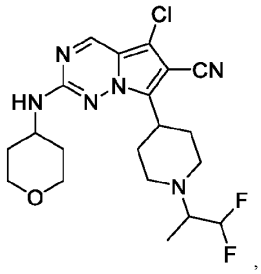
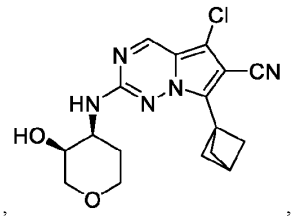
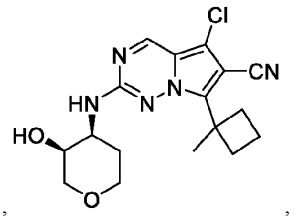
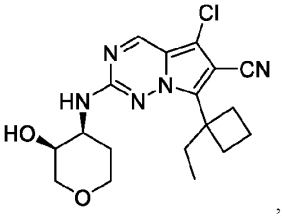
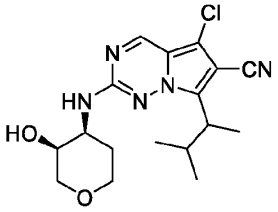
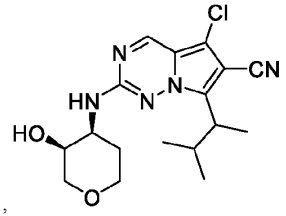
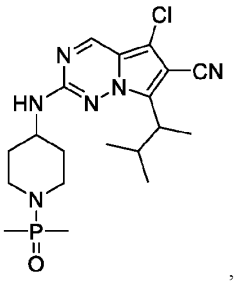
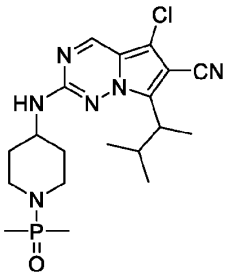
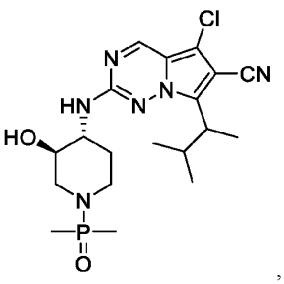
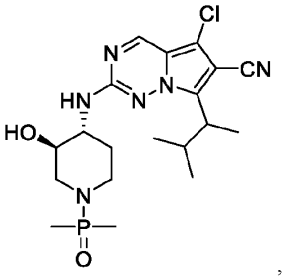
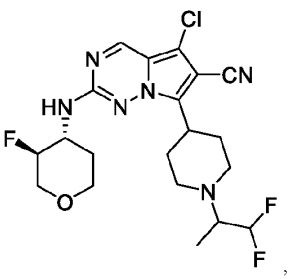
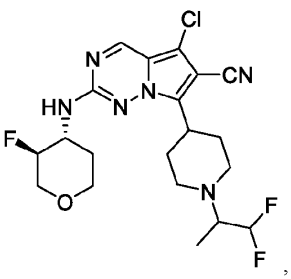


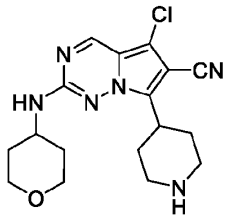







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2. A pharmaceutical composition comprising a compound, a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, as described in claim 1 and a pharmaceutically acceptable excipient.

3. A method of preparing a pharmaceutical composition comprising mixing a compound, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, of claim 1, and a pharmaceutically acceptable carrier.

4. A compound of claim 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, for use in a method of treatment of the human or animal body.

5. A compound of claim 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, for use in a method of treatment of cancer or neoplastic disease.

6. Use of a compound of claim 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, in the manufacture of a medicament for the treatment of cancer or neoplastic disease.

7. A method of treating cancer in a patient in need thereof, comprising administering to the patient a compound as described in claim 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof.

8. A method of treating cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising a compound as described in claim 1, or a pharmaceutically acceptable salt or solvate, or stereoisomer thereof, and a pharmaceutically acceptable excipient.

9. The use of claim any one of claims 4 to 6, or the method of claim 7 or 8, wherein the cancer is selected from breast cancer, skin cancer, melanoma, or leukemia.

10. A method of inhibiting a CDK2, CDK4 or CDK6 kinase enzyme comprising contacting the enzyme with a compound of claim 1, or a stereoisomer thereof, wherein the CDK2, CDK4 or CDK6 kinase is contacted in an *in vitro* setting.

11. A method of inhibiting a CDK2, CDK4 or CDK6 kinase enzyme comprising contacting the enzyme with a compound of claim 1, or a stereoisomer thereof, wherein the CDK2, CDK4 or CDK6 kinase is contacted in an *in vivo* setting.